Dear ARDS Meeting Participant,

Once again, we are delighted to offer you this booklet of notes, supplemented by the majority of slide presentations from our recent meeting. The notes were taken and assembled by two young, talented, rising retinal stars – Dr. Irene Rusu and Dr. Basil Williams – who attended every talk and captured the essence of the vigorous post-talk discussion, for which the ARDS is deservedly famous. We would also like to acknowledge the editorial oversight of Dr. R.V. Paul Chan.

This work was made possible by a generous contribution provided by Genentech, Inc.

We are grateful to Dr. Rusu, Dr. Williams, and to all of you for contributing to the intellectual vibrancy of ARDS. We hope you will find this booklet interesting, and also of value to you in the care of your patients.

Please join us March 4 – March 8, 2017 for the 45th Annual ARDS Meeting.

Sincerely,

The Course Co-directors

Donald J. D’Amico, MD
Weill Cornell Medical College
New York-Presbyterian Hospital
New York, NY

Timothy G. Murray, MD, MBA
Murray Ocular Oncology and Retina
Miami, FL
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The Aspen Retinal Detachment Society gratefully acknowledges

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**ARDS 2016 Program**

**Sunday**  
**March 6**

4:00–4:35 PM  
Recurrent Macular Holes in the Era of Small Gauge Vitrectomy  
Tarek S. Hassan, MD

4:35–5:10 PM  
Intravitreal Pharmacotherapy in Complex Ocular Disease: Where Are We in 2016  
Timothy G. Murray, MD, MBA

5:10–5:45 PM  
OCT angiography  
Giovanni Staurenghi, MD

6:15–6:55 PM  
Panel 2: Vitreoretinal Surgery  
Moderator: R.V. Paul Chan, MD  
Panelists: Donald J. D’Amico, MD,  
Harry W. Flynn, Jr., MD, Tarek S. Hassan, MD, Mark W. Johnson, MD

7:00–7:30 PM  
**Founders Lecture**  
Ocriplasmin Retinopathy: Characteristics, Mechanism, Incidence, and Reversibility  
Mark W. Johnson, MD

**Monday**  
**March 7**

4:00–4:35 PM  
New Treatments for Intermediate, Posterior, and Panuveitis  
Glenn J. Jaffe, MD

4:35–5:10 PM  
Promising New Treatments for Retinal Diseases: Gene Therapy and Engineered Cells  
Szilárd Kiss, MD

5:10–5:45 PM  
Management Options for VMT: What’s New in 2016  
Harry W. Flynn, Jr., MD

6:15–6:55 PM  
Panel 3: Vascular Endothelial Growth Factor  
Moderator: Szilárd Kiss, MD  
Panelists: Neil M. Bressler, MD, Glenn J. Jaffe, MD,  
Giovanni Staurenghi, MD

7:00–7:30 PM  
**Founders Lecture**  
Ocriplasmin Retinopathy: Characteristics, Mechanism, Incidence, and Reversibility  
Mark W. Johnson, MD

**Tuesday**  
**March 8**

4:00–4:35 PM  
Different Preferences between US and European Vitreoretinal Surgeons  
Donald J. D’Amico, MD

4:35–5:10 PM  
Changing the Rules in the Management of Pediatric Retina Disease  
R.V. Paul Chan, MD

5:10–5:45 PM  
Macular Atrophy in Anti-VEGF Treatment  
Giovanni Staurenghi, MD

6:15–6:50 PM  
Healthcare Policy and Payment in 2020  
David W. Parke, II, MD

6:55–7:30 PM  
**Taylor Smith Lecture**  
Impact of Recent DRCR.net Randomized Clinical Trial Results on Managing Diabetic Retinopathy in 2016  
Neil M. Bressler, MD

**Wednesday**  
**March 9**

4:00–4:35 PM  
Endophthalmitis: Real World Cases for the Vitreoretinal Surgeon  
Harry W. Flynn, Jr., MD

4:35–5:10 PM  
A Controlled Comparison of the Dexamethasone Implant vs. Intravitreal anti-VEGF Therapy for Diabetic Macular Edema  
Tarek S. Hassan, MD

5:10–5:45 PM  
Myopic Traction Maculopathy: Mechanisms and Treatment  
Mark W. Johnson, MD

6:15–6:50 PM  
Medical and Surgical Management of Enhanced S-Cone  
Donald J. D’Amico, MD

6:50–7:30 PM  
Panel 3: Practice Management 2016  
Moderator: Timothy G. Murray, MD, MBA  
Panelists: R.V. Paul Chan, MD, Donald J. D’Amico, MD, Tarek S. Hassan, MD, Szilárd Kiss, MD

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R.V. Paul Chan, MD
University of Illinois at Chicago (UIC)
Chicago, IL

Tarek S. Hassan, MD
Associated Retinal Consultants
Royal Oak, MI

Szilárd Kiss, MD
Weill Cornell Medical College
New York-Presbyterian Hospital
New York, NY

Neil M. Bressler, MD
Johns Hopkins Wilmer Eye Institute
Baltimore, MD

Glenn J. Jaffe, MD
Duke Eye Center
Durham, NC

David W. Parke, II, MD
American Academy of Ophthalmology
San Francisco, CA

Harry W. Flynn, Jr., MD
Bascom Palmer Eye Institute
Miami, FL

Mark W. Johnson, MD
Kellogg Eye Center
Ann Arbor, MI

Giovanni Staurenghi, MD
University of Milan
Milan, Italy
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**Founders Lecturers**

1983 Thomas M. Aaberg, Sr., MD  
1984 Robert E. Morris, MD  
1985 Michael Shea, MD  
1986 Alexander Ray Irvine, Jr., MD  
1987 William H. Spencer, MD  
1988 Victor T. Curtin, MD  
1989 Alan Bird, MD  
1990 J. Donald M. Gass, MD  
1991 Robert J. Brockhurst, MD  
1992 Stephen J. Ryan, MD  
1993 Wayne E. Fung, MD  
1994 Charles P. Wilkinson, MD  
1995 George W. Blankenship, MD  
1996 Mary Lou Lewis, MD  
1997 Donald J. D’Amico, MD  
1998 Stanley Chang, MD  
1999 Harry W. Flynn, Jr., MD  
2000 Ian J. Constable, MD  
2001 Thomas R. Friberg, MD  
2002 William S. Tasman, MD  
2003 Evangelos S. Gragoudas, MD  
2004 Steve Charles, MD  
2005 Thaddeus P. Dryja, MD  
2006 Jerry A. Shields, MD  
2007 Mark S. Blumenkranz, MD  
2008 Allan E. Kreiger, MD  
2009 Alexander R. Gaudio, MD  
2010 Carmen A. Puliafito, MD, MBA  
2011 David W. Parke, II, MD  
2012 J. Brooks Crawford, MD  
2013 Michael T. Trese, MD  
2014 Julia A. Haller, MD  
2015 George A. Williams, MD  
2016 Neil M. Bressler, MD

**Founders Lecturers**

2012 Steve Charles, MD  
2013 Joan W. Miller, MD  
2014 Carl D. Regillo, MD  
2015 Dean Elliott, MD  
2016 Mark W. Johnson, MD

**Exhibitors**

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Management of Recurrent Macular Holes in the Era of Small-Gauge Vitrectomy

TAREK S. HASSAN, MD

SUMMARY
Macular hole repair rates have improved significantly since 1991 but have leveled off in the past decade, commensurate with the widespread adoption of small-gauge vitrectomy. More experience, better ILM peeling technique, improved OCT technology, and better surgical visualization have all contributed to these improvements.

Macular hole closure occurs with vitrectomy, posterior hyaloidal removal, and ± ILM removal because traction is relieved from the hole and a bridge of glial tissue closes the full thickness defect. Reopening of initially closed macular holes has been reported to occur in approximately 5-9% of eyes but most series assessing this were done in the 20g vitrectomy era.

We performed the first extensive look at recurrent macular holes in eyes treated entirely with 23 or 25g vitrectomy techniques in a retrospective review of nearly 400 eyes. We found 13 eyes with reopened macular holes (3.3%), occurring at a mean of 28 months following the initial repair. All eyes underwent reoperation and all macular holes closed again. Three of these 13 eyes reopened for a second time, and two of the patients decided not to pursue further surgery. The third macular hole closed with another vitrectomy procedure.

We note the low incidence of macular hole failure and describe the potential anatomic findings that may explain reasons for the hole reopenings. We also note correlations between the other eyes of such patients with recurrent macular holes and the published literature.

NOTES
The expectations for success in macular hole repair are extremely high. It is almost thought of as a curable condition amongst most of us.

Why are we so much better now at closing macular holes? First of all, we’re more experienced with this surgery. Most macular holes are surgical candidates and they present earlier. Therefore, we operate on them earlier, so they’re likely smaller and earlier stage macular holes. Our surgical fellows are also very experienced and very well trained at peeling the internal limiting membrane (ILM) and repairing macular holes. They go into their practice, and they’re all very effective at doing this. We also have OCT everywhere, and the OCT is much improved and has improved our ability to identify macular holes. Intraoperatively, we are able to see things better during surgery than we did before, whether it’s because our viewing systems are better or the use or different dyes that improve staining and our visualization.

So, how do macular holes close? We know that vitrectomy, posterior hyaloid separation, and removal of premacular tractional tissue, whether it’s epiretinal membrane and/or internal limiting membrane, relieve traction. There’s some data that says not only does it relieve traction, but it actually increases cytokines locally which could help close macular holes. There are histologic changes which we now know would close macular holes. Glial plug bridges the macular hole, and in that glial plug we have Mueller cells, fibrous astrocytes that replace the photoreceptors.

Interestingly, if you look at a closed macular hole, we notice that the ILM histologically at the hole margins is actually gone, even in cases in which there’s no ILM peeling. That’s may implicate the ILM as part of the pathologic process. Histologically, we know the RPE is usually normal; there’s not much of an inflammatory response locally, and the cystoid macular edema, if present, usually resolves.

Most macular holes close; some don’t. The time to closure of most macular holes typically happens in less than a day and can take up to about seven days to close. With increasing time, that glial plug matures, and you get a more robust closure of the hole. When does hole closure fail? We can define things in different ways, but a primary failure is basically a hole that never closes, didn’t close on the table, and never closes post-operatively. We can talk about things as being an early reopening, if you never really get the solid glial plug, so sometime in that first 7 days. A late reopening is typically one that is thought of at least several weeks later, when you have a mature glial plug that is formed.

Terminology is important. There are persistently open or incompletely closed holes. This is a hole that never closed or reopened within the first few days. You’ll have a flat, but open configuration, which is sometimes seen. A recurrent macular hole is when the macular hole reopens immediately. A late reopening occurs after the immediate post-operative period, so typically over a month. We’re going to look at recurrent macular holes that happen over a month out, after the glial plug is formed and it has been stable for some length of time.
Generally accepted rates of recurrence for macular holes in the published literature are approximately between 5 and 10 percent. The mean time for reopening is from 12 to 15 months in the published literature. There are a lot of papers that support this, but these series are entirely, or at least predominantly, from the pre small-gauge vitrectomy era. All or almost every case in the published literature was done with twenty-gauge vitrectomy techniques, with different visualization systems.

The question of our study is, “What about recurrent macular holes in the current era where we use modern techniques and small gauge instruments, whether it be 23, 25, or 27 gauge systems?” Is there a known impact of small-gauge vitrectomy macular hole repair? Is small-gauge surgery theoretically advantageous? It’s less invasive which may cause less inflammation, which might cause less post-op CME, which might have some impact. The advent of small-gauge vitrectomy really came about at a time when the anatomic results for macular hole repair leveled off. What about macular hole reopening? Does small-gauge vitrectomy have any impact on the outcome?

**Study Purpose**
This study assessed patients who developed recurrent macular holes in eyes treated with small gauge surgery.

**Study Methods**
The study included about 400 eyes that were operated on over the past decade. Inclusion criteria included all eyes that had successful macular hole closure after initial vitrectomy. Closure was defined as having at least a month where it was felt the vision had improved significantly and the hole was closed. These cases were mostly done by 23-gauge and a few by 25-gauge.

**Study Results**
Of the 392 patients, 13 had reopening of the hole. 5 were men and 8 were women. All eyes had ILM peeling, half with indocyanine green (ICG) staining and half without a stain. About half had a C3F8 bubble and half had an SF6 bubble. All the macular holes initially closed, and we had commensurate visual improvement from 20/137 to 20/61 for the cases that reopened. There was a wide range of time after initial vitrectomy to reopening (5 weeks to 10 years), and 11/13 (83%) eyes had clinically identifiable ERMs present after the initial vitrectomy. Cataract extraction occurred in 5/13 patients between initial surgery and reopening of the hole.

All the macular holes that reopened had a second vitrectomy. At that second vitrectomy, nine of the eyes were identified as having an epiretinal membrane peeled at that time. All of the of eyes were subject to further ILM peeling, which means an attempt was made. ICG staining was used in 11/13 repeat ILM peels and the surgeon thought ILM remnants were removed from around the hole in 9/13 cases. Gas tamponade of C3F8 was used in 12/13 cases. All 13 eyes had the whole closed again and there was a significant VA improvement from 20/148 to 20/115.

**Video of 2nd hole surgery** – Some pieces of stained ILM were lifted, but there were only minimal ERM parts remaining. This is atypical considering the membrane normally goes out to almost to the arcade. The peel was noted to be rather unimpressive. Most of the peeling was also not occurring at the site of the hole.

So, amazingly, even though all of these recurrent holes closed after the second surgery, three eyes had reopening of the macular hole again. Two of them occurred at five months, one of them occurred at 49 months after their reoperation for the open macular hole. Two of these patients decided not to have additional surgery. Their final visual acuities were 20/200 and 20/400. One patient decided for a third vitrectomy, and they improved to 20/60 after the third vitrectomy. That patient has remained closed now for over a year. The mean visual improvement in those eyes was significant. We had only one intraoperative retinal tear and there were no other complications.

What was very interesting to us was the status of the fellow eye. Of these thirteen eyes, at some point either before or after surgery, 77% (10/13) of patients developed a full-thickness macular hole in their other eye. That was very surprising to us.

The impact of small gauge surgery on macular hole repair remains unknown, but our study showed a slightly lower rate of reopening. Maybe there is less inflammation and resultant CME (only 15% in our series). But there is also more experience in dealing with these cases now.

**Why do holes re-open?**
A number of things may cause holes to re-open including: ERMs, remnants of the vitreous or ILM adherent to the edge of the hole, macular edema, or any additional event that produces a pro-inflammatory cascade.

On histologic evaluation, Fekrat et al used blue staining to identify the ILM and found material on the undersurface of the re-opened hole (places that we don’t normally peel). This may indicate that by simply scratching around the edges of the recurrent holes, they may close.

ERMs have been found in reopened holes in rates ranging from 60-75% in the literature. In the ERMs of these patients with recurrent holes, there are contractile...
elements like fibrous astrocytes and Müller cells with myoblastic features. In the current series, some tissue was peeled (ILM, ERM, NFL) in all cases.

Were the epiretinal membranes actually significant? Did they cause the reopening? What would be the outcome if nothing was peeled and just another bubble was placed? There is a series from Ophthalmology in 2008 by Valldeperas, which showed 100% closure with re-bubbling in the absence of ERM peeling. Epiretinal membrane formation is likely an extension of the normal healing of a macular hole. In fact, most (about 75%) macular holes have some epiretinal membrane tissue at its margins.

We know CME causes macular holes to reopen after vitrectomy in some cases, but there is a low incidence. If cataract extraction happens after macular hole repair, you can get CME. Bhatnagar showed in EJO a few years ago that if you have cataract extraction after vitrectomy, there's a four times increase in macular hole recurrence in eyes that had cataract extraction after macular hole repair. If macular edema was present after this cataract surgery, there was a seven times increase. There are actually series that show that even after YAG capsulotomy, the cystoid macular edema can cause an increase in macular hole occurrence (Garcia-Arumi et al J Cataract Refract Surg 2006).

Recurrent macular holes have a very high incidence of bilateral macular holes. In our series, we showed that this was present in 77% of cases. Interestingly, there's another very good series out there by John Thompson published in Ophthalmology in 2000 that shows similar results. He used all 20-gauge vitrectomy. He noted nearly 70% incidence of bilateral holes in his series of recurrent macular hole patients. Again, the generally reported incidence of bilateral macular holes is 10 to 15%. Maybe these eyes with recurrent macular holes have an even more abnormal vitreomacular interface than what we see in other patients. Maybe they have tangential traction, intrinsic ILM contracture or an overabundance of ILM that we can't get to on the outer surface of the hole. Whatever it is, something is different about these patients with recurrent macular holes that their other eye develops a hole also.

To conclude, I don't know if there is any difference in small-gauge surgery for these cases. There is a low incidence of recurrence regardless. It was a little bit lower in our series, but that may be due to other conditions as opposed to the gauge of surgery. Interestingly, recurrence happens many months later after closure, it is associated with epiretinal membrane tissue, and to a lesser degree, having cataract extraction after vitrectomy. There appears to be a higher likelihood of closure with re-operations than I thought.

Something is different about patients with recurrent holes. Their pre-disposition to macular traction, even with the level of ILM that leads to reopening, may be very significant. Again, the other eye should be watched closely. What do I take away from that? Well, I aggressively treat the possibility of CME after performing macular hole surgery. Also, if your patient has a moderate cataract, you may consider having the cataract done just before you do the macular hole surgery. If an epiretinal membrane develops after a macular hole, and it's symptomatic, consider peeling it before the macular hole recurs. I aggressively treat any pro-inflammatory conditions that may lead to CME, whether it is uveitis or trauma, and I monitor the fellow eye very carefully.

COMMENTS:

Q/C: I agree that treating the cystoid macular edema is really important. You might consider this when the hole reopens or when a spontaneous hole occurs. I've recently had a couple of holes in the last few months. One relatively small spontaneous hole and one medium hole that reopened. Both had significant associated CME. I treated both medically, put the patient on the surgical schedule, and the hole closed before they had to undergo the re-operation.

The other thing you had mentioned about picking around the ERM. In some of those cases, it looked like you really didn't have much to pick. I think you're probably just stimulating a wound healing response and recreating that glial plug with glial corporation.

Q/C: That was almost the same question that I was going to ask. Many of us were around long ago when we did macular holes before we even knew there was ILM to peel, and we had a much higher rate of macular holes either not closing or reopening. As was stated in the previous question, I think there are a very small percentage of patients; especially the ones who reopen late, that will spontaneously close if you don't do anything. I don't know how fast you go to the OR when they reopen, but did you see any spontaneously closed macular holes?

A: We didn't. Looking at the series, we didn't see a single one that spontaneously closed. We typically get them into the OR within a couple of weeks. To see it once means it's not an unreasonable concept to at least investigate.

Q/C: Do you have any experience with treating with a gas bubble? For example, you have a patient who's done well for a number of months and they reopen, just giving them a gas bubble?
A: I deal with a lot of these macular holes in office. I give them C3F8 and it seems to work well. Even the ones years ago that didn’t have an ILM peel would close with the C3F8. I haven’t read the study that you’re quoting about the guy doing recurrences with an air fluid exchange, but with expansile gas, if he’s not really peeling anything, there’s not a big difference between doing an office gas injection and air fluid exchange.

Q/C: I just wanted to comment about the rates of reopening. We’ve looked at a large database that was published in Ophthalmology here a few months back, and we have about 6,000 macular holes. The rate of recurrence was around 4%. If you follow the patient for a year or more, it had a higher rate than if you follow the patient 3 to 6 months. Obviously, that makes sense. As far as bilaterality, the only large series was by Don Gass and Mary Lou Louis. They showed a bilateral rate of 14%. Again, if you follow the patients long enough, the rates went up. All of that was pre-OCT, so now we have to look at series that have OCT documentation of the fellow eye. If they have no traction, then obviously, the rates were low.

A: That’s for sure. Obviously, there’s a big difference between 15% recurrence and 70%. There’s clearly something we’re not taking into account. We’re not talking about stage I holes. These are all full thickness macular holes.

Q/C: Two quick aspects about simultaneously or separate cataract extraction. In Europe, we very often do it simultaneously. There are two reasons to perform cataract extraction before. One, if the patient undergoes gas first they expect to see better because the hole is closed but often the cataract is now worse and they don’t. They become upset that they expected good vision, and now they have to go for the second surgery. If you do cataract extraction as the first procedure, they don’t expect improvement because they understand the hole is still present. Then the gas reabsorbs after the second surgery, and they improve. If you do the surgery simultaneously the patient pays much less and sees better once the gas is reabsorbed. Overall, they are much happier.

A: We would certainly welcome more of an opportunity to do simultaneous procedures in the United States. However, it’s harder to do combined procedures here.

Q/C: Yes, it’s pretty much the rule in Europe. Frequently, vitrectomy is done with cataract surgery in Europe.

A: A couple of things on the incidence of macular hole development in the fellow eye. I always look for the vitreous separation. If they’ve already had a PVD, I think their incidence is much lower than the average 5% or 10% chance of those who don’t have a PVD. I did have one patient who had a recurrent hole. She developed a cataract, had the cataract removed, anticipating surgery and it spontaneously closed. Five years later it reopened and I had to do surgery. It closed again. Some of them are just going to reopen.

Q/C: I think the same thing, but I wonder if there’s any evidence for that. I wonder if there are any OCT features that can predict whether the fellow eye will develop a hole.

A: No

Q/C: Just an observation. The color photograph of the ILM peel under heavy staining was leaving a little doughnut of ILM right around the hole opening. Then on the histopathology later you could see that. I’m wondering if there are any videos looking back at the failed cases to see if they had that little ring that you showed in the still shot of the little green circle around the fovea. That might be something that increases the risk of recurrence.

A: It’s definitely something to look at. It’s a variable group of surgeons whose cases were conglomerated together for the series, but it’s a great idea.

Q/C: In these cases that you showed, you have a macular hole; the patient is 20/100. You do the surgery, and the hole remains open, but the retina is flat just not completely closed. The vision at this point is 20/60 indicating that there is some improvement. Has anybody ever gone with a spatula and tried to improve that contour or is it best to leave it alone.

A: No, it just struck me that once a hole is closed there has to be some type of tractional force to pop it back open. I think you’ve outlined the possibilities. One is an epiretinal membrane that’s pulling tangentially on what was a weakened fovea; in that case, it would seem that re-operation is probably the best road. Another would be CME, either inflammation or postoperative. In that case, I like the idea of trying medical treatment before going back to the OR. I haven’t done a lot of it, but there are a number of cases that have reported closure by getting rid of the CME. That would resolve that sort of drawbridge of traction that develops. Then trauma would be a third potential cause of acute traction. There, we probably don’t need to go back to the OR; if there’s no epiretinal membrane, we could probably close that with just the gas bubble. There’s a possibility we could be good at really tailor-making our treatment for recurrent holes if we look very carefully at the circumstance and the OCT results.

Q/C: So along those lines, regarding the epiretinal membrane. You have a lower threshold for operating on any epiretinal membrane that may form, correct?
A: Well, a lower threshold about doing it if the patient becomes symptomatic.

Q/C: In terms of the initial surgery, what's the role of intraoperative OCT there? Do you think there will be a benefit in using that technology?

A: I think intraoperative OCT will help us ensure that you've done your maximal ILM peeling, if we can resolve things to that level. In this particular series, I don't think it made any difference. It's certainly going to help us in the future.

Q/C: Do you have an opinion on this ILM folding technique that some people were using in the series in Europe and elsewhere?

A: I find it interesting. I have not done it. I think we don't see too many failed macular holes anyway in the United States. I suppose there's some rationale if you've had a giant hole that is beyond the boundaries of what you think you are closing in a normal surgery. The problem is, if you stick something in the hole, what you're doing is, you're really accentuating that glial plug. You don't have any photoreceptors there, so you may get an anatomic closure, and you may get some visual improvement but there are still no photoreceptors in the middle.

Q/C: Well, I actually have a question for the audience. I've done one of the cases with a large hole, it wasn't a re-opened hole it was a large hole that simply wouldn't close. I went in and stained with ICG (I usually do not use ICG) in this case to find a little piece of ILM from outside the macula where it hadn't been peeled. I put that in the hole, the hole closed, I was ecstatic. Then I watched what looked like geographic atrophy develop exactly corresponding to the ILM piece. I think the issue is that you take ICG (the ILM was stained with ICG) and you put it right where you don't want it, which is against the RPE. Then you prevent the photoreceptors from coming in contact with the RPE which leads to RPE atrophy as well. Has anyone done this? Has anyone seen this?

A: The group from Barcelona discussed that in Guadalajara. They were the first group that had reported good visual outcomes. There were four cases that were reported, and all of them had vision of 20/40 or better with macular holes that were two disc diameters in size. That was the first time I saw that kind of impressive improvement without any RPE changes. There was a big discussion about RPE toxicity. Remember, though, they don't use ICG. So maybe these are cases where if you are going to peel ILM, you want to avoid ICG because of that exact possibility. So maybe avoid ICG when peeling ILM and plugging the hole with it.

Q/C: There is a series of full thickness retina and choroid transplanted into the macular hole and reported good results. So, I'm curious, who's tried that?

A: I thought it was amazing to see. I was in the room. It's hard to imagine the mechanism or why that's necessarily a good thing, but I suppose anything that stimulates that glial plug to form is beneficial, in this case the full thickness retina and choroid. I don't think it's the type of thing I would necessarily do, but it's interesting. What are your general thoughts? What does the rest of the faculty think?

A: (clarification) So he is taking a full thickness retina plug from what is basically a biopsy site in the mid-periphery, then dropping it into the hole.

Q/C: The first question is, so did he get it right side up or not? It did look like it was the correct orientation. It was interesting to watch the OCT over time because it did look like there was reconstitution of the retinal layers.

A: It probably would have had the same result in any orientation.
Management of Recurrent Macular Holes in the Era of Small-Gauge Vitrectomy

Financial Disclosure

NO RELEVANT FINANCIAL RELATIONSHIPS

Full Disclosure

How Macular Holes Close

Vitrectomy, posterior hyaloid removal, removal of other premacular material: ILM, ONL
• Relief of traction (due to increased cytokines)
  → HISTOLOGIC CHANGES
• Glial plug bridges macular hole
• Müller cells, fibrous astrocytes replace photoreceptors

CLOSED MACULAR HOLES

HAT at hole margin ‘GONE’ even when no RM peeling is done

RPE appears normal
No significant inflammatory response
Resolution of CME

Most Macular Holes Close:

Some Don’t

Time to closure

Most eyes: < 1 day to 7 days

↑ time, glistening plugs matures, robust healing continues

When does MH surgery fail?

Primary failure: Hole does not close during and/or immediately after surgery

Early reopening: Failure prior to formation of solid glistening plug

Late reopening: Failure after at least several weeks...

Failed Macular Hole Surgery — Did the hole ever close?

Terminology:

Persistently open or incompletely closed

MH never closes, or...

MH closes within first several days/weeks of surgery

(b) (c) (d) correct: Flat edges but open central MH

Recurrent

MH closes after the immediate postop period (> 1 month)

After the glistening plug has matured and been stable

Recurrent Macular Holes

Historical incidence (published papers: 1993-2008)

Generally accepted: 4.8% – 9.2% (Wright, Driscoll, Repin, & Alm, 2003)

Mean time to reopening = [2-15 months] (Wright, Repin, 2003)

Series are entirely or predominantly from pre-small-gauge vitrectomy era

All — or most — cases done with 20 gauge vitrectomy techniques

Visualization not as good as today...

What about recurrent MMs in an era in which we use modern techniques of small-gauge (23, 25, and 27 gauge) vitrectomy?

IMPROVED Macular Hole Outcomes

More experience

Most MHs are surgical candidates
• They present earlier
• We operate on them earlier
• Surgical fellows trained are well trained to peel ILM and repair MHs

Ubiquitous and improved OCT

Earlier diagnosis

Earlier surgery for smaller holes

Better surgical visualization

More eyes: improved staining

Vitrectomy for Macular Hole

MH closure rates have improved significantly since 1991

VERY HIGH EXPECTATIONS for success

Nearly "curable"
Impact of Small-Gauge Vitrectomy on MH repair...

- Ultimately Not Known
  - Small-gauge Vit: Theoretically advantageous?
  - Less invasive
  - Less inflammation
  - Less postoperative CME
  - Anatomic results = Same
  - What about macular hole reopening?

Current Series: Recurrent MHs
Associated Retinal Consultants, Royal Oak, Michigan

- First extensive look at recurrent MHs in eyes treated entirely with small-gauge vitrectomy techniques
- 392 eyes (8 surgeons); retrospective review, 2001-2014
- All had successful closure of idiopathic FTMH with initial Vit
- All small-gauge vitrectomy (25g > 23g)
- STUDY GROUP: All eyes that had reopening of MH after documented closure, at least 1 month post-initial Vit
  - N = 13 eyes (3.3%): Subject to evaluation...

Current Series: Recurrent MHs
The MHs That Reopened

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<td>Mean age</td>
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- Surgical parameters from the initial MH repair
  - All eyes had ILM peeling
  - 6/13 ICC assisted, 7/13 no ILM
  - 6/13 with C3F8, 7/13 with SF6 tamponade
  - All MHs closed postop after 1st vitrectomy
  - VA ↑ 20/137 → 20/11 before reopening

Current Series: 13 Recurrent MHs
Features of the 1st surgery for the MHs That Reopened...

- Time to MH reopening
  - Mean = 28 months
  - Range = 5 weeks - 10 years
  - 11/13 (85%) = ERN identified clinically post 1st vitrectomy
  - 5/13 (38%) = CME identified post 1st vitrectomy

- Reoperation
  - 9/13 eyes (69%) — ERM peeled
  - 13/13 eyes (100%) — More ILM peeling
  - 9/13 — Surgeon felt ILM remnants were removed from areas around the MH
  - 11/13 — ICG used
  - 12/13 — C3F8 used
  - Mean VA ↑ 20/148 → 20/115 postop
  - 13/13 MH closed > 1 month

Vit for Recurrent MH

- Initial presentation VA = 20/100
- After 1st Vit VA = 20/30
- MH reopening 2 yrs later VA = 20/200
- After repeat Vit VA = 20/60

Our series: Examples

- 15 mos after 1st MH repair
  VA = 20/40; slight distortion

- 18 mos after 1st MH repair
  VA = 20/100, some distortion

- 20 mos after 1st MH repair
  VA = 20/200
  After repeat Vit VA = 20/70
MANAGEMENT OF RECURRENT MACULAR HOLES – HASSAN

13 Recurrent MHs Closed BUT... Some MHs Reopened AGAIN!

- 2nd MH reopening: 3/13 eyes (23%)
  - Time to reopening
    - 5 mos, 5 mos, 49 mos
  - Management...
    - 2 chose no more surgery
    - Final VA = 20/20, 20/40
  - I had a 3rd Vit with ERM peeling
  - VA improvement: 20/400 → 20/60

Current Series: Recurrent MHs
Associated Retinal Consultants, Royal Oak, Michigan

- AT MOST RECENT F/U
  - MHs closed in all eyes that had all surgeries
  - Mean VA improvement
    - 20/148 → 20/89

- Complications (excluding cataract)
  - 4 intraoperative retinal tears
  - Received laser
  - No others

- STATUS OF THE OTHER EYE
  - Of the 13 eyes that had reopened MHs
    - 10 (77%) either had, or later developed, a PTHM in the other eye

Impact of Small-Gauge Vitrectomy on Recurrent MHs?

- MH reopening: Historically low incidence
  - Lower after small-gauge Vit? MAYBE!
  - Why?
    - ↓ inflammation → ↓ CME → less MH reopening!
    - More refined surgical technique after years of experience
    - Better understanding of pathophysiology
    - Better visualization of all aspects of the surgery...
    - More complete ILM/ERM removal!

Why Do MHs Reopen?

- Post-initial repair...
  - ERM
  - Residual vitreous w/ ILM remnants adherent to the MH edge
  - CME
  - RD, Trauma, Iritis, Etc.
  - Likely any event that could initiate a pro-inflammatory fibrinolytic cascade

Reasons MHs Reopen:
ERM

- Multiple authors report high rate of ERM in reopened MHs
  - 73% (Hiibara et al, Ophthalmology 2008)
  - 57% (Hiibara et al, AJO 2007)

- Pathologic correlation
  - Finkl et al (Retina 1999), Koek et al (AJO 2001)
  - In ERM, Muller cells with atrophic features, glial astrocytes — CONTRACTILE elements

- OUR SERIES
  - 69% had ERM removed
  - 100% had some tissue peeled (ERM, ILM, ERM/ILM complex, or maybe even some nerve fiber layer of the retina) — even if a remnant...

Reasons MHs Reopen:
ERM

- Is the ERM found in recurrent MHs actually significant?
  - Does it actually cause the recurrence?
  - Does it need to be peeled?
  - Maybe just add another bubble...

- Vallejo et al (Ophthalmology 2008): 100% closure of recurrent MHs achieved with no ERM peeling

- ERM: Likely an extension of normal postoperative healing of MH

- No et al, (Arch Ophth 2006) OCT study: 64% closed MH had associated ERMs

- Agrees with older Guyer study: 73%

Reasons MHs Reopen:
CME

- After Vitrectomy... generally low incidence
  - After CE
  - Bhatnagor et al (AJO 2007)
  - 4X ↑ MH reopening in eyes with CE after Vit vs. eyes with Vit alone or combined Vit and CE
  - If + CME after CE: 7x ↑ MH reopening

- After YAG capsulotomy
  - Some suggest CE and capsulotomy before or during Vit for MH

Reasons MHs Reopen:
Is there something else going on?

- Eyes with recurrent MHs
  - High incidence of bilateral MHs
    - Our series: 77%
    - Thompson et al, (Ophthalmology 2000): 69%
    - General reported incidence of bilateral MHs: 10-15%

- Eyes with recurrent MHs
  - EVEN MORE ABNORMAL VITREOMACULAR INTERFACE...
    - Possibly greater tangential traction — potentially from intrinsic ILM contractility
    - Higher likelihood of significant ILM formation
Recurred MHs: Issues are the same as in the era of small-gauge Vit as in the past
- Low incidence
- Generally happens many months later
- Associated with same ERM issues and post-vitrectomy CE in a lesser degree
- Higher likelihood of successful closure with reoperation with only VIT, MP, FGA
- 77-100% Multiple reports from 20G Vit era and OUR SERIES
- VA improvement is seen but not as much as if closure was seen without recurrence
- Such eyes may have an intrinsic predisposition for macular traction, maybe even at the level of the ERM, that may lead to reopening
- The majority are associated with a PTMH in the other eye

Final Considerations: Recurrent MHs after Small-Gauge Vitrectomy
- Thoughts to potentially reduce recurrent MHs
  - Aggressive treatment of CME after Vit
  - Consider pre-Vit CE or a combined procedure at time of Vit
  - Peel ERM after Vit if symptomatic even if no recurrent MH is seen
  - Aggressively treat pro-inflammatory insults
  - Uveitis, Trauma, etc.
- MONITOR THE OTHER EYE CAREFULLY

In the published literature, recurrent macular holes are reported to occur in approximately what percentage of eyes?

In the majority of cases, macular hole reopening typically occurs approximately how long after vitrectomy?

The contralateral eye in a patient with a recurrent macular hole:

1. Has a higher likelihood of developing a macular hole at some point in the future than the reported incidence of macular holes in the general population
2. Has a lower likelihood of developing a macular hole at some point in the future than the reported incidence of macular holes in the general population
3. Has the same likelihood of developing a macular hole in the future as the generally reported incidence of macular hole development in the general population
4. Is not reported to develop a macular hole at any point in the future
Intravitreal Pharmacotherapy in Complex Ocular Disease: Where Are We in 2016

TIMOTHY G. MURRAY, MD, MBA

SUMMARY
The last 5 years have seen marked advances in vitreoretinal surgical management. Enhanced, integrated surgical platforms now incorporate high speed cutting, fluidic stabilization, and widefield imaging. Significant shifts include valved trocar entry systems, improved single-use instrumentation, and intraoperative pharmacotherapeutic agents to stabilize retina, image tissue structures, and modulate surgical morbidities. This presentation will use case based video analysis to highlight the indications, applications and expected outcomes for the use of advanced intravitreal pharmacotherapy as it relates to vitrectomy surgery. Clinical pearls will be discussed including approaches to minimize intraoperative and postoperative complications associated with the use of these novel agents.

NOTES
Radiation therapy
We’ve shifted from enucleation to radiation therapy in uveal melanoma which has enabled us to save more of the eyes that we treat. Today the focus is on the visual consequences of radiation therapy. Radiation retinopathy is a major cause of visual loss and is thought to be related to vascular endothelial damage. Ischemia is the underlying trigger for neovascularization and/or edema. Binding of VEGF stabilizes the blood-retinal barrier leading to reduced exudation and a down regulation of inflammatory cytokines involved in edema. There is no leading trigger for neovascularization. Ischemia is the underlying trigger for neovascularization and/or edema. Thus, anti-VEGF treatment did not eradicate the macular edema. Rather it just modulated it.

Study purpose
To evaluate the impact of spectral domain OCT (sdOCT) imaging to target intravitreal bevacizumab in the early detection and treatment of radiation maculopathy associated with 125Iodine brachytherapy for posterior uveal melanoma.

Study methods
Consecutive case series of 110 eyes of 110 patients with visually compromising radiation maculopathy in the setting of brachytherapy controlled posterior uveal melanoma. All patients underwent the COMS configured 125-Iodine plaque radiotherapy protocol and had serial evaluations every 4-6 months consisting of complete ophthalmologic examinations, fundus photography and OCT imaging. Patients were treated with intravitreal injections of 1.25 mg bevacizumab if they had visual decline or OCT findings of macular thickening.

Study results
About 60% of the 110 patients in the series developed sdOCT changes. Pre-treatment baseline visual acuity was 20/55 and OCT foveal thickness was 487 microns. The time from brachytherapy to the development of the OCT changes and enrollment in the trial was about 10.8 months, which was an early shift from what had been reported in the COMS. Mean follow-up was 34 months. By two months, there was a significant decline in the central point OCT thickness. That continued to decline until about a year, then it fluctuated from about 312 to 330 microns. The visual acuity improved by 12 months, then it fluctuated in that 20/40 to 20/50 range. Remarkably, in the COMS, the mean visual acuity at 36 months was 20/400. In this series, the mean visual acuity at 36 months was 20/40.

Conclusions
This is the first large series that showed that radiation maculopathy could be treated resulting in improved vision. SdOCT is critical in the early detection of radiation maculopathy. Intravitreal bevacizumab improves visual acuity and anatomy in eyes developing visually significant radiation maculopathy. Interestingly, in the majority of patients there was still a small component of persistent clinically significant macular edema. Thus, anti-VEGF treatment did not eradicate the macular edema. Rather it just modulated it.

Take home point
Utilizing sdOCT detected radiation maculopathy early. Targeting radiation maculopathy with intravitreal anti-VEGF therapy is an effective strategy to improve visual acuity outcomes in these patients. There were no treatment complications in our study.

Intravitreal steroid therapy
Intravitreal steroid is another agent used to modulate radiation maculopathy based on the belief that there is an inflammatory alteration along with the ischemic changes affecting radiation maculopathy. The following study assessed whether patients who responded poorly to anti-VEGF agents had a better response to intravitreal steroids.

Methods
IRB approved retrospective review from 2007 to 2013 of patients refractory to intravitreal anti-VEGF therapy. After informed consent, patients were treated with...
intravitreal triamcinolone acetonide at a concentration of 4 mg/0.1mL; Kenalog from 2007 to 2009, preservative-free triamcinolone compounded internally from 2009-2010, and triamcinolone, commercially available as Triesence from 2011 to 2013. Patients were evaluated every 4-6 weeks.

**CASES**
Selected cases demonstrate that patients initially not responsive to bevacizumab had virtual resolution of their macular edema with triamcinolone.

**Results**
A total of 2267 patients received 4574 intravitreal triamcinolone acetonide injections. The pre-treatment visual acuity was approximately 20/240 and the central macular thickness was 547 microns. The mean follow-up was 34 months. The average number of injections for patients was approximately two. The mean intraocular pressure at conclusion of the study was 14.7 mm Hg. About 40% of our patients had at least one visit with an intraocular pressure over 21 mm Hg. The mean number of topical glaucoma agents was 1.3 by the end of the trial at three years, and this group had a mean IOP of 14 mm Hg. The OCT thickness decreased from 547 to 327 microns. Visual acuity at a mean of 18 months improved from 20/240 to 20/112, in this group that had previously failed anti-VEGF therapy with 51% showing vision better than 20/50. There was a statistically significant improvement in visual acuity, but not as significant an improvement as was seen in the cohort that responded well to anti-VEGF therapy alone.

**Preparation dependent steroid properties**
In 2006, Bascom Palmer reported on a cluster of sterile endophthalmitis cases that prompted them to move from Kenalog to preservative-free triamcinolone acetonide. Around the same time, similar clusters prompted the move to Triesence when it became available. These drugs, even though all are called triamcinolone acetonide have different particle sizes and composite vehicles.

**Conclusions**
Intravitreal triamcinolone acetonide improved macular edema from a variety of causes; but most importantly, in those patients with radiation maculopathy that was unresponsive to anti-VEGF as mono-therapy. The future is to look at alternatives for mono-therapy, but also to look at strategies for integration of different drugs.

**Intravitreal pharmacotherapies as surgical adjuncts**

**Study purpose**
To evaluate the impact and outcomes of molecular genomic testing on primary and adjunctive therapy for uveal melanoma.

**Study methods**
Retrospective review of a consecutive case series of 138 eyes of 138 patients with posterior uveal melanoma undergoing definitive tumor treatment coupled with molecular genomic analysis. Every patient in the series underwent vitrectomy with small-gauge surgery, removing the hyaloid and any vitreoretinal traction overlying the tumor, followed by lasering the tumor and biopsy of the laser site. Intravitreal steroid was also given, specifically to suppress post-surgical inflammation.

**Results**
Virtually all eyes had vitreo-tumoral traction manifested as either a taut posterior hyaloid to the tumor or an epiretinal membrane. A focal exudative retinal detachment was found in 92% of eyes. These eyes have a marked inflammatory component, both before, and often after surgery. The management of the inflammatory component is critical to obtaining good visual acuity. By 24 months in this series, the mean visual acuity for these patients was 20/30. The importance of a good biopsy specimen at the time of surgery is emphasized.

**Conclusion**
Uveal melanoma treatment is undergoing significant enhancements enabling improved survival, globe retention and visual acuity preservation. Genomic profiling is both feasible and informative. We have to take the best available data and translate it into how we manage our patients. We can take strategies from neovascular AMD, proliferative retinopathy, and retinal vascular occlusive disease and apply them into managing patients that don’t fit into the standard clinical trial data.

**DISCUSSION**
Q: You talked about sdOCT to manage these patients. Do you use angiography to see how much of it is purely macular ischemia versus distant nonperfusion contributing to the macular trauma?

A: It’s been interesting to me how OCT has overwhelmed angiography, and how OCT defines the majority of the care that we provide. Having said that, there's been some recent excellent widefield angiography studies that have suggested that widefield angiography findings are associated with sdOCT findings and may help us take better care of those patients, especially patients with tumors. I think that OCT is the mainstay of care, but I believe that widefield fluorescein angiography is also very helpful.

Q: What is your experience with other anti-VEGFs agents such as aflibercept?
A: The problem with using one of our first-line, approved anti-VEGFs is that they’re not approved for this. The cost profile and the repetitive injection structure makes use of nonapproved drugs prohibitive. Similarly, approval of the extended release corticosteroids would be useful.

Q: I like your use of triamcinolone in the fluid gas exchange of the patient. I think that works great with non-preserved triamcinolone, but I have seen one patient who had Kenalog used. Kenalog has benzyl alcohol, and this patient had a mild scotoma centrally which may have been caused by the benzyl alcohol.

A: I don’t usually like to make specific recommendations of compounds, but I think in this case, the availability of a commercially prepared, non-preserved ophthalmic preparation makes a lot of sense.

Q: In the beginning you talked about bevacizumab and later on you moved to the role of corticosteroids. Wouldn’t it make sense in rare entities like radiation maculopathy to first AC tap or get probes from the vitreous to know what mechanism to target with treatment?

A: People have actually characterized the cytokines and ischemic profiles in melanoma and post-melanoma already. The question is: is there a benefit to characterizing at each injection schedule? That certainly is something that may play a role for us. I think that that’s an excellent question for a clinical trial. The problem we’ve had with clinical trials in orphan diseases is that it’s difficult to obtain funding from industry or the government.

Q: Years ago, we did an animal study where we injected bacteria into animal eyes, and then either did or didn’t inject triamcinolone. The eyes that had triamcinolone were 12 times more likely to develop endophthalmitis. The eyes that had triamcinolone were 12 times more likely to develop endophthalmitis, suggesting that triamcinolone massively reduced the local immune response. Since that study, I’ve had the sense that if I can avoid injecting triamcinolone at the time of surgery, since we know that we introduce bacteria into an eye at the time of the surgery, then I can just do it a couple of weeks later when I know the eye has sterilized itself. The risk is only theoretical in our patients but I know in the animal models it was an actual risk and made a huge difference.

A: Great point but the benefit in the immediate post surgical period of suppressing inflammation outweighs the infection concerns in our case series. The endophthalmitis rate was remarkably low in our series. I think that valved trocars, enhanced fluidics, shorter surgery times, and faster cutting rates have made infections less frequent.
Intravitreal Pharmacotherapy

Intravitreal Anti-VEGF Therapy

- Rationale – ischemia underlying trigger for neovascularization and/or edema
- Impact – binding of VEGF stabilizes blood/retinal barrier, reduction of exudation, down regulation of inflammatory cytokines and/or chemokines

Study Purpose

- To evaluate the impact of sDOCT imaging to target intravitreal bevacizumab (Avastin) in the early detection and treatment of radiation maculopathy associated with 125Iodine brachytherapy for posterior uveal melanoma

Study Methods

- Inclusion criteria
  - Local tumor control
    - Clinical and imaging documentation of tumor stability
  - Documented visual acuity decline
  - OCT macular analysis
    - Intraretinal fluid
  - Informed Consent – “off-label” use of intravitreal bevacizumab (Avastin)

- Consecutive case series of 110 eyes of 110 patients with visually compromising radiation maculopathy in the setting of brachytherapy controlled posterior uveal melanoma
- 125 Iodine brachytherapy 85 Gy (Apical dose)
- Serial evaluation every 4 to 6 months
- sDOCT, fundus photography and echography

Study Results

- 110 patients received 443 intravitreal bevacizumab (Avastin) injections
- Pre-treatment baseline
  - Visual acuity: 20/55
  - OCT foveal thickness: 487 microns
- Mean follow-up: 34 months (12 to 54 months)
Study Results

- Incidence of sDOCT visually significant radiation maculopathy (cumulative): 110/187 (59%)
- Time to development of sDOCT documented visually significant maculopathy: 10.8 months
- Total study follow-up from 125Iodine brachytherapy treatment: 44.9 months

Study Results

- Post-treatment: (Mean follow-up: 34 months (12 to 54 months)
  - OCT foveal thickness
    - 2 months: 383 microns
    - 4 months: 357 microns
    - 12 months: 317 microns
    - 36 months: 325 microns (p< .02)
  - Visual acuity (12 months): 20/40
  - Visual Acuity (36 months): 20/51
  - Final VA > 20/40: 51% (52/110)
  - Intravitreal injections (36 months): 4.3 (1 to 18)

Study Results

- 110/110 patients alive and well
- 0/110 metastatic disease
- 110/110 local tumor control
- 0/110 infectious/inflammatory events
Case 2

Pre-treatment: 2/7/08 VA 20/40

Post-treatment: 14/10 VA 20/23

Case 3

Pre-treatment Imaging

Case 3

Pre-treatment: 2/26/07 VA 20/20

Post-treatment: 4/16/05 VA 20/40

Case 4

76 year old 11 months s/p 125I brachytherapy for medium sized uveal malignant melanoma. Noted 6 weeks of decreased VA.

Visual Acuity: 20/80

Case 4

19 month follow-up status post treatment for radiation maculopathy with 6 intravitreal bevacizumab injections.

Case 5

79 year old gentleman 14 months status post 125I brachytherapy for medium sized uveal malignant melanoma. Noted 5 week decrease in visual acuity.

BCVA: 20/20

Case 5

12 month follow-up status post treatment of radiations maculopathy with 5 intravitreal bevacizumab injections.

BCVA: 20/25

Note: persistent intraretinal cystic edema
Controversies

- Mechanism of radiation retinopathy
- Need for re-treatment
- Long-term prognosis for visual preservation
- Potential impact on local tumor control

Tumor Characteristics

- Malignant melanoma (110 eyes)
  - Apical height: 4.0 mm (2.5 to 7.2)
  - Basal dimension: 13.5 mm (10.5 to 17.5)

Conclusions

- Spectral domain OCT critical in early detection of radiation maculopathy
- Intravitreal bevacizumab (Avastin) improves visual acuity and anatomy in eyes developing visually significant radiation maculopathy
- No treatment associated complications
- Potential benefit of prospective clinical trial

Intravitreal Pharmacotherapy

Intravitreal Steroid Therapy

- 1950’s – topical modulation of ocular inflammation
- Rationale – inflammation underlying trigger for neovascularization and/or edema
- Impact – stabilization of blood/retinal barrier, reduction of edoxation, down regulation of inflammatory cytokines and/or chemokines

Limitations

- Single institutional study
- Small sample size (110 patients)
- Lack of long term follow-up (34 months)

Triamcinolone Acetonide (intravitreal)

- Clinical practice transition at Bascom Palmer Eye Institute – KENALOG, compounded preservative free triamcinolone acetonide, TRIESCENCE
- Therapeutic effects and complications appear to be preparation specific
- Treatment concerns: glaucoma, cataract, endophthalmitis, pseudo-endophthalmitis
Evaluation of indications, outcomes, and adverse events utilizing Triamcinolone Acetonide

- IRB approved, retrospective consecutive treatment case series 2007-2013
- Inclusion criteria
  - Refractory to intravitreal anti-VEGF therapy
  - Intravitreal injection of triamcinolone acetonide by one specialist (TGM)
  - Informed Consent – “off-label” use of intravitreal triamcinolone acetonide

Study Methods

- Intravitreal triamcinolone acetonide 4 mg/0.1 ml
- Clinical evaluation at 4 to 8 week intervals
- Complete ophthalmologic examination, fundus photography and OCT imaging
- Re-treatment if OCT findings of persistent/recurrent macular thickening, intraretinal edema, subretinal fluid with decreased visual acuity to include anti-VEGF or triamcinolone acetonide

Study Data

- 2,267 patients
- Patient age (mean): 68 years (12-89)
- Gender: 65% women/35% men
- Evolving TA preparation selection
  - 2007-2009 KENALOG
  - 2009-2010 Preservative free TA
  - 2011-2013 TRIESCENCE

Study Results

- 2,267 patients received 4,574 intravitreal triamcinolone acetonide injections
- Pre-treatment baseline
  - Visual acuity (mean): 20/240
  - OCT foveal thickness (mean): 547 microns
- Follow-up (mean): 34 months (6 to 72)
Study Results

- Post-treatment: (Mean follow-up: 34 months (6 to 74 months)
  - Visual Acuity 18 months (mean): 20/112 (p<.02)
  - Visual Acuity > 20/50: 1156/2267 (51%)
  - OCT Foveal Thickness: 327 microns (p<.005)

Conclusions

- Intravitreal triamcinolone acetonide improves visual acuity and anatomy in eyes refractory to anti-VEGF monotherapy
- TRISENCENCE & preservative free TA
  KENALOG in lowering rates of endophthalmitis/pseudoendophthalmitis, decreasing IOP elevation while improving macular edema reduction
- EHR incredibly powerful in large data set analysis
- Potential benefit of prospective clinical trial

Preparation Dependent Properties

- Sterile Endophthalmitis
  - 2006 cluster analysis noted increase to 3.5-6.3% prompting transition from KENALOG to PTA (Stepien, Eaton, Jaffe, Davis, Raja, Feuer, Retina 2009)
- Particle size/differential flow rate
  - KENALOG: 18.86 microns
  - TRISENCENCE: 11.51 microns
  (Cabrera, Gonzalez, Albin, Flynn, Pauley, OSLI 2014)

Future

- Combination therapy with anti-VEGF AND steroid treatment
- Evaluation of pre-emptive anti-VEGF therapy to prevent/delay/minimize radiation maculopathy
- Evaluation of alternative agents for treatment: aflibercept

Limitations

- Single surgeon study
- Broad inclusion criteria
- Non-standardized treatment approach
Study Purpose

- To evaluate the impact and outcomes of molecular genomic testing on primary and adjunctive therapy for uveal melanoma

Study Methods

- Retrospective review of a consecutive case series of 138 eyes of 138 patients with posterior uveal melanoma undergoing definitive tumor treatment coupled with molecular genomic analysis
- All eyes managed with FNAB with either primary 125Iodine brachytherapy or MIVS delivered laser therapy

MIVS Biopsy Technique

Uveal Melanoma

- 23/25+ gauge pars plana vitrectomy
- Remove hyaloid
- Remove vitreo-retinal traction overlying tumor
- Direct endo-laser confluent tumor treatment
- 25 gauge needle
- Multiple needle passes within the tumor
- Inspect for bleeding
- Intravitreal triamcinolone acetonide

MIVS Surgical Approach

Intraoperative Surgical Findings

- Vitreo-tumoral traction in all eyes (100%)
- Taut posterior hyaloid to tumor
- Epiretinal membrane
- Focal exudative retinal detachment in virtually all eyes (92%)
- Often subtle
- Located at tumor margin
- Tractional component
- No retinal tears/rhegmatogenous retinal detachments

Patient Data

- 138 patients
- Age (mean): 69 years
- Exudative focal retinal detachment: 134/138 (97.1%)
- Tumor Size: 50 Small, 48 Medium, 40 Large
- Pre-treatment baseline
  - Visual acuity (mean): 20/120
  - Apical tumor height (mean): 4.9 mm (1.2 - 10.0 mm)
- Mean follow-up: 24 months (12 to 30 months)

Intraoperative Surgical Findings

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- Located at tumor margin
- Tractional component
- No retinal tears/rhegmatogenous retinal detachments

Study Results

- Post-treatment: (Mean follow-up: 24 months (6 to 54 months)
  - Small Tumor apical height (mean): 1.4 mm
  - Progressive retinal detachment: 3/138 (2.2%, $p < .01$)
  - Visual acuity (6 months): 20/40
  - Visual Acuity (24 months): 20/30 ($p < .02$)
  - Final VA > 20/50: 92% ($p < .01$)
Study Results

- 138/138 patients alive and well
- 0/138 metastatic disease
- 138/138 local tumor control
- 0/138 infectious events
- 3/138 inflammatory events

Genomics Case Series
Molecular Classification - SMALL

- Class 1 45/50 patients (90%)
- Class 1a 34/50 (68%)
- Class 1b 11/50 (22%)
- Class 2 4/50 patients (8%)

Only one patient with non-diagnostic test (1/100, 1%)

Conclusions

- Uveal melanoma treatment is undergoing significant enhancements enabling improved survival, globe retention AND functional visual acuity preservation
- Genomic profiling both feasible and informative allowing tumor risk assessment, targeted patient follow-up and consideration of adjunctive therapy
- Novel primary AND adjunctive treatment now based on personalized tumor genetic evaluation

Limitations

- Single institutional study
- Single surgeon (TGM)
- Small sample size (138 patients)
- Lack of long term follow-up (24 months)

Thank you!
MURRAY OCULAR ONCOLOGY and RETINA
Miami, Florida

- Dr. Aaron Gold
- Azeeza Latiff
- Fiona Haines
- Andrea Widdner
- Jennifer Thomson

Pharmacologic staining of the ILM improves removal of the ILM AND decreases complications associated with surgical removal.

ILM staining concerns including photo-toxicity are rare events but can be minimized by:

1. Minimizing contact time with the retina
2. Using “protected” injection techniques
3. Minimizing light exposure
4. All of the above
5. None of the above
Intravitreal Triamcinolone Acetonide can be used as:
1. Direct staining agent for the vitreous
2. Anti-inflammatory modulator for post-surgical changes
3. All of the above
4. None of the above

Intravitreal triamcinolone acetonide placed during vitreo-retinal surgery CAN modulate post-vitrectomy retinal edema:
1. True
2. False

Pre-surgical intravitreal anti-VEGF CAN positively impact intra-operative surgical bleeding:
1. True
2. False
OCT Angiography

GIOVANNI STAURENGHI, MD

SUMMARY
Optical coherence tomography angiography (OCT-A) has evolved significantly over the past few years. Unlike traditional angiography, it does not require an injection for the patient because the OCT relies on the motion of blood cells through the blood vessels as contrast.

There are on the market already two devices and others will come in the near future. Different companies use different algorithms. Some use variance of amplitude, full or split spectrum, other the combination of changes in phase and amplitude.

There are a series of consideration that we should keep in mind when we interpret an OCT-A image.

- To summarize the images of an OCT-A are the representation of moving particles in the eye vessels but do not always correspond to the anatomy of the vessels.
- The location of the slab for the best vascular lesions visualization do not always correspond to the right anatomical location.
- Most of the time it is impossible to differentiate arteries and veins.
- Due to speed limitations some vessels or vessel dilatation such as microaneurisms are not always visualized.
- The projection artifacts should be considered for the best interpretation of the images.
- The lack of leakage detection.
- The advantage of high contrast allowed a better identification of not perfused retinal areas and choroidal new vessels.
- For the choroid can substitute a static indocyanine green angiography (ICGA).
- It is the best imaging tool to visualize choriocapillary.

The evolution of technologies and the improvement of interpretation of the images will give us another imaging tool to add to our armamentarium to help in a better differential diagnosis of eye diseases.

NOTES
I am a multi-modality imaging supporter, and that may influence the talk. It is important to know that OCT-A is not much different than a normal OCT but the analysis is done differently to yield the information needed. In order to yield an image, there needs to be 2 time points. If the 2 time points are too fast or too slow, you don't get an image. This is important for knowing if you can identify what you are seeing. Assessing a still frame image for something that is moving prevents one from differentiating an artery from vein.

There are a series of instruments because each company uses a different algorithm. This is a comparison of the same patient with different instruments. The superficial and deep layers are not the same. Some machines provide more information than others. It's hard to determine if more information is always worthwhile as it may be more difficult to analyze.

Here is a case of a retinal vein occlusion with laser and neovascularization (NV). Fluorescein angiography shows part of the vessel that appears closed. On OCT-A we can see the flow because the lumen and wall of the vessel are different sizes.

This patient has been treated with anti-VEGF and anti-PDGF medication, which appears to be reducing the lesion. How can we be sure? Maybe it just isn't filling. OCT-A may not be the best way to evaluate this.

What about artifacts? On the Optovue you can see the horizontal scan showing some white lines, which represent movement of the eye. The instrument also does a vertical acquisition so moving fixation eliminates the ability to combine horizontal and vertical scans because they won't line up at all.

When a patient blinks, it eliminates the signal, giving an artificial tartan-like pattern similar to the plaid design.

Another artifact that is typically seen in OCT-A is a projection artifact. It makes the retinal vessel appear to be in a deeper layer than they are actually in. Why? This is because there is no reflecting at a certain level. The image stops at that level then appears deeper. This is because of the orientation. The nerve fiber layer is not visible on some structural OCTs based on the orientation. If you switch the angle then it will reappear.

In this example of AMN, the nerve fiber layer is visible. There is no neovascularization present, simply the projection effect of a retinal vessel in a location where it is not normally seen. In this case you should look at the structural OCT to see if something has changed in that image.

This is an example of 3 areas of choroidal neovascularization and there appears to be some subretinal fluid (SRF) present. If you add a structural OCT, autofluorescence and FA early and late you can see that point is due to a lack of RPE. There is increased transmission of signal and better visualization of the choriocapillaris compared to the adjacent areas where the RPE is normal. It was actually just RPE atrophy.
A recent paper by Dr. Richard Spaide talks about all the artifacts that you can get on OCT-A.

It is important to note that small movements of the slabs will cause image changes. The best visualization of the lesion is deeper than where it is expected to be because of the projection artifact. The image can also change based on the size of the slab. The thickness of the slab changes and that affects the amount of contrast, making the lesion appear completely different.

Here is an example of an inflammatory choroidal neovascularization seen with both FA and ICG. The difference is that ICG fluoresces more with more dye. OCT-A shows increased signal and that is theorized to be due to increased flow. However, depending on where the slab is located, the contrast changes. Different locations of the slab change visualization.

The speed of perfusion also makes a big difference. In this branch retinal vein occlusion, there is an early high contrast FA using the confocal. By overlapping the OCT-A you are able to see where the retina is perfused or not. Side by side microaneurysms are not shown on OCT-A because the flow is too slow to show up. If the flow was faster they may be able to be seen. Vessels may also show up differently for the same reason. Color photographs and FA may show some aneurysms, but they are not visible on OCT-A.

Looking at movies of the FA and ICG, you can see the feeding and draining vessel. On OCT-A the lesion looks the same as ICG, but you can't tell which is the feeder and which is the draining vessel because you don't actually see it fill. Usually the draining vessel is more prominent.

OCT-A is extremely useful for identifying and analyzing different types of atrophy. In Stargardts disease, ICG demonstrates a dark area not visible in AMD. In the case of AMD, there is an isofluorescent area of central atrophy. We know all the info about photoreceptors and RPE, but maybe there is a lack of choriocapillaris in Stargardts?

You cannot see choriocapillaris on a structural OCT, but the visibility is improved with OCT-A.

On Autofluorescence you can see the areas where the RPE is present or absent. A dark choroidal vessel can become white on OCT-A. Comparing an angiography B-scan compared to structural OCT, you can see a lack of RPE affecting the structure. One vessel has no light penetration and the other does have light going through it. This is all about RPE protection. When the light goes through, you get a projection artifact making it black. If protected then it will be white on OCT-A.

Why is it white in some segments on the vessel? That is the projection effect of the choriocapillaris. Small vessels project the light. When there is no RPE present, you get the appearance of a white choroidal vessel, making it hard to differentiate the vessels from each other.

It is hard to determine if we are correct in our assessment, so we need histology to confirm. There is some histology compared to OCT-A thanks to a new staining method. From this information, we can see that in advanced cases of Stargardts disease, there is no choriocapillaris.

OCT-A is a new imaging modality, and we are still learning. Multimodal imaging is still very important, especially for geographic atrophy. The lack of choriocapillaris is good to measure.

**DISCUSSION**

**Q/C:** Is anyone using OCTA currently in their office? Would you make a comment?

**Q/C:** I have a couple of questions. Do you think accumulated lipofuscin can cause an artifact in Stargardts’s?

**A:** The large vessels are dark. If it's just RPE, it doesn't change with an increase in lipofuscin. In fact, the big difference is in the atrophy where you don't have any RPE cells so you don't have lipofuscin.

**Q:** What's your experience with early stage pattern dystrophy on OCT-A?

**A:** So without atrophy, it really is no different than a normal PED. The OCT light does not penetrate differently so you will not get additional information.

**Q:** What was the solution to the too fast and too slow problem? How can you capture that? Is there an answer to that?

**A:** Different instrumentation may be needed. Fujimoto has different swept source technology, which may yield an image if it is slow. If it is fast, it may be hard.

**Q:** Do you have any insight into utility of OCT-A in macular degeneration and CNV? Should we be treating more aggressively based on vessels being better visualized?

**A:** I think it's too early to say anything for sure. There is not enough long-term or strong data. One thing that is clear that when you can go back to 1995, the same observations were made with ICG. ICG and OCTA overlap well. Of course, if you have a huge vessel, a true vessel, it's difficult conclude that the vessel is leaking. It's easier to think that it's a small vessel at the edge that leaks. So the appearance in OCT-As is more convincing than what you actually see in ICG.
**Q:** Some say that the real utility of OCT-A is going to come in that middle layer of blood vessels that we've been sort of ignoring on our FAs and ICGs because they get washed out. Any comments about that?

**A:** You can get great information by putting together FA and ICG. It's like having an image from the superficial to the deeper layer. You have all the information together. The big advantage of OCT-A, particularly for the great amount of vessels in CNV, is that you can actually see the different layers. For the choroid you can often see better when you sample deeper. You can avoid some artifacts. The other big advantage of OCT-A is the higher contrast. On ICG, the smaller vessels may be masked.

**Q:** Does anybody know what a Bucky Grid is?

No! Okay, I'm surprised that we didn't think about that in the fluorescein here. In radiology, when they take your chest x-ray, you get everything crushed together. But they discovered that if they have this grid, the Bucky grid, you can shift the grid to change depth of focus. You can throw focus to different levels and separate the layers. Somebody should figure it out for fluorescein.

**Q:** Did they explore MRA technology for the eye? It would seem to be analogous?

**A:** I don’t know.

MRA is a useful technique, so there’s got to be hope for it.

**Q/C:** One of the big advantages of OCT-A is that you can get a much better idea of the location of the vessels as you move down the slab. Assuming that you are able to overcome the projection and motion artifacts etc. So if you’re trying to categorize type one, type two, type three, neovascularization that may ultimately influence our treatment. We may be less aggressive if we can identify those vessels that are under the RPE. They may form a fairly broad network under the RPE that maintains the health of the retina, and we may not need to treat as aggressively. I think we’re just in the early stages of understanding that.

**A:** I completely agree. We’re only in the early stages of understanding. This can all be done with ICG and FA but in a more invasive way. In a nice ICG, you can actually distinguish type one, type two, and type three.

**A:** That’s true; it’s just that most people don’t have them.

**Q/C:** I’ve found it difficult to find a way that OCT-A is changing the way I treat patients, but it is changing the way I educate. It’s been remarkable how much better it is when you can show them the OCTA of their diabetic retinopathy or mac tel, or their CNV compared to the other eye. They can finally comprehend it. It’s much better than just a smudge on FA.

**A:** I agree.

**Q/C:** Should we buy this machine right now? Is this really something that we want to invest the money into having in our practices right now?

**A:** I think at the end of the day for a retinal specialist, it’s the future, in some ways. It doesn’t mean you discontinue what you currently have. I think that the approach with multi-modality images is very useful because each one gives different information.
OCT ANGIOGRAPHY – STAURENGHI

Disclosures

Heidelberg Engineering\(^1,2\), Optos\(^3\), Ocular Instruments\(^4\), Optexq\(^5\), Quantel Medical\(^6\), Centervue\(^7\), Carl Zeiss Meditec\(^8\), Alcon\(^9\), Allergan\(^10\), Bayer\(^11\), Boehringer\(^1\), Generium\(^12\), GSK\(^13\), Novartis\(^14\), Roche\(^15\)

multi-imaging supporter

\( I(x, z) = \int R(x) M(x, z) \lambda \text{d}x \text{d}z \) \hspace{1cm} (1)

\( G(x) = \exp\left(-\frac{(x - m)^2}{2\sigma^2}\right) \) \hspace{1cm} (2)

\( \hat{I}(x, z) = \text{FFT} \{ I(x, z) \} = A(x, z) \exp(\phi(x, z)) \) \hspace{1cm} (3)

\( a_{n, k} = \sum_{n=0}^{N-1} A(x, z) A^*(x, z) \) \hspace{1cm} (4)

\( b_{n, k} = \sum_{n=0}^{N-1} A(x, z) A^*(x, z) \) \hspace{1cm} (5)

\( \hat{a}_{n, k} = \sum_{n=0}^{N-1} A(x, z) A^*(x, z) \) \hspace{1cm} (6)

OCT Angiography

PhaseVariance (Carl\'s University)
OMAG - Optical Microangiography (Washington University - Zeiss - Angioplex)
Complex - Phase plus Amplitude (Hildes)
SSADA - Split-Spectrum Amplitude-Derived Angiography (Optexq - Angiovue)
PSADA - Full-Spectrum Amplitude-Decorrelation Angiography (Heidelberg Engineering, Canon)
Amplitude - Full-spectrum ratio-based (Topcon)
PRO-OCT - Phase-Resolved Doppler OCT (Amsterdam University)
What we have to keep in mind:

- different segmentation layers
- different speed
- the absence of filling
What we have to keep in mind

- different segmentation layers
- different speed
- the absence of filling

What we have to keep in mind

- different segmentation layers
- different speed
- the absence of filling effect
When could be useful

- ...
- to differentiate macular atrophy
- ...

OCT ANGIOGRAPHY – STAURENGHI
Conclusions

- OCT angiography is a new imaging tool
- Still in the learning curve
- Multimodal imaging allowed a better differential diagnosis of macular atrophy
- This could be important in the future treatments
Imaging in Posterior Uveitis

GLENN J. JAFFE, MD

SUMMARY
An increasing number of imaging modalities are available to evaluate and manage patients with uveitis. Uveitis is a group of diseases with varied presentations. Accordingly, it is appropriate to tailor the imaging methods, often with a multimodal approach, based on the specific type of uveitis, or group of conditions that are considered in the differential diagnosis, to extract the maximum diagnostic information, and to minimize unnecessary testing. Each of the imaging techniques has strengths and weaknesses, and are often complementary. They may be useful not only to establish a diagnosis and to monitor treatment benefit, but to assess the efficacy of a therapeutic intervention in a clinical trial.

Specific imaging methods include fluorescein angiography (FA), indocyanine green angiography (ICGA), color fundus photography (CFP), ultrasonography, fundus autofluorescence, optical coherence tomography (OCT), and OCT-angiography (OCTA). Fluorescein angiography is used to assess CME, white dot syndromes, VKH, sympathetic ophthalmia, and posterior scleritis, placoid syphilitic uveitis, AMPPE and serpiginous choroiditis, and retinitis. ICG is appropriate to assess white dot syndromes, sarcoid, AMPPE and serpiginous choroiditis, and VKH. CFP, particularly ultrawidefield CFP is useful to monitor change in chorioretinal lesions in a variety of conditions.

Ultrasound is helpful when media opacity precludes imaging by other methods, and is especially helpful for pre-surgical planning. OCT is useful to assess retinal and choroidal thickness, morphological characteristics including vitreoretinal interface changes, retinal microstructure, intraretinal, subretinal, and choroidal fluid, and hyper-reflective dots, and A/C cells. OCTA can be used to determine vascular flow, and location of abnormal vessels. As imaging methods evolve, they will play an even greater role in the management of uveitis.

NOTES
Imaging involves a variety of methods, often complementary, each with strengths and weaknesses, useful for diagnosis and management, and useful in clinical trials. The main imaging methods used in uveitis are fluorescein angiography, ICG, fundus photography, ultrasound, and autofluorescence.

Fluorescein angiography
Fluorescein angiography (FA) is an important imaging modality in uveitis that can be used in the evaluation of CME, white-dot syndromes, MCP, VKH/Scleritis/SO, placoid syphilitic uveitis, AMPPE/serpiginous, and retinitis. Uveitis processes that cause CME include pars planitis, sarcoid, and birdshot. CME is characterized by fluid filled spaces that angiographically show early perifoveal hyperfluorescence and late petaloid leakage. Clinically, a yellow spot in the fovea is an early sign. Angiographically, MEWDs shows early hyperfluorescence in a wreathlike configuration, In AMPPE there is initial blockage with late hyperfluorescence. In birdshot FA shows pronounced perifoveal capillary leakage with CME and quenching. In VKH FA shows multiple punctate hyperfluorescent areas of subretinal leakage and pooling. In uveitis, FA is very helpful for identifying neovascularization, vascular occlusion, vascular leakage and for differentiating retinitis from an ischemic event. Patients with intermediate uveitis may have staining along vessels in the periphery so ultrawide field FA is very useful in these cases.

ICG in Uveitis
ICG is especially useful in the following diseases that will show hypofluorescent spots: MEWDs, birdshot, sarcoid, MCP, AMPPE, and serpiginous. In VKH there is early choroidal vessel leakage which can be picked up on ICG. Hypofluorescent spots disappear after treatment. In sarcoid, granulomas in the choroid manifest as hypofluorescent spots on ICG. In a patient with MEWDs, deep lesions not otherwise seen on exam may be picked up by ICG as hypofluorescent spots. In serpiginous, hypofluorescent spots on ICG are also seen.

What about about fundus photography?
Fundus photography is especially useful in comparing one exam to the next, with more accuracy than just fundus drawings. For patients with uveitis, Optos ultra wide field imaging allows imaging farther in the periphery. One of the problems with the Optos is that the color is not always a correct representation of the color seen with ophthalmoscopy.

Ultrasound
Ultrasound is very useful in patients with uveitis, especially those who have media opacities. In these patients, you may not be able to use OCT, OCTA, or angiography, but you may pick up thickening in the macula in a patient with macular edema by ultrasound. Choroidal thickening may also be picked up, especially when media opacity prevents good images with OCT. Ultrasound is extremely helpful in pre-surgical planning when evaluating a vitreous hemorrhage or a retinal detachment.
Autofluorescence
Autofluorescence is useful to assess disease activity. The methods above all give cross-sectional information except for ultrasound which has relatively low resolution. It's difficult to do quantification with these different techniques.

OCT
OCT complements these technologies very well, particularly with quantitative data. With OCT, edema can be followed quantitatively over time. You can also determine the relationship of edema or atrophy, or vitreoretinal interface changes to the foveal center and correlate that with visual acuity. You can assess choroidal thickness which is important in patients with uveitis. It's non-invasive and it's a good teaching and motivational tool for patients. Enhanced depth imaging (EDI) picks up choroidal thickness very nicely and that's a diagnostic clue in many patients with uveitis. Disadvantages include the following: images are degraded in patients with hazy media, the quality of your images may depend on the technical skill of the technician, the hardware is still pretty expensive, and the software is always lagging behind.

OCTA
With OCTA you can assess vascular perfusion. Essentially, the machine captures a sequence of scans and you are looking at the same point, multiple times, for a change in reflectance, which is manifested by the signal. As you scan down, you’ll get each of the different vascular layers as you go down deeper and deeper. In uveitis the most common type of choroidal neovascularization is Type II choroidal neovascularization that sits on top of the RPE. Using multimodal imaging including ICG, FA and OCTA, you can identify the anatomical level of the lesion. OCTA has helped us learn that the vasculature in eyes with birdshot is sparser with increased spaces between the capillaries and is not as normal as once thought.

OCT and Uveitis clinical trials
OCT is frequently used in uveitic clinical trials either to establish baseline eligibility, to identify factors that’ll predict outcome, and/or to monitor treatment effect. It is important to not switch machines during a study, and to not switch machines in the clinic if OCT thickness is used as treatment or monitoring criteria.

Where are we going with the OCT?
In the future it would be nice to automatically segment different layers. Increasing resolution has allowed us to give names to layers we were not seeing before such as the ellipsoid zone. It would be interesting if we could quantify these different layers but this is limited by increasingly complex data sets that are very time consuming and labor intensive. Uveitis is an example of a group of diseases where multimodal imaging is especially helpful in diagnosing and treating patients both in the clinic and in clinical trials.

DISCUSSION
Q: With all these imagine modalities are we over treating patients in some cases?
A: We are getting better at assessing what we’re actually seeing on the images. In the past with time domain OCT, macular edema was treated if present, sometimes without vision improvement. Now, with spectral domain OCT we can see the structures of the outer retina and that is guiding our management. For example, the integrity of the external limiting membrane correlates with potential for recovery of vision after treatment so a patient with a lost ellipsoid zone but an intact external limiting membrane, may be treated for longer since there’s a pretty good chance those photoreceptors will recover.

Q: If a patient comes in with posterior uveitis how do you know what imaging to order?
A2: I always get an sdOCT regardless of whether it’s a patient with uveitis or macular degeneration. I think fluorescein really does have a role in differentiating particular conditions. I think you really need a tailored approach. For example if a patient has something where on autofluorescence you’re going to be able to pick up disease activity like serpiginous, then autofluorescence is a useful test to do. The fluorescein may not be so helpful in that patient.

Q: I’m using EDI OCT to help manage patients with VKH to see how they’re doing on their immuno-suppressive therapy. Are you using EDI OCT for that, and other entities?
A: There are specific uveitic conditions in which choroidal thickening is a typical finding. Those include VKH, sympathetic ophthalmia and posterior scleritis.

Q: Have you looked at hyperspectral imaging at all in your reading center?
A: Spectroscopy looks at functional outcomes, and so you’re no longer limited by the wavelength of the light you’re using. You can go down to the molecular level and start to query things in the retina, but it is quirky and it’s difficult to use. The pharmaceutical companies are getting increasingly interested though in functional tests along with the anatomic tests, and then correlating that.

Q: The logistics of seeing the volume scan, raster scan and EDI along with all the other testing seems time consuming. How do you efficiently structure your visit?

A: I use the Spectralis and it takes a few seconds to scan through the volume scan, look at the EDI and analyze the high resolution images. It is more difficult if you have a PAC system. We have a large screen that can accommodate all the images at the same time. The advantage of Spectralis is that all the OCTs and other modalities can be combined so that if you are interested in one point on the OCT you can get the autofluorescence, ICG and fluorescein all at that point.

C: What I’m learning from these talks is that our imagining is always going to be throwing more and more complex data at us, faster than we will be able to understand it. It’s hard to shrink down the data, other than what’s clinically useful, or perhaps even more crudely, what’s reimbursable. I think we need leaders to continue to look at all these things to give us these insights.

C: As these modalities start to mature, the software gets better, faster, and it becomes easier to look at all the information. OCTA is not quite there yet.
Uveitis Imaging Methods
- Variety of methods
- Often complementary
- Each has strengths, weaknesses
- Useful for diagnosis
- Useful for management
- Useful in clinical trials

CME-Differential Dx
- Pars planitis
- Sarcoid
- Birdshot
- Severe IC

Uveitis Imaging Methods
- Fluorescein Angiography
- ICG
- Fundus Photography
- Ultrasound
- Autofluorescence

CME-Differential Dx
- Pars planitis
- Sarcoid
- Birdshot
- Severe IC

Uveitis Imaging Methods: FA
- CME
- “White dot syndromes”
- VKH/Scleritis/SO
- Placoid syphilitic uveitis
- AMPPE/serpiginous
- Retinitis
- Neovascularization/non-perfusion

CME-Differential Dx
- Pars planitis
- Sarcoid
- Birdshot
- Severe IC

FA and CME

CME-Differential Dx
- Pars planitis
- Sarcoid
- Birdshot
- Severe IC
CME Clinical Characteristics
- Fluid-filled spaces
- Yellow spot in fovea

Uveitis Imaging Methods: FA
- CME
- "White dot syndromes"
- VKH/Scleritis/SO
- Placoid syphilitic uveitis
- AMPPE/serpiginous
- Retinitis

White Dot Syndromes
- MEWDS
- Birdshot
- MCP

CME Angiographic Characteristics
- Early coarse perifoveal hyperfluorescence
- Late petaloid leakage

CME Angiographic Characteristics
- Early coarse perifoveal hyperfluorescence
- Late petaloid leakage

Wreath configuration
Featureless FA

Uveitis Imaging Methods: FA
- CME
- “White dot syndromes”
- VKH/Scleritis/SO
- Placoid syphilitic uveitis
- AMPPE/serpiginous
- Retinitis
IMAGING IN POSTERIOR UVEITIS – JAFFE

AMPPE
Acute Phase

Serpiginous-Chronic Phase

Fluorescein Angiography

• NV
• Vascular occlusion
• Vascular leakage

Imaging and Uveitis: FA

• CME
• “White dot syndrome”
• VKH/Scleritis/SO
• Placoid syphilitic uveitis
• AMPPE/serpiginous retinitis

Multifocal Toxo

FA Ultra Wide Field Imaging

• CMV
FA Ultra Wide Field Imaging

Intermediate Uveitis

MEWDS

Uveitis Imaging Methods

- Fluorescein Angiography
- ICG
- Octaves Photography
- Ultrasound
- Autofluorescence

Sarcoid

Previous Talk

ICG

- Hypofluorescent spots
  - MEWDS
  - Birdshot
  - Sarcoid
  - MCP
  - AMPPE
  - Serpiginous

Serpiginous Healed Phase

Asymetrical Uveitis

MCP

VKH

Early choroidal vessel leakage

IMAGING IN POSTERIOR UVEITIS – JAFFE

Retinal Imaging Methods
- Fluorescein Angiography
- ICG
- Fundus Photography
- Ultrasound
- Auto-fluorescence

Color Fundus Photography
Standard Modified 3-Field Fundus Photography in Stereo

Optos Ultra Wide Field

Ultrasonography
- Macular thickening
- Choroidal thickening
- Vitreous hemorrhage
- Retinal detachment
- Pre-surgical planning
Retinal Imaging Methods
- Fluorescein Angiography
- ICG
- Fundus Photography
- Ultrasound
- Autofluorescence

OCT for Uveitis-Disadvantages
- Degraded image with hazy media
- Operator dependent quality
- Hardware relatively expensive
- Software development lags behind hardware
- Artifacts

Retinal Imaging Methods Limitations
- FA, ICG, AF, photos-no cross sections
- US-low resolution
- Quantification difficult

OCT Scan Modes?
- Varies by manufacturer
- Varies by pathology

OCT Complements other techniques
- Provides cross-sectional, topographic images
- Yields quantitative data

SD-OCT Scan Protocol Rationale
- Volume scan: covers macula
- 5-7 line raster scans: high resolution
- EDI

OCT for Uveitis-Advantages
- Follow edema over time-quantitative
- Relationship of edema/atrophy/VR interface changes to foveal center
- Assess choroidal thickness
- Cross sectional/morphological data
- Vascular perfusion
- Non-invasive
- Good teaching tool
- Good motivational tool

OCT Scan Modes
- Cirrus
- Spectralis
**Cirrus Scan Modes**

- 512x128 volume scan
- 5 line raster
- EDI

**SD-OCT Volume Scan**

**SD- OCT Scan Modes**

- Cirrus
- Spectralis

**OCT EDI**

**What are We Looking For?**

**OCT and Uveitis**

- Macular edema
- SRF
- Vitreoretinal interface changes
- Retinal microstructure
- Hyper-reflective foci
- CNV
- Choroidal thickness
- A/R cells
- Retinal-choroidal vasculature

**Spectralis Scan Modes**

- Volume scan (49-97 line volume scan)
- 7 line scan
- EDI

**Macular Edema and Uveitis CME**
Macular Edema and Uveitis
Concentric Thickening

OCT-Angiography

OCT-Angiography

OCT-Angiography

OCT-Angiography

OCT-Angiography

OCT-Angiography

Segmentation of retinal layers to define OCT slab.
Summation of flow signal within OCT slab.

Segmentation of retinal layers to define OCT slab.
Summation of flow signal within OCT slab.
Perform very dense volume scan.

A sequence of B-scans is acquired at a fixed retinal location.
Changes between OCT images reflect blood flow.
OCT-A: Correlation to FA

Superficial Vascular Plexus

Deep Vascular Plexus

Uveitis-CNV (type 2)

OCTA and Uveitis

- Indications evolving
- Retinal vessels and choriocapillaris
- White dot syndromes
- Vasculitis
- CNV
- ?

Pt with MCP
C/O metamorphopsia, decreased Va

IMAGING IN POSTERIOR UVEITIS – JAFFE
OCT and Uveitis Clinical Trials

- Establish baseline eligibility
- Identify baseline predictive factors
- Monitor treatment effect

OCT and Uveitis Clinical Trials

Establish Baseline Eligibility
- Presence of ME
  - Rx CME
  - Rx uveitis
- Absence of ME
  - Prevent inflammation

OCT and Uveitis Clinical Trials

- Establish baseline eligibility
- Identify baseline predictive factors
- Monitor treatment effect

OCT and Clinical Trials

Monitor Rx effect
- Treatment/re-treatment criteria
- Determine trial endpoint

OCT and Clinical Trials Disease

Identify baseline predictive factors
- Therapeutic responders
- Clinical trial planning

Example
Subject in Clinical Trial
- Interventional trial
- Subject exits if >50 μm increased retinal thickness

Visit 2 Thickness = 374 μm

Visit 3 Thickness = 450 μm

PI Exits Subject
- 450 μm - 374 μm = 76 μm (>50 μm)

What’s Wrong Here?

No Change in Thickness
Machines changed!

Visit 2 Thickness = 374 μm

Visit 3 Thickness = 450 μm
Retinal Thickness Algorithms

Do Not Switch Machines During Study!

OCT and Clinical Trials
Future Directions
- Automated inflammation assessment
- Automated segmentation
- Volume quantification (e.g., edema, CNV)
- More data integration
- Better inter-machine standards

AS SD-OCT Quantification of A/C cells

Are We Capturing Max Information?
- TD-OCT limited by resolution
- SD-, swept source OCT more options

OCT Image Interpretation:
- Zeiss OCT 1
- Stratus OCT 3
- SD-OCT

Multiple Layers
It Would be Great to Quantify Multiple Layers

What is the Problem?

Automated Segmentation
Uveitis/Retinal Disease

How to Handle Data When…
- Increasingly complex data sets
- Need to segment multiple layers
- Limited time, resources

Macular Edema
- AMD
- DME
- CRVO
- BRVO
- Uveitis

Automated Segmentation
- Normalize common reference point
- Quantify multiple retinal layers
- Quantify edema

Results
Normal Adult Eye
8 Retinal Layer Boundaries
How Can this be Applied to Clinic, Clinical Trials?

Consider This Case...

We Can Automate Microstructure Segmentation
- ELM
- ELZ (IS/OS junction)
- Outer nuclear complex

OCT B scans
- Baseline
- 12 months later

Why Isn’t Va better?

Ellipsoid Zone Defect
Setting a Threshold
IMAGING IN POSTERIOR UVEITIS – JAFFE

Ellipsoid Zone Area Over Time

- Baseline
  Area = 66 mm²
- 12 months later
  Area = 13 mm²

Where Are We headed?

Better Structure/Function Correlation

SD-OCT Volume Cube

- Surface projection from the entire volume stack

Overlay of OCT Morphology Co-registered with Angiogram

1. Intense hyperfluorescence confined to margin of RPE disruption
2. Central cysts visible, late hyperfluorescence extends in zone of intraretinal cysts
3. Subretinal Fluid and retinal thickening do not correlate with angiographic changes at 6 minutes after injection

CNV Volumetric Analysis

In SD-OCT scan one can map location of break in Bruch’s Membrane, SRF, and CME.

- Cystoid Macular Edema (Yellow)
- Subretinal Fluid, SRF
- CNV Membrane, (Purple)
- Break in Bruch’s Membrane, (Red)

Volume of drusen can be measured from stack of SD-OCT scans (same patient as previous slide).
Overlay of drusen can be mapped from SD-OCT imaging onto fundus photograph.
SD-OCT Automated Retinal Layer Segmentation

Fluorescein Angiography to image Uveitis Patients:
1. Is no longer needed with the advent of OCT Angiography
2. Is helpful to diagnose discoid syphilitic uveitis
3. Is needed to diagnose uveitic cystoid macular edema
4. Has a similar early and late pattern in the white dot syndromes

ICG Angiography:
1. Shows hyperfluorescent spots in eyes with MEWDS, birdshot retinochoroidopathy, and multifocal chorioretinitis and panuveitis
2. Shows focal hyperfluorescent choroidal spots in VKH
3. Shows choroidal vascular leakage in VKH
4. Shows hyperfluorescent spots in AMPE

OCT Angiography:
1. Is a useful method to show vascular leakage in uveitic eyes
2. Is an excellent method because unlike standard OCT, it produces relatively artifact-free images
3. Can show blood flow in different vascular beds non-invasively
4. Typically has an 80° field of view of on commercially available units

Data Integration Now Possible
Angiography
OCT
Auto-fluorescence
Fundus photography
Microperimetry (function)

Microperimetry with Drusen

Conclusions Imaging in Uveitis
- Critical in uveitis Dx/Rx
- Essential in clinic/clinical trials
- Multimodal approach
- Data integration
- Structure/function correlations
PANEL 1:
Age-Related Macular Degeneration

MODERATOR:
SZILÁRD KISS, MD
Panelists: R.V. Paul Chan, MD, Glenn J. Jaffe, MD, Harry W. Flynn, Jr., MD, Giovanni Staurenghi, MD

SUMMARY
The last decade has been marked by a revolution in the diagnosis, treatment and prognosis for our patients with wet age-related macular degeneration. The anti-vascular endothelial growth factor revolution, ushered in 10 years ago with the FDA approval of ranibizumab, has been paralleled by a revolution in retinal imaging, especially with the ever-growing reliance on optic coherence tomography to guide our treatment. The panel of esteemed experts will discuss their current approach to diagnosing, treating and following patients with neovascular AMD. They will also provide insight as to what lies on the horizon – including the potential clinical utility of OCT angiography, combination therapy, sustained delivery strategies, and potential treatments for dry age-related macular degeneration.

NOTES
CASE 1
M: (moderator) Here’s a 69 year old non-smoker, who presents for initial evaluation. What do you do? Are you doing every test or just observing?
A: I’m not someone who tests heavily. In this case I would do a complete exam with fundus photo, auto-fluorescence and OCT. If there was some fluid on the OCT, or I saw something that’s suspicious, I get an FA. I tend not to get ICG angiography unless there’s something that drives me to do so like subretinal hemorrhage.
M: Does anyone disagree on the panel? Would also look for fluid. Without fluid, there is no indication for an ICG. We don’t have OCTA just yet.
A: I would determine if there are symptoms. If they’re symptomatic when they come in, and the OCT shows nothing, I get an FA.
M: They are symptomatic.
A: One of the imaging modalities that we didn’t mention is infrared imaging. Infrared in this case probably can show reticular pseudodrusen, and then an OCT can show fluid.
Q: So with reticular pseudodrusen do you need an ICG?
A: If they’re symptomatic.
Q: If they’re symptomatic. How many would do an ICG if somebody comes in with symptomatic AMD? Let’s call it dry? How would you follow? Let’s say that whatever imaging modality you did, there’s no indication of CNV. What do you tell the patient? Three months, six months, or when you’ve become symptomatic?
A: It’s a combination of the symptoms and a regular follow up period, so six to twelve months. If they have symptoms, I have them come in right away and get OCT and FA.
Q: What about supplements? While you’re thinking about that, this is a Frontline investigation. For those of you who haven’t seen it, it aired January 19th. It really goes into the fact that we really don’t know what’s in these supplements. It’s an amazing documentary. What would you advise this patient? Let’s assume it’s in the dry category.
A: If the other eye looks about the same, I think that you could give supplements. I tend to be a little bit more conservative in giving AREDS supplements to patients. In this case I would tell the patient to have a healthy diet, don’t smoke, and control their blood pressure. If the other eye is wet, then I’m more prone to encourage vitamin supplementation.
Q: What do you do in Europe, in terms of supplements and AREDS? Some of our colleagues are selling these supplements.
A: Well, I’m actually doing exactly what he’s doing. If it’s dry AMD I’m not suggesting anything except good diet and no smoking. If one eye is wet and the other is dry, then we can suggest supplements.
A: I think there’s a problem in Europe. The formulation of the AREDS is not available, because it was classified as a drug and it needs a Phase II and Phase III study.
Q/C: That’s actually an important point and interesting point. The way that the AREDS studies were run, it became labeled as a drug in Europe. The patented formulation in the US is not available in Europe and cannot be marketed as such.
Q/C: How many people sell vitamins in their offices? Anybody who would not recommend AREDS supplements routinely?
Poll of the room: large majority prescribe AREDS, a few people sell it and a few only recommend it.
A: There are some concerns with the AREDS trial. Also beta-carotene can be harmful in the smoking population.
A: I also find that those who are eager to take the AREDS also take naturopathic supplements and take a combination of other things. It’s hard to know exactly what they’re taking.

A: An Italian study on the level of vitamins in our population, demonstrated that patients with AMD have much higher vitamin levels compared to those without. A similar finding was reported in a publication of a US population.

A: I think people like to go to supplements to solve their problems.

Q: When I was training, I had seven mentors. They did injections seven different ways. How do you do your injections? Do you have a separate injection day for each eye, a lid speculum, no talking?

A: I do not have separate injection days. It’s impractical in the flow of our clinic. I certainly use the betadine prep; I personally like a small subconjunctival injection for anesthesia. I do not use a lid speculum. I do a no talking policy, although I don’t know if the studies that support this policy are great studies, but it makes sense.

M: How many are doing subconjunctival lidocaine in the audience? How many are using a lid speculum? How many have a no talking policy?

Audience poll: 50% of the room do subconjunctival lidocaine injection, most use a lid speculum and about 60% have a no talking policy.

Q: In Europe, are they doing injections in the office?

A: It’s a completely different protocol.

We actually use an aseptic area; the same way we do most surgeries or IV’s. We don’t do subconjunctival anesthesia, and we do the prep ourselves. We first clean all the skin and then drape.

Q: How many do you do in a day?

A: The record is my colleague who did 159 injections. I did 158. Regularly we do 120 in the morning. 8:30 to noon.

Q: How many rooms?

A: One room, two beds. Aseptic space not an OR.

Q: Who wears a mask during injection?

Audience poll: 40% wear masks

A: I just want to add one thing. Instead of speculum, I use tape, it’s basically tape to cover the eyelashes, which is actually the main source of the infection.
CASE 2
Here's an 89 year old. Two weeks of worsening metamorphopsia in the left eye with a hemorrhage. This is your first time you’re seeing this patient. What are you doing for this patient in terms of imaging?

A: I’m actually getting FA on most of these cases. In addition to providing information to manage the patient, the FA may be helpful in learning how to interpret the OCTA. I don’t routinely get ICG. On initial presentation I would get the fluorescein but not afterwards. I do get autofluorescence imaging as well, because I monitor atrophy over time. I always get infrared, along with the OCT because it can outline the areas of atrophy very nicely.

Q: I agree. I probably would do everything here except for the ICG.

A: In this case I would say that because of that type of hemorrhage, I would do everything because I think it could be a RAP lesion.

Q: Yes absolutely. What is your first line treatment? Are you doing it at the time of diagnosis, or do you have the patient come back?

A: For the most part I use the branded drugs more often than bevacizumab (Avastin). It depends somewhat on insurance, but my mother gets branded drugs and it works nicely.

Q: I start more with Avastin

A: Can you use Avastin in Milan?

Q: The law in Milan says you cannot use the off-label drugs until you try the on-label first and it fails. However, the hospitals push for Avastin so much that it is used as first line.

A: I use Avastin first because of the CATT study. It showed it was equivalent and a huge cost saver for the healthcare system. I will continue using Avastin in patients that are dry and doing well. If it is not working, I will obviously switch. Otherwise, I feel an obligation to save healthcare dollars if I can.

Q: Would you use Avastin as first line therapy in your own eye?

A: Yes, as long as I am confident in my source.

Q: What is your treatment strategy?

A: In Europe, PRN dosing is required by law. We usually see them monthly for one year and then we start to extend.

Q: Wonderful results from the CATT trial. That protocol was every 4 weeks. What is your follow up strategy?

A: I am seeing them every 4-6 weeks unless I am confident on my treat and extend protocol that they are very stable and then I can go out to 2-3 months.

Q: Someone comes back and they are on Eylea. What do you do on follow-up?

A: On every follow up I do an OCT, and occasionally an FA if the OCT does not match the symptoms. What will be interesting is what OCTA will add. Will we be treating based on OCTA even if the patient is not symptomatic?

Q: Does anyone do a series of injections and only do the work-up every few visits.

A: We do three injection-only visits. Then we bring them back one week short of their next injection to have a full exam and OCT. If their vision has changed or they are symptomatic then on an injection-only visit we will re-route to a full exam. But if their vision is stable or improved we continue with the plan. We are aggressive that first year with monthly injections and after that first year we will re-evaluate and use treat and extend if possible. At the injection only visit we check vision, pressure and ask about symptoms.

Q: Why do you check pressure?

A: Some of my patients also have glaucoma. There are also studies showing that pressure can creep up over time with injections.

Q: Why do you check pressure?

A: I disagree with the treat monthly for the first year approach. From CATT, after a year the patients were re-randomized to monthly treatment or PRN treatment and the patients that were re-randomized from monthly to PRN lost the effect of the initial year of monthly treatment. They went back to the same level as the PRN group.

Q: Yes, but we reassess and we don’t push out more than 6 weeks. We have patients that have been treated monthly for five years. We assess each patient on an individual basis.

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Q: Why do you check pressure?
CASE 3
78 y/o patient with distortion and decreased VA OU. Wet AMD OU

Q: Are you doing bilateral injections same day with different lots? Or what’s your approach?
A: Depends on level of visual function, did they bring a driver, how quickly was the onset of their symptoms, etc. I do offer bilateral injections to patients who have lost significant vision rapidly as long as insurance will cover it and they have a driver.

Q: Do you use different lots with bilateral injections of Avastin?
A: Ideally I use different lots, but unfortunately we often do not have different lots of Avastin. As a result, we have to use Eyelea or Lucentis for bilateral injections.

Q: Now what if this patient wants cataract surgery?
A: Well you have to be practical, once you have a better understanding of this patient’s stability. You can inject the week before surgery and let her proceed. Make sure its well-controlled right before and after.

Q: Patients always ask: will cataract surgery worsen my macular degeneration?
A: I don’t think it exacerabtes the macular degeneration.

A: Most of the time the decrease in vision is due to a neovascular membrane, and waiting for 1 month after surgery to check the retina will allow the lesion to grow. I have never seen one of my patients with just drusen progress to wet AMD after cataract surgery.

CASE 4
This patient has a massive hemorrhage. What are you going to do?

A: Vitrectomy with TPA injection into the clot. The OCT matters as to what level is the blood. That image looks mostly sub retinal instead of sub RPE, so then vitrectomy with TPA into the clot and air-fluid exchange works well.

Q: Anyone not take this patient into surgery?
A: This is one surgery that I have never been able to get it to work well. According to the data, it’s hard to prove that surgery creates better outcome than the natural history.

A: The CATT study looked at eyes with hemorrhage and injected them with anti-VEGF and they did just as well in terms of visual gain. I have an underlying bias that I believe all of these have an underlying problem with the RPE such as a tear. So the picture may look better postoperatively, but we are really after the vision. So I just keep treating with anti-VEGF.

A: When you get these really thick hemorrhages they can cause damage to the macula so I don’t think you can say just continue with anti-VEGF. The thinner hemorrhages I agree with injections, but not this thick.

A: The time frame is important; if it is fresh (1-2 days) then surgical intervention is indicated. But if it is 10 days out I agree that visual outcome won’t be different between surgery and injection.

CASE 5
72 y/o with a father that went blind from AMD. She has dry AMD

Q: Are you doing genetic testing?
A: I don’t think there is a right answer. If you are talking about therapies for dry AMD then potentially with positive genetic testing the therapies could be more effective.

Q: We had a patient come in with genetic testing, and her AMD risk was 1.4. She has a higher relative risk. I don’t know what snip they used. I don’t know what to do with this.

Q: Should they tailor their supplements based on genetic testing?
A: You can’t be dogmatic because we do not know.

Q: There was an AREDS 2 sub-study that looked at if you could catch a lesion earlier with at-home monitoring. What’s the take in Italy?
A: We just use the amsler grid, none of these more advanced home monitoring systems. If you are seeing the patient monthly and educate them to come early if they notice any changes in their vision then changes will be caught.

Q: Anyone in the audience use home monitoring, aside from the amsler grid?

Audience poll: none

A: It’s too early. The patients that are likely to do the home monitoring are also the patients that are likely to come in pretty regularly. The ones that won’t monitor are not going to come in, and you are going to miss the changes anyway.
CASE 6
Patient lost 14 letters over 4 years and 32 injections.

Q: Did we win?
A: The vision got worse. I don’t know if the diagnosis was correct.

A: This is why our current treatment is not fully adequate. She has a scar. This happens in 20-30% of patients. That’s why these new drugs that fight scarring are promising.

A: None of our injections are a cure. There is a certain percentage that will not do well, but compared to natural history they did much better.

Q: In the next 5-10 years what are you most excited about... combined therapy, sustained delivery, imaging, dry AMD therapies etc.
A: I think that delivery systems are going to critical. But all of the above are exciting.

A: A combination of all of these things.

A: Sustained delivery will be very useful. Of course, treatment of dry AMD will be critical. We are currently using only 10% of the OCT capability.
PANEL 1: AGE-RELATED MACULAR DEGENERATION

69 year old non-smoker presents for initial evaluation

- Would you recommend any supplements and/or lifestyle changes?

89 year old presents with 2 weeks of worsening metamorphopsia OS, vision 20/80

- What is your initial work-up?
  - Dilated fundus exam
  - Fundus photo
  - Autofluorescence
  - OCT
  - OCT-A
  - FA/ICGA

Intravitreal Injections

89 year old presents with 2 weeks of worsening metamorphopsia OS, vision 20/80

- How would you treat?
  - Bevacizumab (Avastin) Injection
  - Ranibizumab (Lucentis) Injection
  - Afiblercept (Eylea) Injection
  - Pegaptanib (Macugen) Injection
  - Photodynamic Therapy (PDT)
  - Treat the same day or return for injection

Intravitreal Injections

- Logistics — inject on same day or separate injection day
- Antibiotics — pre-/post-injection
- Anesthesia — topical/sub-conj
- Betadine — lid scrub/drops
- Misc. — lid speculum/gloves/mask/tanking

89 year old presents with 2 weeks of worsening metamorphopsia OS, vision 20/80

- Which factors do you consider in choosing an initial anti-VEGF drug?
  - Relative efficacy — Relative safety
  - FDA approval status
  - Cost to patient (e.g., co-pay)
  - Patient preference
  - Insurance company preference

89 year old presents with 2 weeks of worsening metamorphopsia OS, vision 20/80

- What is your treatment strategy?
  - See and treat monthly/bimonthly.
  - See monthly and treat as needed
  - Treat and extend
  - Primary factors driving re-injection — symptoms, vision, exam, OCT...
PANEL 1: AGE-RELATED MACULAR DEGENERATION

89 year old presents with 2 weeks of worsening metamorphopsia OS, vision 20/80
- Would your choice of drug and/or treatment strategy be altered if:
  - The type of bevacizumab, ranibizumab, and aflibercept is the same
  - If it were your own eye.

78 year old woman with history of dry AMD presents with decreased vision and...

89 year old presents with 2 weeks of worsening metamorphopsia OS, vision 20/80
- What is your work-up for a follow-up wet AMD patient receiving anti-VEGF therapy?
  - Dilated exam/photo
  - Autofluorescence
  - OCT/OCT-A
  - FA/ICGA
  - Injection rate

78 year old woman with history of dry AMD presents with decreased vision and...

67 year old mathematics professor; VA OD
- How would you treat bilateral wet AMD?
  - Inject 1 eye per visit
  - Inject both eyes on same visit — same or different for numbers
  - She started taking 81 mg ASA on the advice of her primary care doctor — did this have any influence on the course of dry vs wet AMD?

78 year old woman with history of dry AMD presents with decreased vision and...

67 year old mathematics professor; VA OD
- Is this “subretinal hyperreflective material”?
  - What is “subretinal hyperreflective material”?
  - Would OCT-A be useful?
  - How does this influence your treatment strategy?

78 year old woman with history of dry AMD presents with decreased vision and...

What would be the timing of cataract surgery?
- When CNVM controlled
- In between injections
- Does cataract surgery accelerate conversion from dry to wet AMD?
81 year old presents with 3 weeks of vision loss OD, 20/200; last seen 6 months ago with

- What treatment would you recommend?
  - Observation for clearing
  - In-office pneumatic displacement
  - Sub-macular surgery, clot removal
  - Vitrectomy with iPA
  - anti-VEGF therapy

Would it make a difference if the VA OS?

72 year old woman here for second opinion; father went blind from AMD

- Would you recommend genetic testing?
- What about supplements?

72 year old woman here for second opinion; father went blind from AMD

- Would you recommend genetic testing?
- What about supplements?
- Complement Factor D inhibition with lampalizumab

72 year old woman here for second opinion; father went blind from AMD

- What is your initial work-up?
  - Dilated fundus exam
  - Fundus photo
  - Autofluorescence
  - OCT
  - OCT-A
  - FA/ICGA

- Home monitoring
What will be the most revolutionary breakthrough for our patients with AMD in the next 3-5 years

- Combination therapy
  - anti-VEGF
  - Anti-TGFβ
  - Ang2/Tie2
  - Supplementation
  - Squalamine drops
  - Stem cell therapy

- Treatment for dry AMD
  - Lamivudine
  - Zimco - C5 inhibition

- Sustained delivery strategies
  - Depot
  - Gene therapy
  - Sustained delivery device

- Imaging
  - OCT-A
  - Adaptive optics
  - Functional imaging

Thank you for your attention

Szlárd Kiss, MD
Well Cornell Medicine | New York Presbyterian Hospital
Director of Ocular Pharmacology
Director of Ocular Pharmacology
Associate Professor of Ophthalmology
Weill Cornell Medical College
New Treatments for Intermediate, Posterior, and Panuveitis

GLENN J. JAFFE, MD

SUMMARY
There are a variety of options available to treat patients with intermediate, posterior, and panuveitis, and newer options that will likely become available within the next 1-2 years. Corticosteroids, given topically, as a periocular, or intravitreal injection, as an intravitreal sustained drug delivery implant (dexamethasone (DDS) and fluocinolone acetonide (FA) delivery systems), or systemically have been the primary therapy for intermediate, posterior, or panuveitis. These agents are very effective, but all may cause cataract and elevated intraocular pressure, and systemic treatment has a myriad of side effects that are often treatment-limiting.

Currently available shorter-term delivery methods, include intravitreal triamcinolone acetonide (TA) injection, periocular steroid injection, and DDS. However, these methods may not produce a drug effect sufficiently long, without relatively frequent re-injection, to manage these chronic inflammatory diseases. Long-term delivery systems such as the FA implant are typically effective for 3 years or more, but must be surgically implanted. Recently, we have investigated an injectable FA implant that can be placed in the office, and that releases drug for 2-3 years. In an individual investigator-sponsored trial, this agent very effectively controlled inflammation for at least 2 years, improved visual acuity, reduced ancillary-anti-inflammatory drug use, and had a favorable safety profile. Furthermore, a phase 3 study of this delivery system met its primary 6-month therapeutic endpoint.

There have been few successful clinical trials of non-steroidal systemic anti-inflammatory therapy. Recently, two pivotal phase 3 studies of adalimumab for active and inactive uveitis, respectively, met the primary, study endpoint, time to treatment failure, when used as steroid-sparing therapy. This agent could be the first steroid-sparing immunomodulatory treatment approved for non-infectious intermediate, posterior, or panuveitis.

NOTES
This presentation is about some of the possible treatments retina specialist would use in the clinic to treat uveitis patients. The treatment goals in uveitis are similar to any type of retinal disease with the additional goal of removing symptoms. The nonspecific treatment methods include topical, periocular injections, intravitreal drug injections, intravitreal sustained drug delivery systems, and systemic therapy. I'm going to focus on the latter 3 of these to talk about the new things that are coming around.

Intravitreal sustained drug delivery systems
Local drug delivery has disadvantages. The disease has a course of many years, requiring patients to give themselves the medicine. The appropriate levels of medication may be reached but have a limited duration and may produce unacceptable side effects.

You can tailor the delivery system to the particular disease. By surgically implanting or injecting the medications, compliance becomes less of a risk factor. These delivery systems include transscleral, suprachoroidal, intravitreal, and subretinal.

Currently we've been using scleral fixated or injected implants. These are also the medications that are being tested in clinical trials. For non-biodegradable implants, polymers surround the drug and are delivered across a port, allowing a linear drug delivery. This allows for long-lasting treatment (years), but the devices are retained in the eye after the drug is depleted.

The fluocinolone implant by Bausch and Lomb is probably the one implant that people are most familiar with. The biodegradable implant that most people are familiar with is the dexamethasone delivery system, which was tested for uveitis, retinal vein occlusion and macular edema from other causes.

What's new? I've been very interested in an injectable format for a fluocinolone implant. This is the equivalent of Iluvien, which is now approved for chronic DME.

I tested this new implant to see how it functions as a clinic procedure (as compared to Retisert) and how effective it is over a 2-year period. The configuration is different than the Retisert as it is in a polyimide tube similar to ozurdex in design. It's three millimeters in length and it's inserted through a 25-gauge modified needle injector and can release for up to three years.

To test the functionality, animals were injected with an antigen to create a severe anterior and posterior uveitis resembling iridocyclitis and pars planitis with snowballs. I used an individual investigator-sponsored study with dose randomization to study this in humans, followed the patients for 2 years and just analyzed the data. You can see the injector has a rubber stopper to prevent inadvertent injection. There is a 3.5-4 mm angled initial entry followed by a straight injection similar to cannula placement for small gauge surgery.
11 patients with chronic uveitis (10 of whom had bilateral involvement) were followed. The main outcome measure was inflammation recurrences, but we also looked at vision, measures of inflammation, medication use, and retinal thickness via OCT. In the 1 year prior to implant placement, there were 17 recurrences, and there were no recurrences in the 2 years post-implantation. There were recurrences in 6/10 fellow eyes, which had less disease at baseline. This implant also reduced or totally eliminated systemic therapy. The visual acuity improved from 20/70 at baseline to 20/30 two years later, while the fellow eye was either unchanged or significantly worse (in a couple of eyes). Complications included hypotony in a couple of eyes despite aggressive therapy, initiation of new glaucoma drops in 2 patients, and 2 required filters. This is a promising approach, and the press release of the phase 3 study 6-month data had favorable results.

**Intravitreal injections**

Sirolimus is a macrolide antibiotic with a ring structure that acts as an mTOR inhibitor and blocks T cell and B cell activation and antigen-presenting cells, like dendritic cells. It is being examined in the Sakura studies for noninfectious uveitis with the primary component in the posterior segment only. The primary endpoint is zero vitreous haze at 5 months and there was an unexpected dose response and the 440-microgram group did the best. There was no difference in improved visual acuity from those 20/40 or better, but the 440-microgram group demonstrated better visual acuity improvement in the <20/120.

**Systemic therapies**

There are some new systemic immunosuppressive therapies that are pretty close to being approved. Typically these medications are given for patients with panuveitis, intermediate or posterior uveitis, or very severe iridocyclitis.

When would you give immunosuppressives for these different conditions? For anterior segment disease it is often due to difficulty in controlling the IOP. Additional indications include: if you need frequent periorcular steroid injections, if the patient is not tolerating periorcular therapies, if you can't control the disease adequately, or if there is severe visual consequences for recurrence. An example would be a patient with serpiginous who already has foveal damage. Recurrence would essentially wipe out their remaining vision.

The 4 main drug classes include the alkylating agents, antimetabolites, calcineurin inhibitors, and the biologic agents. To date, there are no approved immunomodulating agents other than steroids to treat uveitis. There are a lot of failed trials.

Voclosporin, the next generation calcineurin inhibitor, had promising initial study results, but the FDA required a 3rd study that did not work. This drug is no longer on the market.

Just recently, a biologic (IL-1 inhibitor), gevokizumab, was tested for Behcet's disease. It did not work for that and is currently not being tested.

The TNF inhibitors are looking promising despite having potential toxicities. If you're going to put somebody on a TNF inhibitor, you really need to make sure they don't have a demyelinating disease or tuberculosis.

Etanercept is not showing promising results as it often makes uveitis worse.

Humera appears to be close to approval. It has been tested for active noninfectious uveitis in the Visual 1 study and is being examined for inactive disease to prevent recurrence in the Visual 2 study. In Visual 1, it is used as a steroid-sparing agent, given with a burst of steroids. There was a multicomponent endpoint including new lesions, anterior chamber cells, vitreous haze, and vision. This drug met the primary end point, which was time to treatment failure. In fact, many never failed treatment. In all cases of treatment failure, it had a better effect than the control. The side effects profile is the same as when using it to treat rheumatologic disease. It will likely be the first immunosuppressive drug to be approved.

Tocilizumab (IL-6 inhibitor) is another interesting drug. The current indications are for rheumatoid arthritis and juvenile idiopathic arthritis, but I have used it in a few patients with chronic CME, and the CME went away with this drug. It has been tested in animal models as an intravitreal injection, but it is currently given as an intravenous medication in humans. The toxicities including infections and GI disturbance mimic some of the other medications. You also have to monitor blood counts and liver function tests.

In conclusion there are a variety of new medications on the horizon. This will increase our options and these medications may last for an extended period of time with fewer side effects.
DISCUSSION

Q: There are multiple case reports of patients who developed HSV or CMV viral retinitis when using immunosuppressive agents, especially with TNF alpha inhibitors. Do you prophylax them with anything?

A: No. I’ve really not seen that. We put a lot of patients on TNF-alpha inhibitors, and at least in my practice, it hasn’t been so much of an issue.

Q: Do the patients see the Iluvien-like implant? What happens at cessation of the implant?

A: The Iluvien-like implant looks a lot like the Ozurdex implant. Patients can see the Ozurdex initially, but it usually moves out of the visual axis with time. The Iluvien-type implant doesn’t inject it quite so forcefully as the Ozurdex, so it tends to remain in the vitreous base. I actually have not had any patients complain of seeing the implant moving around.

I have not put the Iluvien-like implant into an eye that is vitrectomized. One question would be whether it would be more likely to move.
Uveitis Non-specific Treatment Methods
- Topical
- Periocular injections
- Intravitreal sustained drug delivery system
- Intravitreal drug injection
- Systemic

Local Delivery Advantages
- Tailor delivery system for disease
- Pt compliance not issue
- Eliminate systemic side effects
- Constant delivery
- Sustained delivery
- Posterior segment delivery

Uveitis Non-specific Treatment Methods
- Topical
- Periocular injections
- Intravitreal sustained drug delivery system
- Intravitreal drug injection
- Systemic

Local Drug Delivery Methods

Why Local Sustained Delivery?

Implants (Scleral Fixated, Injected)
- Non-biodegradable
- Biodegradable

Topical, Systemic Therapy Disadvantages
- Depend on pt compliance
- Drug levels not constant
- Limited duration, levels
- Side effects

Intravitreal Sustained Delivery Implant
NEW TREATMENTS FOR INTERMEDIATE, POSTERIOR, AND PANuveitis – JAFFE

Intravitreal Sustained Delivery Implant

Non-biodegradable Implants
Disadvantage

- Device retained in/on eye

Intraocular Non-Biodegradable Implants

Example of Non-biodegradable Implant

Intraocular Non-biodegradable Implant Prototype

Fluocinolone Acetonide Implant

Non-biodegradable Implants
Advantages

- Linear drug delivery
- Device non-toxic
- Suitable for sustained delivery

Implant Construction

- Made by CDS/B+L
- 1.5 mm PA drug core
- Silicone/PVA polymer coating
- PVA suture strut
- 0.5, 2.0 µg/day release rate
Fluocinolone Acetonide Intravitreal Implant
- Approved by FDA
- April 08 2005
- Chronic non-infectious uveitis affecting the posterior segment

Key 3 Year Study Results
- Few recurrences in the implanted eye c/w historical control
- Decreased recurrences c/w fellow eye
- Decreased adjunctive therapy
- VA stabilized/improved in most eyes
- Frequent adverse events
  - Cataract requiring extraction (93%)
  - IOP rise requiring filter (40%)

Dexamethasone Implant
FDA Approval Sept, 2010
- Non-infectious uveitis
- Affecting posterior segment

Biodegradable Implant: Example

DDS for Uveitis
- Biodegradable
- Dexamethasone implant
- Injectable
- Releases over 6 wks-3 mos

DDS Implant for Uveitis
Phase III Trial
- Randomized clinical trial
- Intermediate uveitis
- Favorable results reported AAO 2009 sub-day

What’s New?

Injectable Fluocinolone Acetonide Long-Acting Delivery System to Treat Non-infectious Intermediate, Posterior, and Panuveitis
**Purpose**
- Test FAi feasibility for uveitis in clinic
- Examine 2 year effect of implant in eye

**Rationale**
- Retisert very effective for uveitis
- Increased IOP/cataract main side effects
- Retisert surgical procedure
- Can configure injectable FA
- ? Office based procedure feasible

**Injectable Sustained Released Fluocinolone Acetonide**
- Polyamide tube
- Fluocinolone acetonide core
- 3 mm in length
- Modified 25 g needle injector
- Release up to 3 years

**Methods**
- 29 NZW Rabbits
- TB model of severe anterior/intermediate uveitis
- Implant injected into right eye of rabbits
  - 1.0 µg/day implant (n=9)
  - .6 µg/day implant (n=11)
  - Empty implant (n=9)
- Clinical observation

**Uveitis Model**
- Subcutaneous TB Ag injection
- Intravitreal challenge 2 weeks later

**Implant Injection**

**Implant Injection (cont’d)**
Conclusions

- Injectable FA implants suppress ocular inflammation in a severe uveitis model
- Office-based Rx feasibility

Patients

- IU, posterior uveitis, panuveitis
- Required repeated injections or IMT
- Received low/high dose implant
- Followed up to 2 years

GJJ IND Study

Design

- Dose randomized
- Dose masked
- Prospective
- Individual investigator IND (GJJ)

Methods

Technique
NEW TREATMENTS FOR INTERMEDIATE, POSTERIOR, AND PANUVEITIS – JAFFE

Technique

Results

Patients
- 11 eyes of 11 patients
- Average uveitis duration 7.3 yrs
- F/U 2 yrs

Outcome Measures
- Inflammation recurrences
- VA, VA Δ
- A/C cells, A/C cell Δ
- Vit haze, vit haze Δ
- Med use
- CSF,CSF Δ;TMV;TMFA
- IOP, IOP Δ

Inflammation
- 17 recurrences/8 eyes 1 yr pre-implant
- No recurrences post implant
- Fellow eye recurrences 6/10 (X=2.33)
- Systemic Rx reduced or eliminated
- No PSTK/IVTA post-implant

A/C cells

Vit haze

Central Subfield Thickness

P=0.024
Total Macular Volume

P=0.009

VA

- Study eye  BL:20/70
  2 yrs: 20/30 (p=0.002)
- 8/11 (73%) gained ≥3 lines
- Fellow eye no change/worse

Conclusions

- Office-based long-term uveitis Rx feasible
- Excellent inflammation control
- VA improved
- Study eye >fellow eye
- Decreased adjunctive Rx
- Promising approach
- Phase III fully enrolled; Interim data favorable

Collaborators

Phoebe Lin, MD
Robert Keenan, MD, MPH
Paul Ashton PhD
Cindy Skalak RN
Sandra Stinnett, DrPH

What Else is New?

Safety

- No endophthalmitis/RD/VH/explantations
- 2/11 new IOP gtts
- 2/11 filters

Uveitis Non-specific Treatment Methods

- Topical
- Periocular injections
- Intravitreal sustained drug delivery system
- Intravitreal drug injection
- Systemic
Sirolimus

- Macrolide antibiotic
- mTOR inhibitor
- Blocks T, B cell activation
- Inhibits APCs (dendritic cells)

BCVA

- <20/40 440–44 5 letters
- <20/120 440>44 10.5 vs 4.5

Sakura Studies

- Sirolimus IVT injection
- Noninfectious posterior segment uveitis
- 24 month phase 3 studies (1 and 2)
- Three arms 44ug, 440ug, 880ug q 2 mos
- Primary outcome (5 mos)-vit haze
- 440 ug dose did best
- Sakura 1 completed
- Sakura 2 enrolling

Safety

- 2.7% cataract
- Mean IOP change:<2

Primary Endpoint Vit Haze=0

<table>
<thead>
<tr>
<th>Dose</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>44</td>
<td>10.3%</td>
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<tr>
<td>440</td>
<td>22.8%</td>
</tr>
<tr>
<td>880</td>
<td>16.4%</td>
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</tbody>
</table>

What Else is New?

Secondary Endpoints
Inactive Disease (Vit haze=0,+0.5)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>35%</td>
</tr>
<tr>
<td>440</td>
<td>52.6%</td>
</tr>
</tbody>
</table>

Uveitis Non-specific Treatment Methods

- Topical
- Periocular injections
- Intravitreal sustained drug delivery system
- Intravitreal drug injection
- Systemic
NEW TREATMENTS FOR INTERMEDIATE, POSTERIOR, AND PANUVEITIS – JAFFE

Immunosuppressive Rx

Immunosuppressive Therapy and Uveitis
- Panuveitis
- Intermediate
- Posterior uveitis
- Chronic severe iridocyclitis

Panuveitis Etiologies
- Sarcoid
- Behcet’s disease
- VKH
- Sympathetic ophthalmia
- MCP

Panuveitis Examples
- Sarcoid
- Behcet’s disease
- VKH
- Sympathetic ophthalmia
- MCP

Panuveitis Examples
- Sarcoid
- Behcet’s disease
- VKH
- Sympathetic ophthalmia
- MCP

Intermediate Uveitis Example
- Pars Planitis
New Treatments for Intermediate, Posterior, and Panuveitis – Jaffe

**Posterior Uveitis Examples**
- Birdshot
- Serpiginous

**Primary Drug Classes**
- Alkylaing agents (cyclophosphamide, chlorambucil)
- Antimetabolites (azathioprine, methotrexate, mycophenylate mofetil)
- Calcineurin inhibitors (CsA, FK506, Luveniq)
- Biologics (TNF inhibitors, IL-1 inhibitors, IL-6 inhibitor, etc)

**To Date-No Approved IMT for Uveitis**

**Severe Anterior Uveitis Example**
- HLA-B27

**Several Failed Trials**

**Immunosuppressives for Uveitis Indications**
- Requirement for chronic systemic corticosteroids
- Frequent PST requirement
- Intolerance to systemic/periocular corticosteroids
- Inadequate disease control
- Severe visual consequences of recurrence
- Poorly controlled IOP
- Control inflammation for surgery

**Close but no Cigar...**
### Calcineurin Inhibitors
- CSA
- FK506
- Voclosporin

### Biologics TNF Inhibitors
- Golimumab
- Etanercept
- Infliximab
- Adalimumab

### Luveniq (Voclosporin)
- Next generation calcineurin inhibitor
- Inhibits T-lymphocytes, lymphokines
- Phase 3 Luminate trials completed
- 558 pts worldwide
- An additional trial conducted
- Did not meet primary endpoint

### Biologics
- TNF Inhibitors
- IL-6 inhibitor
- IL-1 inhibitor

### Biologics
- TNF inhibitors (Etanercept, Infliximab, adalimumab, golimumab)
- Indications-Evolving
- Toxicities
  - Sepsis
  - Lymphoma
  - Demyelinating disease
  - TB

### Biologics
- TNF inhibitors (Etanercept, Infliximab, adalimumab, golimumab)
- Indications-Evolving
- Toxicities
  - Sepsis
  - Lymphoma
  - Demyelinating disease
  - TB

### Adalimumab (Humira)
Adalimumab in Patients With Active, Non-infectious Uveitis Requiring High-dose Corticosteroids: The VISUAL-1 Trial

Glenne Brücher, Antoinette Bérizzi, Philipp Kaselost, Joachim Van Calster, Jennifer Bock, David Scharfe, Fabio Fondi, Andrea Dijk, Quyen Dong, Nguyen, Eric Suhler, Anne-Carre, Alexandra Song, Martina Krom, Simon Tarr, Amit Heiligenhaus (on behalf of the VISUAL-1 study investigators)

VISUAL 1 Purpose

- Safety efficacy of Humira active uveitis
- Steroid sparing agent

VISUAL 1

Screening
Double-Masked (80 weeks)

Aged ≥18 years
Active disease despite standard treatment, 10-40 R/T for ≥12 weeks

AC cells
Placibo
Adalimumab

Placebo, n=507
Adalimumab, n=119

Patients assessed for treatment failure

Primary Endpoint – Time to RX Failure

Time to Event Analysis

Primary Endpoint – Time to TF Failure

Secondary Variables

- Ranked endpoints: ITT population
- Changes in:
  - AC Cell grade
  - VH grade (NEI/SLIT criteria)
  - logMAR BCVA
  - CME by OCT
  - % change CSF thickness

Primary Endpoint – Time to TF

The median time to treatment failure was prolonged by 59% from 13 weeks for placebo to 24 weeks for adalimumab. There is a 50% decrease in risk to have treatment failure.

Components of TF

AC cells
Vitreous haze

BCVA
New Lesions

Ranked Secondary Variables

<table>
<thead>
<tr>
<th>Ranked secondary variable</th>
<th>T-test</th>
<th>Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Change in AC cell grade Left eye</td>
<td>0.65</td>
<td>0.15</td>
<td>0.01</td>
</tr>
<tr>
<td>Right eye</td>
<td>2.02</td>
<td>0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>Difference, mean (95% CI)</td>
<td>-0.37 (0.15 to -0.70)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>2. Change in VH grade Left eye</td>
<td>0.53</td>
<td>0.10</td>
<td>0.01</td>
</tr>
<tr>
<td>Right eye</td>
<td>0.41</td>
<td>0.11</td>
<td>0.01</td>
</tr>
<tr>
<td>Difference, mean (95% CI)</td>
<td>-0.12 (0.05 to -0.28)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>3. Change in BCVA, logMAR Left eye</td>
<td>0.10</td>
<td>0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>Right eye</td>
<td>0.10</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Difference, mean (95% CI)</td>
<td>0.08 (0.06 to 0.10)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>4. Time to OCT evidence of ME Shunt failure (95% CI)</td>
<td>0.12 (0.05 to 0.25)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>5. Percent change in CRT Difference, mean (95% CI)</td>
<td>-2.8 (2.85 to -2.76)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

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### Visual I

- Favorable results
- FDA filing planned

### Tocilizumab (Actemra)

- Mechanism: Fully humanized Mab binds soluble, membrane IL-6 receptors
- Indications: Approved for RA, JIA
  
  Anecdotal vs CME, Rx resistant uveitis
- Dose, route: 1-8 mg/kg q 8 IV
- Toxicities: Infections, GI, anaphylaxis
- Monitoring: CBC, LFTs q 1-3 mos

### New Uveitis Treatments

- On near horizon
- Increase Rx options
- Potentially fewer side effects
- More convenient
- Retina specialists more likely to treat

### The Visual 1 Study:

1. Did not meet the primary study endpoint
2. Tested the safety and efficacy of a calcineurin inhibitor to treat posterior uveitis
3. Tested the safety and efficacy of Humira to treat active non-infectious uveitis
4. Is a phase II trial of Humira that serves as the basis for currently enrolling phase III trials

### The Non-Biodegradable Injectable Fluocinolone Implant Used to Treat Uveitis:

1. Is designed to release for 1 year
2. Is associated with glaucoma filtering surgery in 40% of eyes
3. Has pharmacokinetics that are similar to the injectable dexamethasone delivery system
4. Can be placed in an office-based procedure

### All of the following are Biologic agents except which one?

1. Tocilizumab
2. Tacrolimus
3. Etanercept
4. Infliximab

---

**Safety**

<table>
<thead>
<tr>
<th>Adverse Events (AE)</th>
<th>Placebo N = 112</th>
<th>Adalimumab N = 111</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>410 (37.2)</td>
<td>657 (59.1)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>7 (15.8)</td>
<td>28 (14.4)</td>
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<tr>
<td>SAE</td>
<td>6 (5.5)</td>
<td>18 (16.3)</td>
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<tr>
<td>AE leading to discontinuation</td>
<td>5 (4.5)</td>
<td>15 (13.6)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>3 (2.7)</td>
<td>5 (4.5)</td>
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<tr>
<td>Inapplicability</td>
<td>0 (0)</td>
<td>2 (3.2)</td>
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<td>AE leading to death</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Any adverse events</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Any acute 1B</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Any acute 1B</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Any demyelinating disease</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>
Promising New Treatments for Retinal Diseases: Gene Therapy and Engineered Cells

SZILÁRD KISS, MD

SUMMARY
The eye – as a self-contained, comparatively small, and relatively immune privileged organ – offers a perfect site for applying gene and cellular therapy techniques for the treatment of a wide range of acquired and inherited disorders. Decades of preclinical proof-of-concept laboratory effort have resulted in several promising and exciting clinical applications. Gene therapy – where a non-pathologic viral vector is engineered to deliver a protein of choice – is being applied not only to mono-genetic inherited disorders which currently cannot be otherwise treated (such as Leber’s Congenital Amaurosis and X-linked Retinoschisis) but also to acquired disorders such as macular degeneration and diabetic retinopathy that require repeated intravitreal injections indefinitely. Engineered cells – where cells are transformed ex vivo to produce the protein of choice (such as Encapsulated Cell Technology) – can be implanted into the eye and removed if necessary, offering a form of reversible and perhaps a fine tunable gene therapy.

Other types of engineered and transformed cells selected for their specificity (such as cytotoxic CMV specific T-cells) can be infused systemically and act in the eye to ward off opportunistic infections that are beginning to resurface. Finally, terminally differentiated as well as pluripotent stem cells can be injected into the eye to ‘regenerate’ areas of the retina and perhaps restore visual function in disorders previous thought to be untreatable (such as reversing geography atrophy from AMD and restoring vision in Stargardt’s disease).

NOTES
Ocular Gene Therapy
The concept of gene therapy using viral vectors has been around since the early 1980s. More recently, mono-genetic disorders in the eye have been targeted. One reason these disorders lend themselves well to gene therapy is that they have no other treatment. Currently there are 10 different mono-genetic disorders that are in clinical trials. These may show good proof of concept, but it’s in diseases that are treated with repeated intravitreal injections where perhaps gene therapy will make its greatest impact. However, most of the companies that are targeting gene therapy are investigating primarily mono-genetic disorders. For example, Spark is targeting the RPE65 mutation in Leber’s congenital amaurosis. In these patients, the particular protein RPE65 that is found in the RPE is abnormal. When gene therapy is used to replace this protein, patients actually function better. There are only 500 patients currently alive in the United States that would benefit from this therapy, which is not even as many AMD patients as many retina specialists see in one month. Nevertheless, it will probably be the first gene therapy that’s going to be available. Realizing the promise of gene therapy requires multiple steps including capsid diversity, gene cassette optimization, formulation, and vector administration. Different promoters and enhancers will result in more or less of a particular protein. The formulation, especially when using viral vectors, is also important because viruses love to stick to things, including surgical instrumentation. Finally, administration of the genes currently involves subretinal placement but it would be nice if we could treat AMD with gene therapy with an in office procedure.

Gene therapy targeting wet-AMD
Some of the companies that are targeting wet AMD include Avalanche, AGTC, and REGENXBIO. Avalanche was the first company to go into clinical trials. Avalanche used the soluble FLT-1 protein with an A82 vector administered by a subretinal injection. One of the reasons that these trials were unsuccessful has to do with the macular anatomy of wet macular degeneration. The CNVM is actually taking up the area where gene therapy targets need to be delivered. This is very different from what happened in the Spark trials, where the macular anatomy was normal. The heterogeneity of the macular pathology includes both the size of the CNVM and the size of the bleb itself. The bleb size is going to determine which RPE cells are transfected and which RPE cells are making the anti-VEGF therapy. The Avalanche trial included the largest series of active CNV-injected patients. There were no serious adverse events, although it didn’t work. The therapeutic implications of this are really not known.

What are the lessons from the Avalanche trial? Subretinal injection is not difficult to perform, but there is a learning curve. Subretinal gene therapy with active CNVM is safe but less predictable than subretinal administration in a macula that’s relatively normal, such as in the Spark trial. Subretinal injection results in outer retinal changes that may persist. Finally, standardization of technique is key for clinical trials to be internally valid.

Cellular Therapy
There are two essential ways that stem cells could be used. You could use the cells and regenerate whatever tissue you need, or you can take these cells and use the trophic factors that they produce to stimulate tissue regeneration. In the Ocata trial, patients with either Stargardt’s or dry macular degeneration, had a subretinal
injection of stem cells with the goal of replacing the retinal cells via the regeneration mechanism. Although this was not a cure for Stargardt’s or macular degeneration, it was a step towards understanding how we may be able to use some of these cells in the future.

The other way to use stem cells is the trophic factor. Jansen and Johnson and Johnson recently injected stem cells into the subretinal space via an external approach using a catheter to place the cells in the area of geographic atrophy in the hope that these cells would provide a milieu for retinal growth or decreased degeneration. As in other trials, a big limitation to success in this study was the surgical procedure. The surgical technique itself was an integral part of actually delivering this therapy. There is going to be a phase 2b clinical trial. The surgical procedure is completely revamped.

What about combining gene therapy and cellular therapy? Encapsulated cell therapy combines gene and cellular therapy. The concept here is to take cells and put the gene of choice into the cells and then place these engineered cells into the eye. The third-generation encapsulated cell therapy was, until last week, in phase two clinical trials. The trial involved a number of cylinders that housed RPE cells releasing a product similar to Eylea with the goal of decreasing injection frequency in patients with the encapsulated cell therapy in their eyes.

Harvesting the power of the immune system
We have been harvesting T cells to treat CMV retinitis. The concept is the following: Cytotoxic T cells float around your body ignoring cells expressing self-antigens but if they come across a cell that is expressing a foreign antigen on its surface the cytotoxic, T cell activates a series of mechanisms resulting in apoptosis of the abnormal cell. Donor T cells are obtained from CMV seropositive patients and are used to generate CMV-specific cytotoxic T cell lines resulting in a library of T cell lines. This library has a variety of MHC class one and class two phenotypes. Given a patient with CMV retinitis, these cells are made to look like self-cells if two of eight of these alleles are matched. These engineered self-cells are amplified and then infused into the patient. Exactly what happens next is under investigation but it is believed that the infused T cells actually help some of the other T cells that are around get activated to also recognize the same antigen.

DISCUSSION:
Q: Do you think there’s a role for intraoperative OCT to see, particularly when we have multiple blebs, if there’s efflux of the vector?
A: I don’t have any experience myself with intraoperative OCT. I don’t know how that would prevent efflux.

A: One of the things that we’re discovering with Avalanche’s help is that it is the radius of the bleb that’s important, not necessarily the height. It is the number of RPE cells that are exposed that’s more important. The efflux becomes very important as well.

Q: Have you seen immune recovery uveitis?
A: No, one of reasons is because these patients don’t immune recover. These cells don’t stick around for years, rather they help native cells become activated and recognize the CMV. There might be some level of immune recovery, but interestingly we haven’t had much inflammation. We have seen a few cases of CME but these did not require treatment.

Q: They’re using engineered cytotoxic T cells for relapsing ALL and these patients get a massive inflammatory response systemically and end up in ICU often. In these patients with CMV retinitis, have they had a systemic response? Are they fully controlled already when they get this therapy?
A: They’re not fully controlled, that’s why they’re getting the therapy. In terms of systemic response, what you’re talking about is car2 T cells. We are using patients that are being treated systemically for CMV and looking at the eye. By definition our patients are immunosuppressed and will continue to be immunosuppressed. Probably this is the reason we are not seeing an inflammatory response in these patients compared to the ALL patients. There’s another technology for EBV as well, but we haven’t seen those developing the uveitis that we’ve seen with the car2 T cells.

Q: Are you thinking your patients are relatively immunosuppressed and that’s why you’re not seeing it?
A: I don’t know. By definition, they are immunosuppressed, and most of them will continue to be immunosuppressed. This is a little bit different than the era of HIV where the goal is to bridge them to the immune-recovery. Here you’re talking about somebody who has had a solid organ transplant and who is going to be immunosuppressed for the long-term.

A: I think that’s what the relative difference is. That these are relatively immunosuppressed, and they can’t mount an inflammatory response to the degree that some of the patients that we’re seeing transplanted for an oncology indication.

Q: Do you think there is any potential for intravitreal therapy to go to subretinal delivery?
A: I think the barrier is several fold. Firstly, the amount of delivery has to be optimized. You also have to optimize promotor and capsid as well. One reason cell capsid technology is not going the way it should is because of the concentration.
Gene and Cellular Therapy for the Treatment of Retinal Disorders

Szilárd Kiss, MD
Well Cornell Medicine | New York-Presbyterian Hospital
Assistant Professor of Ophthalmology
Director of Clinical Research
Associate Professor of Ophthalmology
Weill Cornell Medical College

GENE THERAPY AND ENGINEERED CELLS – KISS

Relevant Financial

- Consultant — Avalanche Biotech, Atara Bio, NeuroTech, RegenX Bio, Spark Therapeutics
- Research Funding — NeuroTech
- Intellectual Property — Gene Therapy for AMD, T-Cells for CMV Retinitis

Ocular Gene Therapy

Inherited Monogenic Causes of Blindness

Need for Repeated Intravitreal Injections for AMD, DR, etc.

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Gene Therapy

autosomal recessive RPE65 mutations

Estimated Prevalence of PDE6B mutations

An estimated 5,000 patients in KS and EVI
96% to 98% of GA patients (LCA2)
~5% to 3% of RP patients (RP23)

< PREVIOUS TALK  TABLE OF CONTENTS  NEXT TALK >
Macular Pathology in wAMD
- Avalanche experience is largest to date in wet AMD with active CNV
- No serious adverse events noted in any of the subjects
- Heterogeneity in macular pathology - including size, location and type of lesion (e.g. vascular vs fibrosis)
- Heterogeneity in sub-retinal bleb size, shape and relative location to active lesion
- Therapeutic implications

Surgical Instrumentation

Surgical Instrumentation and Methods May Play Important Role in Treatment Outcomes

Vitrectomy Platforms
**Gene Therapy and Engineered Cells - KISS**

### Lessons from the Avalanche
- Sub-retinal injection is not difficult but there is a learning curve.
- Sub-retinal gene therapy in wet AMD with active CNV appears to be safe, but is different from inherited retinal disorders with normal macula.
- Sub-retinal injection results in outer retinal changes that may persist.
- Sub-foveal injection risks macular hole formation — may require surgical adjuncts (PFO).
- Multiple blebs may be required.

### Stem Cells
- Induced Pluripotent Stem Cells
- Adult Stem Cells
- Embryonic Stem Cells

### Stem Cells for Regeneration

<table>
<thead>
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<th>Product</th>
<th>Description</th>
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<th>Target</th>
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<td>Embryonic stem cell derived RPE</td>
<td>RPE tissue</td>
<td>RPE layer</td>
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<td>Neural stem cell derived RPE</td>
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### Surgery and Sub-Retinal Bleb Placement

- Immediately following
- 2 weeks following procedure

### Sub-Foveal Bleb

- Immediately following
- 2 weeks following procedure

### Multiple Blebs

- Immediately following
- 2 weeks following procedure
GENE THERAPY AND ENGINEERED CELLS – KISS

RPE Cell Replacement

Pre-retinal cellular growth

Combining Gene and Cellular Therapy

Stem Cells for Trophic

Encapsulated Cell Therapy

Genetically Engineered to Produce Biologically Secreted Proteins

Surgical Delivery of CNTO 274 will be Phase 1b/2a

Harvesting the Power of the Immune
T cell Immunotherapy for CMV Retinitis

Case
- HLA-match to the patient / his stem cell donor at 3 of 8 alleles at high resolution
- Underwent 3 weekly infusions of 1x10^6/kg CMVpp65 CTLs, followed by a 2 week break, and then 3 additional weekly infusions - 2 cycles
- After infusions, CMV-specific T-lymphocyte precursors were demonstrated to have expanded in the peripheral blood
- CMV viral load remained undetectable without antiviral therapy during the infusions
- No worsening of systemic graft-versus-host disease during treatment

Sustained resolution of CMV retinitis 27 months after last CTL

A novel approach developed at
- Donor T-cells obtained from healthy CMV seropositive patients
- Used to generate CMV-specific cytotoxic T-cell lines
- Library of cryopreserved T-cell lines available for off-the-shelf use
- Appropriate T-cell line selected from library for each CMV patient:
  - Matched to the patient at 2 or more HLA alleles at high resolution
  - Restricted in their cytoxicity to CMV epitopes presented by one or those matching HLA alleles (i.e. an HLA allele present in the patient)
  - The CMV-specific cytotoxic T-cells are HLA-restricted and CMV-specific effector T-cells

Gene Therapy
- Cellular Therapy
- Combining Gene and Cellular Therapy
- Harvesting the Power of the Immune System

Case
- History of pre-B-cell acute lymphoblastic leukemia status post allogeneic stem cell transplant on immunosuppression for severe graft-versus-host disease
- Developed CMV viremia with UL54 mutation — resistant to foscarnet, cidofovir, ganciclovir
- Referred for T cell immunotherapy for worsening systemic CMV — esophagitis and retinitis
- CMV retinitis treatment — Biweekly intravitreal ganciclovir injections administered elsewhere 31

Thank you for your attention
GENE THERAPY AND ENGINEERED CELLS – KISS

Ocular Gene Therapy:
1. Is being used only for monogenetic inherited retinal disorders (e.g., Leber congenital amaurosis).
2. Is PDA-approved for X-linked retinoschisis.
3. Has not been applied outside of the laboratory setting.
4. Can be used for non-inherited retinal disorders, such as age-related macular degeneration.

Encapsulated cell therapy with NT-503:
1. Continuously releases a soluble anti-VEGF receptor antagonist.
2. Is being tested for retinitis pigmentosa.
3. Has not yet entered clinical trials.
4. Requires repeated intravitreal injections.

Systemically infused cytotoxic T-cells:
1. Are not able to target ocular disorders.
2. Work via the complement and VEGF pathways.
3. Have been successfully used to treat CMV retinitis.
4. Cause anterior and posterior uveitis.

HARRY W. FLYNN, JR., MD

SUMMARY
Management of patients with symptomatic vitreomacular traction (VMT) include: 4 options: 1) Observation, 2) Pneumatic vitreolysis, 3) Intravitreal ocriplasmin and 4) Pars plana vitrectomy. Limited studies are available on observational management but these publications indicate a generally benign course for most patients. Approximately 1/3 of patients undergo spontaneous release of vitreomacular traction. Only 4% of patients required surgery for macular hole development or worsening vitreomacular traction in one large series.

Pneumatic vitreolysis is an emerging popular approach. A review of current publications indicates a high rate of success (greater than 80%) using C3F8 gas to accomplish syneresis and synchesis. Anxillary techniques include the “dipping bird” maneuver to assist in movement of the bubble and cleavage of vitreoretinal traction.

Enzymatic cleavage of the VMT with ocriplasmin is successful in many patients but side effects can be significant. Most visual symptoms and visual loss associated with enzymatic vitreolysis will resolve spontaneously over 6 months but other side effects may have persistent visual effects.

Pars plana vitrectomy is a consistent way for removing VMT but the surgery may be associated with unroofing the foveal center resulting in a full thickness macular hole. This complication has been reported to occur in up to 10% of patients in 1 study. Surgical techniques for VMT will be discussed. These include staining the posterior hyaloid with triamcinolone in order to facilitate removal of the posterior cortical vitreous while avoiding traction on the fovea. ILM peeling toward the macular center may also avoid traction on the fovea.

NOTES
This talk is going to focus on the 1st 3 categories of treatment for VMT. I want to quickly discuss the most recent publication from Yu G et al (Arroyo group) [Retina epub ahead of print] and the Meta-analysis from George Ayoub’s group.

Arroyo study - No one in the observation group had release of VMT at 28 days. Ocriplasmin had release in 3/7 patients, pneumatic vitreolysis had release in 7/8 patients, and vitrectomy had 100% release.

Ayoub’s study - About 80% of the pneumatic vitreolysis group had a release of VMT, but no one in the saline or ocriplasmin groups had complete release.

Because of the improvement in imaging techniques, Duker et al created a classification based on OCT findings. The Gass classification is still used, but OCT based findings is the future. Nowadays when there is no surface abnormality it is called vitreomacular adhesion. The term vitreomacular traction is used when the surface is distorted whether or not the hole is associated with vitreomacular adhesion.

Management Option #1: Observation
This approach is used in many diseases.

1st Case: 83 y/o patient concerned that he needed urgent surgery because that was encouraged by someone in the community. Just with observation he had complete resolution. You can see the floater scotomas on OCT.

2nd Case: 66 y/o patient with diabetic retinopathy. We watched him for a few years and the traction actually worsened before spontaneously resolving. His vision remained stable at 20/20 the whole time.

At BPEI, we put together a 3-center study examining patients with VMT that were followed with observation. This was then expanded to 230 patients. A limitation was that we excluded eyes that had a macular hole in the fellow eye, so this population likely had less risk. Out of the entire population, 31.7% had spontaneous release of the VMT. Interestingly, grade 3 cases had improvement in vision while the more mild cases maintained good vision. There were 10 eyes (4.3%) that underwent vitrectomy. Six of the eyes developed a macular hole and 4 eyes had worsening symptoms after failure of ocriplasmin therapy.

Case Examples
1st Case: The patient initially has distortion, which worsened after 2 months before the VMT eventually separates. The vision improved to 20/25, and the patient did well with observation.

2nd Case: This patient had a grade 2 VMT with 20/60 vision. The contour worsened, but vision remained stable. The VMT released, her distortion improved, and her vision remained the same.
3rd Case: This was a patient I saw for the first time in November of 2008, who had a grade 2 VMT and 20/30 vision. This is eight years later. She remains grade two and her vision is still 20/25.

Here are a couple of cases when observation fails.

4th Case: This one didn’t fit into our grading system very well. The patient was 20/30 with a macular hole, except for the inner retinal tissue remaining. She got worse to 20/50 then had a vitrectomy and came back to 20/25.

5th Case: Here’s another case of worsening of symptoms. After vitrectomy, the symptoms improved, and after cataract surgery the vision came back to 20/25. The macula is flat and there is no foveal depression.

Management Option #2: Vitrectomy

There are a number of studies that discuss vitrectomy. The study by George Williams and associates was in the time-domain OCT, pre-ocriplasmin era. 87% of these eyes improved by one or more lines. There was a retrospective study of 36 eyes from Bascom Palmer Eye Institute also from the time-domain OCT, pre-ocriplasmin era. Two of the eyes developed a macular hole after surgery for vitreomacular traction. Another study from Jay Duker’s group in Boston demonstrated an improvement in OCT and in most cases, vision.

A meta-analysis from Moorfields looked at 21 studies involving 259 eyes. The mean overall visual acuity improvement after vitrectomy was from 20/94 to 20/53. About 1/3 of patients improved by 2 lines and 2/3 improved by 1 line.

In another study from BPEI, 41 patients underwent vitrectomy for VMT and almost 10% developed a macular hole. This video is of triamcinolone approach.

Management Option #3: Pneumatic Vitreolysis

Some of these treatment decisions are based on where the patient is geographically. The local trends will determine which treatment the patient receives.

The technique that has been advocated is known as the “dipping bird.” Filtered 0.3 mL of C3F8 gas was injected in the same way as in pneumatic retinopexy and the dipping bird method is used for 5 minutes every hour. The study by the Chan group evaluated patients who underwent the procedure from 2010 to 2015. For patients with VMT only, 20 of 24 eyes (83%) developed a posterior vitreous detachment. There were 11 patients with stage two or early macular holes less than 250 microns in size. All had separation of the posterior vitreous, but closure of the hole occurred in only 73%. There appear to be minimal costs and beneficial results compared to the MIVI Trust study.

1st Case: This is a patient who had a macular hole in the left eye and underwent pneumatic vitreolysis. A PVD was present at four months. There were no signs of traction and the vision was 20/30 at 17 months.

2nd Case: This is a small stage two macular hole with traction. Following treatment, the macular hole closed and the visual acuity returned to 20/25.

The Tim Jackson study looked at 15 eyes that had various etiologies of vitreomacular traction, including idiopathic, DME, AMD, and an impending macular hole. A single injection of 0.3 cc of 100% C3F8 gas was given and 6/15 (40%) released at one month and 9/15 released by six months. Four of 15 ultimately underwent vitrectomy. Those with focal VMT did particularly well.

There are also a few different types of methods for pharmacologic vitreolysis. Ocriplasmin will be discussed by Mark Johnson, but I want to mention that vitrectomies were determined to be more cost-effective than ocriplasmin in an evaluation of QALYs by Jonathan Chang and Bill Smiddy. Aflibercept is also a potential therapy. We have seen that while injecting patients with DME repeatedly, the VMT may release. The newest item is the use of integrin antagonists. This approach has been discussed by Kaiser et al., and is involved in a phase 2 randomized double-blind safety-efficacy trial with the primary outcome of a release of VMT at 90 days. VMT release was noted to be 65% with the 3.2mg dose. This may have promise for the future.

I think you should consider observation for eyes that have better visual acuity or in patients that have complex ocular or systemic diseases. Vitrectomy offers 100% success of relieving traction, but it has a risk of retinal detachment and creation of macular hole. If interventional treatment is considered, pneumatic vitreolysis may be the best and most cost-efficient initial treatment. The risks, benefits, and costs of ocriplasmin must be evaluated for individual patients.

DISCUSSION

Q: In the Bascom Palmer study where you had a 10% macular hole rate, was the ILM peeled?

A: Yes, in 93% of them. That’s why I’m switching to this triamcinolone approach.

Q: Any episodes of macular hole in the triamcinolone group? How many eyes have you done?

A: I’ve done about three, and no macular holes so far.
Q: We’ve shared a number of these cases, and I have experience with observation and vitrectomy. Very limited experience with the other two techniques. Two short questions. Do you think there’s any OCT patterns that are different in categories you mentioned? Other than the ocriplasmin group, in the other three techniques of observation; spontaneously separated VMT, vitrectomy, and pneumatic vitreolysis do you think there are any OCT changes that are characteristic that would indicate better success with a particular method?

A: I think they’re going to be fairly similar. I think that in these eyes that we observe for a long time and they have late separation, they always get the schisis, some persistent cystic change. So one of the arguments for early treatment was, you could relieve the OCT traction and avoid that distortion of the fovea. I think again, you’re talking about the complications, retinal detachment and macular hole formation, with vitrectomy.

Q: Do you think the macular hole occurs at the time of vitrectomy and if so do you use an air bubble? I use an air bubble if I suspect that there’s a hole, and I tell the patient to lie facedown for a day or two.

A: I always look at the patients with OCT as soon as the bubble is small enough to find out the status of the hole.

Q: Are you putting a bubble in all of these eyes? If so, what type of bubble?

A: Yes, air.

Q: Even for the VMT that you don’t suspect has a macular hole?

A: Yes.

Q: How many people are putting a gas or air bubble in the eye when they do a VMT surgery?

Audience poll: About 50% raise their hands

Q: Why are you putting in air if you don’t suspect a hole?

A: I just like it for tamponade of my sclerotomies in small-gauge surgery.

Q: How many people are still putting air in as a tamponade for their sclerotomies in small-gauge surgery?

Audience poll: about 50% raise their hands

Q/C: I never use air. I have had 2 full thickness macular holes this year. One patient was a 2nd day post-op and the other was a 1-week post-op. Instead of taking them back to the OR, I did a full 20% gas, fluid exchange in office and they both closed.

A: We used to do it all the time. I did this during my fellowship commonly.

Q: How did you confirm a total PVD with pneumatic vitreolysis?

A: A lot of patients did not have total PVDs; they just had macular separation. If I saw a Weiss ring on clinical exam, then it confirmed total PVD.

Q: Didn’t you have a 78% rate of complete PVD?

A: There was a high rate of complete PVDs. Many were partial initially, and they eventually progressed to a complete one.

Q: Did you confirm that with a B scan or OCT?

A: No, I determined by clinical examination only.

Q: I’m not used to seeing that high of a rate of retinal detachment after vitrectomy, so something about these eyes may be different. Do you think the retinal detachment rate would be just as high for pneumatic vitreolysis?

A: I have had one patient with RD. With the learning curve, I would quote someone about a 4% chance of retinal detachment.

A: The take home point is that eyes with VMT do have a higher rate of peripheral breaks and retinal detachment.

Q: What is your procedure of choice?

A: Pneumatic vitreolysis if observation is not an option. Observation is almost always my first choice.

Q: The natural history data is so important. I think there has been an over-reaction to seeing VMT on OCT instead of listening to the patient.

Q: I love the dipping bird technique. Is it necessary? How did you come up with this?

A: If they have a small hole then I tell them to put their head down. If they have VMT without a hole, I tell them to go about their normal business.

Harry W. Flynn Jr., M.D.

Disclosures: None

SD-OCT based classification

- Vitreomacular adhesion – elevation of central vitreous above retinal surface with remaining attachment within a 3 mm radius of fovea
  - Subclassification
    - Focal ≤ 1500 μm
    - Retinal > 1500 μm
- Vitreomacular traction – VMA with anatomic changes in the contour of the foveal surface
  - Subclassification
    - Focal ≤ 1500 μm
    - Retinal > 1500 μm

Vitreomacular Interface Disorders

- Full thickness macular hole – anatomic defect in the foveal featuring interruption of all neural retinal layers from the RPE to the RPE
- Lamellar Hole
- Macular pseudohole

83 y/M, with VMT OS

66 y/M with NPDR and VMT
MANAGEMENT OPTIONS FOR VITREOMACULAR TRACTION – FLYNN, JR.

**Observational Study:**

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**Patient Demographics**

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<td>20/25</td>
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<tr>
<td>Initial VA</td>
<td>20/50</td>
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**Initial VA:** 20/40

**Final VA:** 20/25

**Case 1**

**CLINICAL COURSE OF VITREOMACULAR ADHESION MANAGED BY INITIAL OBSERVATION**

108 eyes were identified as having VMT by spectral-domain optical coherence tomography and divided into 3 grades.

- **Grade 1:** Complete resolution of subclinical retinal detachment.
- **Grade 2:** Complete resolution of retinal detachment.
- **Grade 3:** Persistent retinal detachment.

**Table of Contents**

- **Observed VMT grade**
  - 100 eyes
  - Presenting VMT grade
  - Final VA
  - Observation

- **Presenting VMT grade**
  - 100 eyes
  - Presence of VMT
  - Presenting logMAR VA

- **Presenting logMAR VA**
  - 100 eyes
  - Presenting logMAR VA
  - Last Exam logMAR VA

- **Last Exam logMAR VA**
  - 100 eyes
  - Presenting logMAR VA
  - Last Exam logMAR VA

- **Case 1**
  - Persistent VMT
  - Final VA 20/25
VMT Observational Study

- **31.7% (73/230)** - spontaneous release of VMT
- Time to spontaneous release on OCT
  - Mean 18 months
  - Median 10.9 months.
- Study eyes undergoing treatment:
  - Eyes undergoing PPV: 10/229 (4.3%)
  - Macular hole: 6/10 (6 out of 10 eyes closed with PPV)
  - Worsening symptoms: 30/30 (1 for Grade 2 VMT, 1 for Grade 3 VMT)
  - 1 eye received intravitreal triamcinolone (no release) VA 20/30

VITRECTOMY

**VITREOMACULAR TRACTION SYNDROME**

Impact of Anatomical Configuration on Anatomical and Visual Outcomes

- **N = 24 eyes undergoing PPV (OCT era)**
- **21/24 eyes (87.5%)** improved by ≥ 1 line
- Visual improvement greater in eyes with focal vitreofoveal attachment (V-shaped) vs broad attachments

Retina 2008; 28(8): 1207-1214.
Outcomes of Pars Plana Vitrectomy for Patients With Vitreomacular Traction

- Consecutive case series (N=41)
- OCT pre and postoperatively (SD-OCT)
- Mean age: 60.5 years (46-77)
- ILM peeling: 38 (93%)
- Results:
  - 56% of eyes improved ≥ 1 line
  - SD-OCT: traction released from the fovea in all eyes
- Complications:
  - 4 (9.8%) eyes developed a macular hole (3/4 repaired)
  - 0.1% retinal detachments (one intravitreal break)

Cost Evaluation of Surgical and Pharmaceutical Options in Treatment for Vitreomacular Adhesions and Macular Holes

- The cost per quality-adjusted life years (QUALys)
  - Vitrectomy: $5,444 to $7,442
  - Ociplexin: $8767 to $10,977

VMT/PPV Case Example

- 84 yo pseudophakic female who presented with decreased vision for 3 months.
  - Pre-Op: 20/70
  - POMA 3: 20/20

Non-enzymatic Vitreolysis

- Treatment of Pseudophakic Macular Holes in Retinal Posterior Vitreous Detachment
  - Oanda, Chau et al. - JAMA, Chicago, 1995

Slides courtesy of Dr. Christopher O’Neal
Non-enzymatic Vitreolysis: Hypothesis

- Gas bubble destabilizes the vitreous integrity by accentuating liquefaction (synchysis)
- Cortical vitreous collapses during absorption phase of bubble → PVD (syneresis)
- Long-acting gas bubble serves as cushion for more "gentle" or innocuous PVD

Case 1: 70 y/o female with VMT OD.

OD: 20/40
OS: 20/30, s/p PPV M6: J
s/p MH: repair

Case 1: s/p 0.3cc C3F8 gas injection OD

At 1 month - PVD
At 4 months
VA: 20/30 17 months

Case 2-VMT OD

- 64 Y/F: blurred and distorted vision, OD, July 2015
- VA was OD: 20/60, OS: 20/40
  - SVD toward nasal VMT, OD
  - nasal cyst and peripheral yellow ring
  - outer foveal delamination—step 1B MH, OD

Dipping Bird Video

Case 2-VMT OD

9/10/15
9/23/15
5 weeks: PVD
10/15/15
8 weeks
Case 3: Stage 2 MH with VMT OD

Day 0
1 wk s/p 0.3 cc C3F8

2070
VA: 20/25 MH closed

Chan & Mein Series: RESULTS

- 34 patients (35 eyes) with symptomatic VMT underwent pneumatic vitreolysis between 2000 and 2013. A complete PVD developed in 34 eyes (97.1%) at a mean (median) of 2.6 (1.5) weeks after C3F8 gas injection

- VMT only:
  - 20 of 24 eyes (83.3%) with VMT only developed a PVD

- Stage-2 MH (≥ 250 microns):
  - 11 eyes (100%) with a small stage-2 MH developed a PVD with MH closure in 8 of the 11 eyes (73%)

Pneumatic Vitreolysis

- 15 eyes (7 idiopathic, 6 DME, 1 AMD, 1 impending MH)
- Single intravitreal injection of 0.3cc 100% C3F8
- 6 of 15 released at 1 month (40%)
  - 9 of 15 released at 6 months (60%)
- 4 of 15 eventually underwent PPV
- No adverse events seen with mean follow up of 398.7 days

Pneumatic Vitreolysis

- Intravitreal Injection of Exograde Perfluoropropane (C3F8)
- for the Treatment of Vitreomacular Traction

- Predictors of treatment success:
  - VMA < 750 μm (focal foveal VMA)
  - Maximum foveal thickness < 400 μm
  - Low vitreous face reflectivity
  - Absence of DME

Ocriplasmin – Overview

- Approved in 2012 by FDA
- 27 kDa recombinant serine protease subunit of human plasmin
- Hydrolyzes collagen, laminin, and fibrinectin

Ocriplasmin – MIVI 006 and 007 studies

- Two multicentered randomized double blind phase 3 trials comparing single intravitreal injection of ocriplasmin compared to placebo injection
- Subjects – Symptomatic focal VMA (macular holes > 400 μm excluded)
- Primary end point: resolution VMA day 28
**Ocriplasmin**

- Acute panretinal structural and functional abnormalities after ocriplasmin (U.Michigan)
  - Acute loss of VA
  - IP/constriction
  - Altered field
  - Retinal hemorrhage
  - Outer retinal SD-OCT changes
  - Severe visual loss

Enzymatic cleavage of intraretinal filaments is a biologically plausible mechanism.

- Acute visual loss (correlation with SD-OCT / ERG)
  - Tufts group: diffuse effect on photoreceptors

**Safety Update**

Report of the ASRS Therapeutic Surveillance Committee

<table>
<thead>
<tr>
<th>ADR Event</th>
<th>Pre-Marking Treatment (n=755)</th>
<th>Post-Marking Treatment (n=757)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute decrease in VA</td>
<td>0.5%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Age-related maculopathy</td>
<td>1.8%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Retinal pigmentary network</td>
<td>2.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Lower macular pigmentation</td>
<td>0.7%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Degenerative retinal edema</td>
<td>5.1%</td>
<td>8.2%</td>
</tr>
<tr>
<td>SRF/EDS</td>
<td>0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Retinal vascular changes</td>
<td></td>
<td></td>
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<tr>
<td>RPE/choroidal effusion</td>
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<tr>
<td>Vascularization</td>
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<tr>
<td>No change</td>
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**Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS)**

- This Phase 3b, 24-months study: randomized, double-masked and enalbically with active treatment
- Single intravitreal injection: 0.435 mg
- Ocriplasmin versus Sham injection
- Primary Outcome: Proportion of Subjects With Pharmacological VMA/VMT Resolution at Day 28
- Secondary Outcome: Proportion of Subjects With a 3 Line Improvement in BCVA at Baseline at Month 24

**OASIS confirms ocriplasmin efficacy for treatment of VMT, VMA patients**

- Primary Outcome: VMA/VMT resolution at Day 28 in 41.7% of patients with ocriplasmin compared to 33.3% of control sham (p=0.013)
- Secondary Outcome: Improvement in BCVA at Month 24 (35 lines) in 50.5% patients in ocriplasmin group compared to 35.3% of patients in control sham group
- VMT/VMA resolution rate in ocriplasmin-treated patients
  - Resolution rate by BCVA (D[25]: 35 lines)
  - 70% at 24 months with lower resolution:
    - 26% higher at 24 months with lower resolution
  - 33% higher at 30 months with lower resolution

**Progressive VMT release in response to aflibercept therapy for DME**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>At 1 Month</td>
<td>siP Aflibercept #1</td>
</tr>
<tr>
<td>At 4 Months</td>
<td>siP Aflibercept #2</td>
</tr>
</tbody>
</table>

**At 5 Months**

- siP Aflibercept #3 |

**At 6 Months**

- siP Aflibercept #4 |

**At 7 Months**

- siP Aflibercept #5 |

**At 9 Months**

- siP Aflibercept #6 |

Last Visit
Management Options for VMA/VMT: Conclusions

- Consider observational management for eyes with better VA or patients with complex ocular and/or systemic diseases.
- Vitrectomy offers 100% relief of VMT but has the risks of RD and creation of MH.
- If interventional treatment is considered, Phaco VMT may be the best and most cost-efficient initial treatment.
- Risk/Benefit/Cost for Ocriplasmin must be evaluated for individual patients.

Management Options: References

A Safety And Efficacy Study Of Alg-1001 In Human Subjects With Symptomatic Focal Vitreomacular Adhesion

- Synthetic integrin antagonist ALG-1001 (Luminate, Allegro Ophthalmics).
- Randomized, Double Blind, Safety/Efficacy Study.
- 2.6mg of ALG-1001 versus 0.6mg of BSS.
- Primary Outcome: Release of VMA by OCT at 90 Days.
- Secondary Outcome: -- at 90 days
  1. Non-surgical closure of VMA
  2. BVMA
  3. Need for PV

Management Options: References

Unpublished Results

- At least 100 individuals with VMT with or without MH.
- Followed for 3 months.
- Approximately 65% of patients in the highest dose group achieved release of VMA by OCT at 90 Days.
- ALG-1001 was well tolerated and no safety issues were seen.
- In the study up to 3 monthly injections were allowed.

According to the International Vitreomacular Traction Study Group Classification of vitreomacular adherence, traction, and macular hole, which statement is correct?

1. The C3 classification for staging of macular holes should be followed today.
2. A strict anatomic OCT-based classification system is recommended.
3. Macular pucker, macular pucker, cystoid macular edema, and subretinal fluid were excluded from the classification.
4. Full-thickness macular holes were not subclassified by the presence or absence of VMT.

In a 2013 Meta-Analysis of safety and efficacy of para plana vitrectomy for VMT, which statement is correct?

- The rate of retinal detachment overall was approximately 4%.
- New postoperative cystoid macular edema occurred in greater than 95% of cases.
- Cataract formation in phakic eyes was 90% by 8 months.
- Improved VA of >2 lines occurred in about 90% of cases.
In a recent series of 41 patients undergoing vitrectomy for VMT, which of the following results is correct?

1. The rate of retinal detachment 20%
2. The rate of full-thickness macular hole formation 10%
3. The rate of all line improved NA 50%
4. Intraoperative retinal breaks rate 20%

![Diagram showing results]
PANEL 2:
Vitreoretinal Surgery

MODERATOR:
R.V. PAUL CHAN, MD

Panelists: Donald J. D’Amico, MD, Harry W. Flynn, Jr., MD, Tarek S. Hassan, MD, Mark W. Johnson, MD

SUMMARY

Drs. D’Amico, Flynn, Hassan, and Johnson will discuss their approach to the evaluation and surgical management of various vitreoretinal conditions including complex diabetic retinopathy, retinal detachment, macular pathology, proliferative vitreoretinopathy, uveitis, and pediatric vitreoretinal disease. The discussion will be focused on current surgical techniques and instrumentation.

NOTES

M: (moderator) What type of wide angle viewing system do you use? Do you use contact, or non-contact? 83.7% use noncontact.

M: Visualization... Let’s discuss Heads-Up 3D Surgery. Should we buy this or do you think it’s a gimmick? Is it something that’s going to be a game changer for what we do?

Gimmick: 74%.

P: (panelist) It is good but I’m not doing it yet. It is headed on a collision course with intraoperative OCT. I’m all for its development as long as the learning curve isn’t too steep.

P: Hard to imagine it will be as comfortable and intuitive as what we have now but I’m open to it if it is easy to learn.

P: I have a fair amount of experience with this and it is absolutely not a gimmick. It is for sure the way things will get done depending on how quickly the manufacturers can integrate the technology into platforms that we use on an everyday basis. The learning curve is shockingly fast. Within minutes into the case we were able to transition to its use.

P: Why are we using a big monitor instead of goggles to view the image?

P: Right now as far as the integration of this technology into our general usage, the monitor is easier to understand but probably we will transition to the use of goggles in the future.

P: Has anyone used this for ILM peeling?

P: Yes, and it is no issue, even for my fellows. We have figured out how to play with various modalities on a camera and on our iPhones. Now with this technology we can play with the colors and brightness resulting in sharper images with better illumination. We have been able to lower the illumination on the light pipe substantially without compromising visualization by playing with the gain. Overlays are where we are going to go. They are going to figure out ways how to integrate OCT as well as other sorts of information that will be useful to us during surgery. It will take us to an area where we already are on our cell phones and cameras and now we will have that in the OR.

P: The set up that was developed initially is very simple. You basically utilize the microscope as a stereo camera and you put that to the screen. Then you are looking with polarized glasses that permit stereoscopic viewing. It’s ergonomically superior. Immediately you’re more relaxed and upright. You’re always looking at the screen, even when exchanging instruments.

M: Twin Duty Cycle (TDC) Vitrectomy: Gimmick or Game Changer or I have no idea what this is? 54% have no idea what it is.

M: This brings up the whole question of whether or not there is an advantage to have all these different types of cutters out there? With these new cutters, do they matter?

P: It probably matters what cutter you use but not sure how much clinical relevance it has. All the companies are moving towards outstanding cutting characteristics that maximize flow in a very safe manner. A twin duty cycle, or rather, a twin port device doubles the cutting speed because it cuts both on the upstroke and down stroke of the guillotine. It allows you to cut up in the ranges of 15,000, up to 20,000 cuts per minute at high aspiration rates, which will be very safe. Whether that turns out to result in safer vitrectomies in the long run, I don’t know.

P: I don’t see a lot of advance in vitrectomy. This obsession of going to very high cut rates doesn’t make a whole lot of sense to me because I don’t see it making a big difference when I do surgery given that there are a lot of things going on with the fluidics simultaneously. It’s fun to play with the higher cutting rates but I’m not sure they make the surgery safer or faster.

P: It’s all about maximizing all aspects of the cutting and aspiration interplay. Whether this tangibly results in a difference in detachment rates is unclear but it is hard to argue advances in cutting rates and fluidics aren’t safer in the long run.
P: The last two vitrectomy machines have been all I need. I prefer simplification of the machine and a cheaper price.

M: Vitesse (Hypersonic cutting technology) – Gimmick or game changer or I don’t know what this is? 76.5% don’t know what this is.

P: This is an instrument being developed by Bausch and Lomb that uses something like ultrasound to vibrate the tip at over 1 million cycles per minute thereby liquefying the vitreous right at the port. This effect is called hypersonic liquefaction. In animal studies, I’ve actually touched the retina with the backside of this while removing the vitreous. Because there is no inner shaft moving back and forth then we can make much smaller sized cutters by eliminating the need for an internal lumen. We can put the port anywhere on the end of this cutter, so there are a lot of interesting geometries that we might be able to create. We haven’t used this device in humans yet.

P: No doubt that sometime in the future we won’t have mechanical instruments to remove the vitreous.

M: Intraoperative OCT – Gimmick or game changer? 50%/50%.

P: Now that you can see what’s left behind after ERM peel, what do you do about it? I would tend to observe. Intraoperative OCT gives you lots of information but doesn’t impact whether I go back to do more.

P: I think this is sort of the training wheels for what really is going to be the version that’s useful to all of us. Much like Heads-Up 3D Surgery, we have to use these things and develop them. We don’t know what we don’t know. We may not know how this will be useful in the future.

P: It’s useful to recall where we were initially with OCT. Show us a case where the result would be worse if intraoperative OCT was not used and then we will go forward.

M: When do you use 27 gauge? 74.6% never used.

P: I don’t use it.

P: I’ve used it on diabetic vitreous hemorrhage cases.

P: Best use of 27g is a bad tractional retinal detachment (TRD). You can open up the 27g cutter and use it as a scissor like device (better than an actual scissor). You can get in between layers and desegment quite well.

I actually think it’s not the right gauge personally for me for macular cases. I think the forceps are not great for peeling membranes. They tend to shred the membranes. I love 25-gauge surgery for macular cases. I think it’s the perfect gauge. What you can do is open up a 27-gauge cutter as sort of a stand-alone instrument and use it in the way that Maria Berrocal showed in the video. It’s outstanding as a scissor-like device and to lift membranes as she has shown quite easily. This is, from my perspective, the best thing about a 27-gauge cutter.

P: I prefer 25 g even in very bad TRDs. The stiffness is preferable. I’m still sticking with 25, but I’m open to 27.

P: I believe peripheral work is more difficult with the 27g given its flimsiness, but for work in the posterior pole it is an excellent standalone instrument.

P: I’ve used 27 g to clean an IOL in the bag in cases where there is significant cortical debris left. I think 27g is actually what anterior segment surgeons may need when they do in-the-bag replacement IOLs.

M: How do you peel ERMs?

P: I pinch and peel. I did not like the Tano. My approach to ERMs is pinch, peel, pull it off, stain with ICG and then peel ILM.

P: I do it the same way but I find that the finesse loop is helpful for fellows to identify ILM and give them a comfort zone before they pinch and peel.

M: How do you like to manage dislocated IOLs?

P: I have a close working relationship with some anterior segment surgeons and I remove the dislocated IOL and let them do the rest.

P: We do a lot of scleral fixating IOLs using a technique that’s been described by numerous authors in the past. You use it with a 3-piece IOL. I have nothing against an ACIOL. I think that they’re absolutely fine, but now you can elegantly, scleral fixate IOLs using 27-gauge.

P: The Akreos lens is getting great results in the short term.

M: Do you worry about air emboli during vitrectomy surgery?

P: We know of a couple cases that have been caused by incorrect infusion of air into the suprachoroidal space and then into the vortex veins and finally to the heart causing heart block. To prevent this, reconfirm the placement of the infusion cannula prior to fluid air exchange.
PANEL 2: VITREORETINAL SURGERY

Vitreoretinal Surgery Panel

Panelists:
- Donald J. D’Amico, MD
- Harry W. Flynn Jr., MD
- Tarek S. Hassan, MD
- Mark W. Johnson, MD

Moderator:
- R.V. Paul Chan, MD

Heads-Up 3D Surgery

A. Gimmick
B. Game Changer

SURGICAL INSTRUMENTATION

SURGICAL TECHNIQUES

Twin Duty Cycle (TDC) Vitrectome

A. Gimmick
B. Game Changer
C. I Don’t Know What This Is

What Type of Wide Angle Viewing System Do You Use?

A. Contact
B. Non Contact

Vitesse
(Hypersonic Cutting Technology)

A. Gimmick
B. Game Changer
C. I Don’t Know What This Is
Intraoperative OCT

A. Gimmick
B. Game Changer

What do you need?... Is there any instrument that we currently don’t have that you would want?

When do you use 27gauge?

A. Macular surgery only
B. Most cases
C. I’ve never used 27g

SURGICAL TECHNIQUE

How do you like to peel ERMs?
Cryotherapy for Retinal Breaks During Vitrectomy

A. I never use cryotherapy
B. I occasionally use cryotherapy

CRYO VS LASER FOR RETINAL BREAKS

How do you like to manage dislocated IOLs?
A. ACIOL
B. Sutured IOL (Scleral Fixation)
C. I’ll remove the dislocated IOL but have the anterior segment surgeon place the new IOL
D. Other

How do manage Subretinal Hemorrhage During Surgery?
**PANEL 2: VITREORETINAL SURGERY**

**How do manage ≥ Stage 3B Coats Disease?**

**Case 1** 3 y-o boy  
OS: Stage 4 (Total RD, NVG), LT=38mmHg  
✓ How should we perform surgery?  
✓ Where to place an infusion port?  
✓ How SRF should be drained?

**How do you remove subretinal membranes?**

**Vitreoretinal Surgery and KPros**

**Do you worry about air emboli during vitrectomy surgery?**
PANEL 2: VITREORETINAL SURGERY

Vitreoretinal Surgery Panel

Panelists:
- Donald J. D’Amico, MD
- Harry W. Flynn Jr., MD
- Tarek S. Hassan, MD
- Mark W. Johnson, MD

Moderator:
- R.V. Paul Chan, MD

What Type of Wide Angle Viewing System Do You Use?

- Contact: 16.3%
- Non Contact: 83.7%

Intraoperative OCT

- Gimmick: 48.4%
- Game Changer: 51.6%

Heads-Up 3D Surgery

- Gimmick: 74.0%
- Game Changer: 26.0%

When do you use 27gauge?

- Macular surgery only: 19.0%
- Most cases: 6.3%
- I've never used 27g: 74.6%

Twin Duty Cycle (TDC) Vitrectome

- Gimmick: 21.2%
- Game Changer: 24.2%
- I Don't Know What This Is: 54.5%

How do you like to manage dislocated IOLs?

- ACIOL: 37.3%
- Sutured IOL (Scleral Fixation): 25.4%
- Remove dislocated; Ant. seg. surgeon place new IOL: 22.0%
- Other: 15.3%

Vitesse (Hypersonic Cutting Technology)

- Gimmick: 16.2%
- Game Changer: 7.4%
- I Don't Know What This Is: 76.5%
FOUNDERS LECTURE

Ocriplasmin Retinopathy: Characteristics, Mechanism, Incidence, and Reversibility

MARK W. JOHNSON, MD

SUMMARY

Review of safety data from phase 2 and 3 clinical trials combined with numerous postmarketing reports reveal that ocriplasmin injection may cause substantial acute pan-retinal structural and functional abnormalities in a subset of eyes. The symptoms and signs of acute ocriplasmin retinopathy include varying degrees of the following: acute reduction in visual acuity (sometimes to very low levels), bizarre photopsias (eg. continuous bright curved or kaleidoscopic lines, sparkles, white floaters on a dark background), dyschromatopsia (eg. chromatic tinting, black and white or “negative” vision), nyctalopia, visual field constriction, afferent pupillary defect, anisocoria, retinal vascular attenuation or constriction, disruption/loss of outer retinal signals on spectral domain optical coherence tomography (SD-OCT) imaging, macular hole enlargement, macular detachment, reduced (sometimes flat) ERG responses, autofluorescence abnormalities, and lens subluxation or phacodonesis. Enzymatic degradation of laminin and/or other intraretinal proteins by this nonspecific protease is the mechanism that most plausibly explains the various manifestations of the retinopathy.

Although the incidence of acute retinal dysfunction after ocriplasmin injection is unknown, the best available evidence suggests that some degree of retinopathy occurs in 30 to 50% of eyes. Most of the retinal adverse effects have been shown to be transient or mostly reversible over time, typically within 2-3 months after injection. However, some reports show that visual acuity loss, nyctalopia, ERG changes, ellipsoid zone alterations and/or subretinal fluid may persist in some patients beyond 6 months of follow-up. Ocriplasmin should be used with caution pending further study results about the mechanism, incidence, and reversibility of its harmful effects on the eye.

NOTES

The purpose of this talk is to answer the following 4 questions. What are the structural and functional characteristics of acute ocriplasmin retinopathy? What is the pathogenic mechanism? How often does it occur? What is the time course of extended recovery from the acute injury?

I saw a patient who had an ocriplasmin injection for a small macular hole. Her pre-injection acuity was 20/40. After the injection she reported continuous light (different from the flashes in a PVD) that evolved to having white floaters on a black background. It improved over 3 to 4 days, but she was left with a very distinct yellow tint, impaired color vision, and severe nyctalopia. When she presented to me, the vision was 20/125, and she had an APD. She developed a PVD, so the medication worked. Fundus photographs demonstrated a distinct attenuation of the retinal arteries in the right eye, and the OCT showed severe attenuation and disruption of the outer retinal signals in the right eye.

She had a contracted visual field, and her ERG showed an essentially flat rod response and severe reduction of the photopic response, as well. She underwent a vitrectomy and 3 months after the injection (10 weeks after the vitrectomy), she still complained of severe night blindness. Her acuity had improved to 20/50, but she complained of substantial metamorphopsia. You can see that she has this persistent fluid, which persisted out to 6 months. The ERG at 3 months showed some recovery, more photopic than rod response, but she was left with a significant impairment.

We now know the symptoms and signs of acute ocriplasmin retinopathy based on reports and our own observations. Patients may have visual acuity loss (rarely to as low as LP), photopsias that are not related to PVD, dyschromatopsia, nyctalopia, visual field constriction, afferent pupillary defects or anisocoria, retinal vascular attenuation, and macular hole enlargement. One of the less frequently discussed complications, are macular detachments. These cases show either frank detachments or multiple small blebs without the significant macular detachment as if the retina is trying to separate. The ERG responses are well known. Reduction can be seen, sometimes to the point of being completely flat. Diffuse autofluorescence changes may be present, lasting as long as 5 months after injection with an accompanying APD. We also have cases of zonular dehiscence that are starting to be reported on a delayed basis, despite the reassurance that it would only be in animals.

Toxicology studies in rabbits demonstrated zonular dehiscence starting at doses of 25 micrograms. There is suppression at lower doses, but persisting change after 90 days with the higher doses. It is unlikely that transient increase in VMT is the cause of the issue. It is more likely the actual molecule is causing these effects. Ocriplasmin is a non-specific protease that digests dozens of proteins (including laminin and fibronectin), many of which are found in the vitreous, retina, and zonules. It is a relatively small molecule capable of penetrating all retinal layers, so it’s very likely that enzymatic degradation or cleavage of inter-retinal proteins is responsible...
for the retinal damage. If those proteins then reconstitute, that may explain why some of these changes are reversible over time.

While there are many proteins being digested, there may be a key role for laminin degradation. Laminin is found in the vitreous gel, in the zonules, and multiple retinal layers including the internal limiting membrane, the outer plexiform layer where it localizes the synapses between photoreceptors and the bipolar cells, the external limiting membrane, and the inner photoreceptor matrix. It’s in all the layers required to cause these problems.

In rat eyes, intravitreal ocriplasmin degrades laminin and fibronectin at the vitreoretinal interface and in the outer retina. Laminin is in red in the photo and you can see all of the red from the photoreceptor layer disappear after ocriplasmin injection. If there’s laminin degradation in the outer plexiform layer, where the photoreceptors synapse with the bipolar cells, we would be expect ERG B wave suppression. If it’s degraded in the ELM, we would expect to see loss of the ELM signal on the OCT. Degradation in the inner photoreceptor matrix would cause acuity loss, APD, dyschromatopsia, nyctalopia, field constriction, A wave suppression, decreased retinal adhesion and sub macular fluid. Degradation in the lens zonules would cause a lens subluxation. All of these are the features that we see.

There are intriguing parallels in mice and zebrafish models that are deficient in laminin. It is not clear what relevance these parallels have to mature retinal structures in humans. In the human version of laminin deficiency, the disease is often fatal before we can get a lot of information about the eye pathology. However, we do know that retinal detachment is commonly seen in this syndrome, suggesting a role for laminin in retinal adhesion.

What is the incidence of these problems? The phase 3 studies didn’t employ either ERG or SDOCT. Published reports of consecutive eyes imaged with SDOCT, demonstrate outer retinal signal changes in 30-50% of eyes. The Prospective Oasis Study, which is not yet published, but was presented at the academy meeting found ERG changes in 40% of eyes. In the Oasis Study, ERG changes were found in the non-study eye or sham-injected eye in 5%. Animal toxicology studies suggest that the acute findings were mostly reversible over time, but there was persistence beyond 8 weeks in eyes receiving the dose that we use in humans. Human retinal adverse effects typically resolve, as we know, within 2 to 3 months. Most patients return to baseline visual acuity or better. Even patients with severe vision and field loss have been reported to resolve completely over extended periods of up to 3 years. There is a major concern that some changes persist beyond 6 months. In the Oasis trial, some were still flat at 2 years. In the small study, 11% of patients had changes out to 15 months.

Although many eyes recover from acute ocriplasmin retinopathy with good vision, aggregate visual outcomes, are somewhat disappointing. In the phase 3 clinical trials, the mean change in vision at 6 months did not differ between the placebo and ocriplasmin groups despite the difference in the higher rate of VMT release. In the Oasis study, similarly there was no significant difference in the percentage of visual gainers at 2 years in ocriplasmin versus sham groups. Published studies have shown the mean final visual acuity is typically the same or only modestly better than the pre-treatment acuity.

I think this last point is what goes unnoticed and there are many examples of eyes that have final visual outcomes that are worse than expected for the condition that they’re being treated for, even if the acuity is not decreased from baseline.

**Example 1**: This patient has a small macular hole. After ocriplasmin injection, the subretinal fluid persists for many months and final VA is 20/70. This is worse than we would expect from the closure of a small hole.

**Example 2**: This patient had 20/60 acuity before ocriplasmin. Four days after treatment, the vitreous is separated, but the outer retina is severely affected. Ten days after injection the acuity is 20/70 and after vitrectomy it comes back to 20/60. In the trial this is listed as a patient that did not lose vision. In my opinion, I feel that this patient actually lost vision because they should have had a 20/25 outcome.

**Example 3**: This patient was 20/80 prior to injection and had a massive enlargement of the hole with a decrease in vision to counting fingers. The vision improved to 20/200, which is not significantly reduced than the starting point, but it should have been better.

**Example 4**: This case was shown at the Macula Society meeting last week. The vision was 20/40, worsened to 20/400 and had a massive enlargement of the macular hole. The vision ultimately returns to 20/50 but falls short of what we would expect.

Daniel Ross presented a series of 23 patients with macular hole treated with ocriplasmin. The macular hole was closed pharmacologically in 39% and the mean visual acuity went from a pre-injection acuity of 20/87 to 20/50 post-treatment. It is not a fair comparison, but when you compare this to the outcomes of the large Bascom Palmer series, despite worse mean pre-operative acuity the surgically treated eyes had a much better post-operative acuity. In Dr. Ross’s series, 64% showed
enlargement of the macular hole. There was a significant difference in visual outcomes in those eyes that had enlargement of the macular hole. They essentially did not improve.

It remains unknown why the macular hole worsens in some patients more than others.

Why do we still talk about this? I saw a patient from Canada a couple of weeks ago, who came to the United States because she couldn’t find anyone in Canada to give her the answer that she wanted. She had received ocriplasmin in this eye 3 weeks earlier, had been told that she was a great success. She was bitterly unhappy with her vision. She had nyctalopia, poor color discrimination, and poor contrast. She said that everything she looked at looked like a pointless painting. It was all broken up. While complaining bitterly about her vision problems, doctors were reassuring her and encouraging her to have the injection in the other eye. I quoted Dr. Flynn’s paper and recommended observation, and she felt much better.

In summary, ocriplasmin causes retinopathy that is sometimes undetectable, sometimes mild and reversible, but occasionally it’s severe and at least partially persistent. We are not currently able to predict which patients are susceptible to significant damage. Until we can identify those patients, it will remain a problem.

There are ongoing phase 4 studies that will provide additional safety data. Until then, my view is that ocriplasmin should certainly be used with great caution.

**DISCUSSION**

**Q:** Our group had 1 complication from ocriplasmin, lens subluxation causing a retinal tear. This was seen in the studies prior to FDA approval. Two questions; One, Is this a failure on the FDA’s part to approve this drug? Should this drug still be on the market considering it has a lower number needed to harm than Vioxx?

**A:** The data and safety committee knew that it caused some problems, but they were thought to be transient. The extent of the problem was not appreciated in the absence of ERGs and SDOCTs. They did know about low incidence of lens subluxations and the small percentage of patients with transient vision loss, but they didn’t have the full data set.

**Q/C:** What should be done now? With the emerging data about pneumatic vitreolysis being so successful, ocriplasmin may no longer play a role in the nonsurgical cases. The patients who do well with ocriplasmin can be very happy, but we can’t identify which patients are going to do well.

**Q:** Nice talk. Why don’t these side effects happen 100% of the time?

**A:** We don’t know. In some eyes it affects the vitreous and the retina. In other eyes, it doesn’t seem to affect either structure. I suspect that there might be genetic differences. Maybe a variation in laminin isoform makes us genetically protected or genetically vulnerable.

There is likely more to it than differing injection techniques or different ways in which it’s diluted in the vitreous. Some eyes have more liquefied vitreous than others.

**Q:** I was impressed by your examples that showed a disconnect between OCT and visual outcome. In our natural history course, the ones that actually look the worst are the ones that are most likely to release the traction. Also, patients often have confounding retinal issues that may limit the visual outcome even in the case of a perfect release.

**A:** Any treatment that we choose has a risk of complications. With ocriplasmin, I feel like I’m subjecting people to a risk that I can’t control and don’t fully understand. I can prevent this completely by not using it.

**Q:** Does anybody know about national usage trends of this drug? Do we have any data on that?

**A:** There’s a suggestion that it has decreased.


**Acute Ocriplasmin Retinopathy**

Mark W. Johnson, MD  
*University of Michigan Kellogg Eye Center*

I have no relevant financial interests.

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**Financial Disclosures**

- Member of Data and Safety Monitoring Committee
  - CSX
  - Tygenex
- Research support (clinical trial)
  - Hoffmann-La Roche

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**Ocriplasmin Safety Data**

- Ocriplasmin injection associated with adverse events related to injection procedure and PVD
  - endophthalmitis, retinal tear, RD, and macular hole
- Detailed review of safety data from phase 2 and 3 trials and post-marketing reports clearly show
  - ocriplasmin also causes acute papilloretinal dysfunction in a proportion of eyes
  - especially those that develop PVD

---

**9 Days After Injection**

- VA
  - 20/125 OD
  - 20/25 OS
- Pupils
  - 1 mm anisocoria (smaller pupil on right)
  - RAPID OD
- SLE
  - Weiss ring OD

---

**Acute Ocriplasmin Retinopathy**

**Purpose**

- What are the structural and functional characteristics of acute ocriplasmin retinopathy?
- What is the pathogenic mechanism?
- How often does it occur?
- What is the time course and extent of recovery from the acute injury?
FOUNDERS LECTURE: OCRIPLASMIN RETINOPATHY – JOHNSON

Myopic Traction Maculopathy
Pathogenesis

- Pathoanatomy intuitively suggests gradual stretching or splitting of retina over time
- Likely caused by relative thinness of the inner retina compared with the outer retina in concavity of posterior staphyloma
- Precise cause of traction still debated

MTM Traction Debates
What is the Cause of Inner Retinal Noncompliance?

- Pre-retinal structure?
  - partial PVD with vitreomacular traction
  - remnant cortical vitreous layer after PVD
  - ERM
- Intrinsic retinal element?
  - ELM
  - retinal arterioles

Acute Ocraiplasmin Retinopathy
Symptoms and Signs

- Visual acuity loss (rarely to LP)
- Bizarre photopsias not related to PVD
- Dyschromatopsia/nyctalopia
- Visual field constriction
- Afferent pupillary defect or anisocoria

3 months after injection
(10 weeks after vitrectomy)

- Persistent nyctalopia
- VA = 20/50 with metamorphopsia

121 ASPEN RETINAL DETACHMENT SOCIETY MEETING NOTES 2016
Acute Ocriplasmin Retinopathy
Symptoms and Signs

- Visual acuity loss (rarely to LP)
- Bizarre photopsias not related to PVD
- Dyschromatopsia/mydriasis
- Visual field constriction
- Afferent pupillary defect or anisocoria
- Retinal vascular attenuation
- Macular hole enlargement

Anterior vitreomacular traction
A day after injection

Decreased retinal adhesion

3 weeks after ocriplasmin injection for VMT


Acute Ocriplasmin Retinopathy
Symptoms and Signs

- Visual acuity loss (rarely to LP)
- Bizarre photopsias not related to PVD
- Dyschromatopsia/mydriasis
- Visual field constriction
- Afferent pupillary defect or anisocoria
- Retinal vascular attenuation
- Macular hole enlargement
- Disruption/loss of outer OCT signals
- Macular detachment
- Increased retinal adhesion?
- Reduced (sometimes flat) ERG responses

Acute Ocriplasmin Retinopathy
Symptoms and Signs
- Visual acuity loss (rarely to UP)
- Bizarre photophasia not related to PVD
- Dyschromatopsia/night blindness
- Visual field constriction
- Afferent pupillary defect or aroscoite
- Retinal vascular attenuation
- Disruption/loss of outer OCT signals
- Macular hole enlargement
- Macular detachment
  - decreased retinal adhesion?
- Reduced (sometimes flat) ERG responses
- Diffuse autofluorescence abnormalities (rare)

2+ RAPID 5 months after ocriplasmin
Courtesy AMD Images, MD

Acute Ocriplasmin Retinopathy
Mechanism
- Transient increase in VMT?
  - doesn't explain peritreatment movement
- Neither spontaneous nor surgical PVD causes similar changes
- Ocriplasmin is a nonspecific protease
  - digests dozens of proteins in addition to laminin and fibronectin
  - matrix present in the retina, choroid, and cornea
  - ocriplasmin (27 kDa) has been shown to penetrate all retinal layers
  - hypothesis that enzymatic digestion of interretinal proteins is responsible for retinal damage
- Not surprising that nonspecific enzyme could cause widespread dysfunction throughout retina and other tissues (basically)

Key Role for Laminin Degradation?
- Intraretinal distribution of laminin
  - inner retina, including
    - ILM
    - outer segmental layer
    - synapse between photoreceptor and bipolar cells
    - external limiting membrane
    - interphotoreceptor matrix

In rat eyes, intravitreal microplasmin (28 kDa) degrades laminin (and fibronectin) (Kim, Sh. et al. Curr Eye Res 2009)
  - VR junction
  - outer retina

Intravitreal Ocriplasmin
Toxicology Studies
- Acute, reversible ERG A and B wave suppression (rabbits, monkeys)
  - changes were persistent with higher doses (e.g., 250 µg)
  - attenuation of retinal vessels (rabbits)
  - retinal atrophy (rabbits, doses > 50 µg)
  - pupillary aphoniasia (monkeys)
  - decreased cell density in LNL and ONL (rats)
  - increased retinal permeability to Avastin (rabbits)
  - lens subluxation (rabbits, monkeys)

Laminin Degradation
<table>
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<th>Potential Consequences</th>
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<td>ILM</td>
<td>Vitreoretinal separation</td>
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### Key Role for Laminin Degradation?

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<th>Laminin Degradation</th>
<th>Potential Consequences</th>
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<tbody>
<tr>
<td>ILM</td>
<td>Vitreomacular separation</td>
</tr>
<tr>
<td>Outer plexiform layer (synapse)</td>
<td>ERG B wave suppression</td>
</tr>
<tr>
<td>ELM</td>
<td>Loss of ILM signal on OCT</td>
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<tr>
<td>Photoreceptor cell layer/PM</td>
<td>VA loss and ARD</td>
</tr>
<tr>
<td></td>
<td>Dyschiria/microphthalmia/microcornea/PN-VN</td>
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<tr>
<td></td>
<td>Visual field constriction</td>
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<tr>
<td></td>
<td>ERG A wave suppression</td>
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<tr>
<td></td>
<td>Loss of outer OCT bands</td>
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<td></td>
<td>Submucosal fluid/decreased retinal adhesion</td>
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### Laminin Deficiency

#### Animal Models
- Laminin 62-deficient mice
  - shortened ciliary processes
  - decreased ERG B waves
- Laminin deficiency in zebrin
  - reduced A- and B-waves on ERG
  - outer segment changes and dysmorphic PR-bipolar synapses
- Although intriguing, the relevance of these findings to acute ocriplasmin effects on mature retinal structures is unknown.

#### Human Laminin Deficiency

##### Pierson Syndrome
- Mutations in laminin 82 gene
- Congenital nephrotic syndrome
  - typically fatal before age 4
- Range of ocular abnormalities
  - small pupils
  - lens and corneal abnormalities
  - persistent fetal vasculature
  - retinal detachment common (with or without PPV)
- *Important for retinal adhesion?*

### Acute Ocriplasmin Retinopathy

- Incidence of retinal toxic effects unknown
  - phase 3 studies did not employ ERG or OCT
  - post-marketing voluntary reporting inherently flawed
- Published reports of consecutive cases mapped with SD-OCT show loss of outer retinal signals in 30-50% of eyes
  - typically accompanied by acute reduction in VA
- ERG changes
  - single center phase 2 study: 58% of eyes
  - single center retrospective study (6/12): 35% of eyes
  - prospective OASIS study: 40% of eyes

---

OASIS: Proportion of Subjects in Substudy With ERG Changes

[Courtesy: Joe Noiseff]
FOUNDAERS LECTURE: OCRIPLASMIN RETINOPATHY – JOHNSON

Acute Ocriplasmin Retinopathy
Reversibility

- Animal toxicology studies
  - acute findings showed reversibility over time
  - persistence beyond 8 weeks was demonstrated in eyes resolving 125 μg or greater
- Human retinal adverse effects typically resolve within 2-3 months
  - most patients return to baseline VA or better
  - even patients with severe VA and field loss have been reported to resolve completely over extended periods of 4 to 8 months
- VA loss, mydriasis, PRL, and OCT and ERG changes have all been documented to persist beyond 6 months
  - preventing safety data in humans; adverse effects remained unresolved in 5 eyes in 11 to 40% of eyes
- OASIS trial: 7.5% of eyes had persistent EGR suppression at 2 years
- Small: 11% of eyes had persistent ENG changes out to 15 months

OASIS: Resolution of ERG Changes

- Median time to resolution of ERG changes was 6 months
- 94% of eyes with ERG changes maintained or gained vision
- 7.5% of subjects in the ocriplasmin group had persistent ENG changes at 2 years

Acute Ocriplasmin Retinopathy
Visual Outcomes

- Although many eyes recover from acute ocriplasmin retinopathy with good vision, aggregate visual outcomes are disappointing
  - Phase 3 clinical trials indicate change in visual acuity after 6 months did not differ between placebo and ocriplasmin groups, despite difference in VMT release and time to injection
  - OASIS study: no significant difference in percentage of visual gains at 2 years in ocriplasmin versus sham groups
  - Published retrospective analysis: mean final VA typically worse than or only modestly better than mean pre-treatment VA
- Anecdotal and published examples of individual eyes with permanent visual loss

Improvement in BCVA (≥2 Lines) at Month 24 irrespective of initial Ocriplasmin Success

- Improvement in BCVA (≥2 Lines) at Month 24 irrespective of initial Ocriplasmin Success

PREVIOUS TALK  TABLE OF CONTENTS  NEXT TALK
Ocriplasmin for Macular Hole (n=23)

- MH closed pharmacologically
  - 90% of eyes (21/23)
- Mean VA (all 23 eyes)
  - Pre-injection: 20/17
  - Final post-treatment (including subsequent VA): 20/53
  - n = 74 idiopathic MHs (median post-injection follow-up 26.5 months)
  - Mean post-op: 20/123
  - Mean pre-op: 20/76


table

<table>
<thead>
<tr>
<th></th>
<th>No MH Enlargement</th>
<th>MH Enlargement</th>
<th>P value</th>
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<tr>
<td>Pre-injection</td>
<td>22/85</td>
<td>20/12</td>
<td>0.555</td>
</tr>
<tr>
<td>Last follow-up</td>
<td>20/35</td>
<td>20/11</td>
<td>0.003</td>
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Acute Ocriplasmin Retinopathy

- Ocriplasmin causes retinopathy
  - Sometimes undetectable
  - Sometimes mild and reversible
  - Occasionally severe and at least partially persistent
  - Not currently possible to predict which patients susceptible to significant damage
  - Enzymatic agent
  - Ongoing phase 4 studies and basic research should yield additional safety data
  - For now, ocriplasmin should be used with caution

Intravitreal ocriplasmin causes detectable retinal adverse effects in approximately what percentage of eyes?

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<th>4</th>
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<tbody>
<tr>
<td>1</td>
<td>1.2%</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>10.15%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40.56%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>50-100%</td>
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Which of the following is the most likely pathogenic mechanism for acute ocriplasmin retinopathy?

1. Transient increase in vitromacular traction during vitreous separation
2. Enzymatic degradation of macular proteins, such as laminin
3. Nonspecific toxic effect of the enzyme on its vehicle

Why are we still talking about ocriplasmin?

54-year-old woman

3 weeks after “successful” ocriplasmin injection for MH.

VA = 20/40. Happy, without symptoms. Quality of vision (fog, floaters, photopsia, poor contrast, etc.)

Strangely pressured to have ocriplasmin injection in fellow eye.

VA = 20/20 with minimal metamorphopsia.
All manifestations of acute ocriplasmin retinopathy are transient and resolve completely within 2-3 months.

1. True
2. False
Different Preferences between US and European Vitreoretinal Surgeons

DONALD J. D’AMICO, MD

SUMMARY
Surgical disciplines are enriched by the wide diversity of techniques employed by surgeons in their particular surgical environments. A surgeon’s preferences for given maneuvers and approaches are influenced by many factors including personal experience, influence of mentors, advances in technology and disease understanding, prevailing preferences of close colleagues in the practice environment, differential reimbursement incentives, instrument costs, personal attitude (conservative versus eager) toward trying new approaches, and bias, to name but a few. This presentation offers the author’s personal observations on different preferences in surgical technique and surgical setting between vitreoretinal specialists in the United States and Europe. These impressions, though clearly subjective, derive from the author’s extensive experience with, and connection to, many vitreoretinal centers and surgeons around the world in a wide variety of venues.

While the results of surgery and the availability of information and instrumentation are quite comparable on both sides, vitreoretinal surgeons in the US are more likely to 1) use local anesthesia, 2) an outpatient setting, 3) perform phakic vitrectomy, 4) use gas as opposed to oil as a tamponade, 5) use pneumatic retinopexy for certain cases, 6) place an anterior chamber lens for secondary implantation, and 7) perform intravitreal injections in the office or exam room. European colleagues more commonly 1) perform combined phacoemulsification with intraocular lens implantation at the time of vitrectomy, 2) use perfluorochemicals during retinal detachment surgery, and 3) utilize heavy silicone oils. These observations suggest that many factors, both medical and non-medical, influence vitreoretinal surgeons and result in differing preferences for surgical techniques and surgical setting.

NOTES
Retina surgery practitioners are influenced by medical and nonmedical factors such as: personal experience, mentors, advances in technology and disease understanding, prevailing preferences of close colleagues in the practice environment, different reimbursement incentives, instrument and supply costs, and personal attitude, i.e. conservative versus eager in trying new approaches and new technologies. Practicing style differences are more pronounced in large areas with common cultures, such as the United States and Europe. Although outcomes are comparable in the two regions, surgical techniques and approaches may vary significantly. Analyzing and sharing these differences without prejudgment or bias, may lead to a better perspective on the field of vitreoretinal surgery. The speaker describes many of these differences, in a lively manner, from a personal perspective, derived from extensive exposure to the best vitreoretinal surgeons on both continents. Following a suggestive metaphor the speaker concludes that there are “different ways we all arrive to a perfect peanut butter and jelly sandwich”.

Personal experience vs. mentoring
Personal experience is the most important factor in professional development, and it derives in a large part from education. While mentoring, as a component of vitreoretinal surgery education, is important in the US, it is much more defining for European surgeons. As the speaker states: “Your mentors are enormous and in some cultures your mentors are so big that even if your personal experience tells you otherwise, it would be considered disrespectful to do otherwise.”

Personal attitude, generally derived from experience, has a greater role than generally expected. While some surgeons are more comfortable following the guidelines approved by the academy, acquired through education, or from their mentors, others tend to “push the envelope” in an attempt to adapt to particular circumstances and innovate.

General vs. local anesthesia
The use of general anesthesia in ophthalmic surgery is much more common in Europe than in the United States where nonpediatric general anesthesia is reserved for a very small minority of vitreoretinal cases. Even in Britain, where it has declined in the last decade, general anesthesia is still approaching 45 to 50% prevalence. As a consequence of using general anesthesia in vitreoretinal surgery, the inpatient hospitalization rate is significantly larger in Europe than in the US. The difference is also in part caused by particularities of reimbursement.

Use of chandeliers for illumination
In the United States, surgeons are not typically chandelier surgeons. Although available for many years, chandeliers or light cannulas, are sparsely used in the United States, but are frequently, even routinely used in
many European centers. The most relevant advantage of chandeliers is the ability to free the second hand for bimanual maneuvers, but among the disadvantages are glare, shadowing, the need for repositioning, the creation of additional wounds, and cost. In Europe, a 27-gauge twin-light system has gained wide popularity.

**Tamponade Preferences**

Silicone oil is definitely more commonly used in Europe than in the US. In Europe it is used in cases that probably in the US wouldn’t use any tamponade, but European surgeons have no problem with putting oil in. The preference for use of silicone oil in Europe vs. long-acting gases in the US, is mostly historic. Europeans developed oils, while Americans developed gases. In the last decades the best silicone oils for ophthalmic use were found in Europe, even for American surgeons who were eager to utilize oil for complex cases. On the other hand, sulfur hexafluoride and perfluoropropane gases were acquired in most cases from the United States’ industrial gas suppliers by retina surgeons around the world. The difficulty of acquiring gases in Europe and high-silicone oil in the US, combined with the timing of FDA approval, contributed to the current difference between the two sides of the Atlantic.

Another tamponade preference relates to the use of 1000 versus 5000 centistoke silicone oil when oil is used. American surgeons use 1000 more often, whereas European surgeons prefer almost exclusively 5000 centistoke silicone oil. Although studies have not shown clear differences in emulsification rates or other features, there is a prevalent claim that 5000 centistoke silicone oil emulsifies more slowly.

Europeans use, and seem fascinated by, some very unusual tamponade substances. Materials that have been experimentally investigated include a number of modified natural hydrogels, partially fluorinated silicone oils, and organic molecules. Intravitreal injections in Europe are also done in the operating room, often without a speculum, which is in stark contrast to what happens in the US. (See below).

**Perfluorochemical (PFO) use in vitreoretinal surgery**

PFO is used much more often in Europe for macular stabilization. In the US we often peel PVR under fluid, a technique unheard of in Europe. In Europe they put brilliant blue on the PVR then they put PFO in and that pushes the brilliant blue onto the premacular retina and then they peel ERM out to the periphery. It’s an astonishing technique and several surgeons are experts. The use of colorant plus expression peripherally of the colorant with peeling allow for a pristine retina and PVR, much cleaner than by doing just a native peel.

The introduction of PFO was a relevant development in vitreoretinal surgery. Its usage include: the mobilization of giant retinal tears, upward expression of subretinal fluid through a peripheral retinal break, elevating dislocated intraocular lenses (IOLs). Despite the great utility of these substances, problems with the subretinal, and typically, subfoveal migration of droplets with reduced postoperative visual acuity, and cost, prompted many surgeons to reconsider their use of PFO and to restrict it to cases in which its use was more unarguably necessary.

In Europe, vitrectomy for retinal detachment repair typically involves the early introduction of a small amount of PFO for effective ‘macular stabilization’ and the case then proceeds with increasing membrane removal and reattachment toward the periphery. In the US more surgeons perform the membrane dissection in proliferative vitreoretinopathy cases in a fluid filled eye and use PFO more sparingly, although many utilize the identical technique as in Europe. Despite these differences in use and surgical preferences, it appears that the development of valved cannulas which minimize intraocular turbulence, and the greater appreciation of subretinal PFO migration, have reduced the subretinal migration associated with intraocular PFOs.

**Pneumatic Retinopexy vs. Scleral Bucking**

The introduction of Pneumatic Retinopexy in 1986 was conceptually a breakthrough in retinal reattachment, but since then, triggered some contentious discussions by retinal surgeons. In general European retina surgeons don’t like pneumatics, and favor scleral buckling more so than their American counterparts.

Studies suggest that the procedures have equivalent outcomes. Pneumatic retinopexy may be more difficult to accept because of a relative lower rate of initial reattachment success but is a greatly simplified procedure. In the United States, approximately one quarter of surgeons perform pneumatic retinopexy regularly and perhaps another quarter do it occasionally. In contrast, very few European surgeons perform pneumatic retinopexy on a regular basis.

**Secondary IOL implantation techniques**

Phacoemulsification with IOL implantation at the time of vitrectomy is much more common in Europe than in the United States, but there is also a difference in the approach to secondary IOL implantation in an aphakic eye. In Europe, vitreoretinal surgeons will overwhelmingly utilize the Artisan ‘iris claw’ lens for secondary implantation. This implant attaches to the iris, and is easily implanted with excellent visual results. Secondary Artisan “Iris Claw” lens implantation is essentially

---

**DIFFERENCES BETWEEN US AND EUROPEAN SURGEONS – D’AMICO**

**PREVIOUS TALK**

**NEXT TALK**

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routine in many European centers. Almost every European surgeon, when doing a secondary IOL implant, adds “iris claw” lens. Since use of the Artisan lens is not yet approved in the United States, surgeons have previously utilized anterior chamber IOLs, although a minority prefer sutured posterior chamber IOLs. Currently in the U.S., FDA studies are ongoing and this should be available to all of us in the next few months.

Intravitreal injections

Intravitreal injections for the treatment of age related macular degeneration, diabetic macular edema, retinal vascular occlusion, and many other disorders have become one of the most commonly performed procedures in ophthalmology today. In the United States, the majority of retinal specialists perform these injections in the office within the daily flow of patients whereas a small minority schedule a dedicated injection clinic. In Europe, by contrast, intravitreal injections are done in the operating room (OR). This represents a significant difference in the use of medical resources. Although it would make economic sense for Europeans to perform this procedure in office, there are non-medical reasons to keep it in the OR, such as: healthcare regulation and practices, patient expectations, and even pressure from the hospitals to increase utilization.

Most the retina professionals expect to perform fewer injections in the future, as longer acting agents become available, and as some of the injections may be transferred to ancillary personnel.
Differences Between Us and European Surgeons – D’Amico

PB and J: Steps Involved in Making
- Retrieve PB and J from their storage places
- Set out the bread
- Get butter knife and perhaps a spoon
- Get a plate
- Set bread on plate
- Open PB and J containers
- Apply PB and J to bread
- Close PB and J containers
- Cut sandwich (crusts)
- Restore PB, J, and perhaps bread to storage places
- Place silverware in sink or dishwasher

I am certain we would all do this in a different way, and also that everyone will arrive at a fine PB and J sandwich on a plate!

And Does Anyone in the Room Doubt That Performing VR Surgery Is Far More Complicated Than Making a PB and J Sandwich?

Influences on a Surgeon’s Preferences for Different Surgical Maneuvers and Operations
- Personal experience
- Mentors
- Advances in technology and disease understanding
- Prevailing preferences of close colleagues in the practice environment
- Differential reimbursement incentives
- Instrument and supply costs
- Personal attitude, i.e. conservative versus eager in trying new approaches and new technologies
- Bias
- And many more...

Combined Phaco-Vitrectomy is Essentially Routine in Many European Centers

General Anesthesia for VR Surgery Is More Common In Europe

Light Cannulas Are More Commonly Used in Europe

Claus Eckardt’s Frankfurt Retina Meeting

Ramin Tadayoni, MD
Grazia Pertile, MD
DIFFERENCES BETWEEN US AND EUROPEAN SURGEONS – D’AMICO

Secondary Artisan® “Iris Claw” Lens Implantation is Essentially Routine in Many European Centers

Silicone Oil is Still More Commonly Used in Europe Compared to Gases

PFO is Used Much More Often in Europe

In General, Europeans Don’t Like Pneumatics, and Favor Scleral Buckling More Than We Do

And With Silicone Oil, 5,000 Centistoke Is More Commonly Used Over 3,000

Europeans Frequently Have Much Higher Case Volumes Than We Do, and They Are Freer To Innovate in Surgical Techniques

In Europe They Use (Inexplicably to Me) Silicone Oil in Phakic Eyes

Europeans Prefer Multifunctional Consoles (i.e. Phaco and Vitrectomy-enabled) More Than We Do
DIFFERENCES BETWEEN US AND EUROPEAN SURGEONS – D’AMICO

Europeans Use, and Seem Fascinated By, Some Very Unusual Tamponade Substances

Materials that have been experimentally investigated include a number of modified natural hydrogels, partially fluorinated silicone oils, and organic molecules. Included in this list are: polyethylene glycol perfluoropolyether, perfluoropolyether, polyethylene glycol, polysiloxanes, polyethylene glycol, fluoroalkylsiloxane, and organosiloxanes. These tamponade substances have been studied for their potential to maintain retinal detachment during and after surgery.

An Intravitreal Injection at 1305 York Avenue

New York-Presbyterian Department of Ophthalmology

Differences in Trends and Techniques in VR Surgery Between Europe and the USA

Thank You! and (Vive la différence)

The 44th Aspen Retinal Detachment Society
The Viceroy, Snowmass CO  March 8, 2016

These items are ALL FALSE EXCEPT:
1. US surgeons more commonly combine phase with vitrectomy.
2. In the US, an AC IOL is preferred for secondary implantation while in Europe, a subretinal IOL is most commonly used.
3. All surgical choices are the result of many factors and influences which vary widely across individuals and locations.
4. Iris claw lenses give poor results and should never be used.

Which statement accurately summarizes the state of chandelier use in Europe and the US?
1. Chandeliers are more frequently used in Europe due to the fact that the eye is typically rendered pseudophakic at vitrectomy.
2. There is no obvious reason to explain those differences aside from the influence of prevalent lumenances and membrane by region.
3. Chandeliers are useless and their use adds costs and wastes time.
4. US surgeons tend to have better microscopes and higher illuminated video cameras, and so they don’t need chandeliers.

Silicone oil and PFO tend to be more widely used than gas in Europe because:
1. They are cheaper and more easily stored by many smaller centers.
2. They give better results for retinal reattachment.
3. The Silicone Study is no longer relevant since PFO was introduced.
4. There is a strong culture of preferred and liberal use of these substances by many prominent European surgeons and their trainees.
Changing the Rules in the Management of Pediatric Retina Disease

R.V. PAUL CHAN, MD

SUMMARY
The management of pediatric retinal disease has been evolving rapidly with significant advances in imaging and surgical technology over the past ten years. Although we have historically based our diagnostic and treatment decisions almost exclusively through the findings seen on examination by indirect ophthalmoscopy, the advent of imaging systems that are able to better accommodate children has improved our medical and surgical management of pediatric retinal conditions. Both non-contact ultra-widefield retinal imaging with the Optos 200Tx or California (OPTOS, Marlborough, MA) and contact imaging systems, such as the RetCam (Clarity Medical Systems, Pleasanton, CA) and PanoCam (Visunex Medical Systems, Fremont, CA), have made it possible to better evaluate peripheral retinal pathology in the pediatric population both in the outpatient and hospital setting.

With these advances we are now provided with new information that will enable us to rethink our previous management algorithms for pediatric retina. We have recently shown that fluorescein angiography and mosaic imaging may affect how pediatric retina experts diagnose and manage retinopathy of prematurity (ROP). Imaging has also influenced our classification of disease, and therefore potentially providing prognostic markers for familial exudative vitreoretinopathy (FEVR) and other pediatric vitreoretinopathies. Current advances in surgical and medical technology also make it necessary for us to reevaluate our surgical decision making for children.

The changing trends for managing pediatric retina patients will be discussed with an emphasis on the role of ultra-widefield imaging, fluorescein angiography, optical coherence tomography, computer-facilitated image analysis, and MIVS.

NOTES
Previous management of pediatric vitreoretinopathies and retinopathy of prematurity:
The classification of children with retinopathy of prematurity has historically been guided by the International Classification of Retinopathy of Prematurity (ICROP). Our diagnosis has been based on indirect ophthalmoscopy and previously this field has had limited access to ancillary imaging and limited options for surgical instrumentation. Our management strategies are mostly based on the findings from the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study and the Early Treatment for Retinopathy of Prematurity (ETROP) study. They CRYO-ROP study was a prospective, multi-center study that provided natural history data and was a good foundation for future studies. However, a lot has changed, since these studies, that has impacted our care for children with ROP and other pediatric retinal conditions. Some factors impacting the management of pediatric retinal disease include: imaging, redefining treatment algorithms, surgical innovation, and new imaging platforms which make it possible to have computer facilitated image analysis, telemedicine, and tele-education.

Imaging:
How does the imaging affect what we do? How do we incorporate it into our patient care?

We have over 40 years of documented experience with ROP using fluorescein angiography (FA) and a number of studies have shown various FA findings in ROP. However, most, if not all of these studies have been descriptive and there is still no consensus on what to do with this information. Therefore, we decided to perform a study to determine how FA affects the diagnosis and management of ROP by experts. In this study, experts were asked to indicate their diagnosis and management of ROP based on color photographs alone then with the color photograph and corresponding fluorescein angiogram. Our results showed that about half of the time when experts were shown the FA, they changed their diagnosis in about 50% of cases and often changed their diagnosis to more severe disease.

In addition, they changed their management about 25% of the time after being shown the FA. Diagnostic accuracy for stage 3 disease also improved with the addition of the FA. Therefore, it does seem that FA changes diagnostic and management decisions made by experts. This has implications for a number of things, e.g. should FA be integrated into telemedicine platforms to provide information that may be necessary to make an accurate diagnosis. I think in the future, we’ll need to have consensus agreement on the FA findings for ROP and other pediatric retinal conditions. And it is possible that imaging modalities such as FA and OCT may become relevant in our classification system for ROP. Also, as we are starting to see increased use of anti-VEGF therapy for ROP, the use of FA may become more critical in our management of these patients.
Another question we had was how do post image processing techniques such as creating mosaic photographs affect ROP diagnosis and management?

In this study we found that experts more accurately diagnosed certain categories of ROP when looking at a single mosaic photograph compared to diagnosis by individual fundus photographs.

**Case 1:** Demonstrates how imaging may impact diagnosis. RetCam fundus photographs of a patient who could be mistaken for aggressive posterior ROP (APROP). However, the more likely diagnosis is familial exudative vitreoretinopathy (FEVR). Widefield imaging techniques have also helped us better categorize FEVR and is helping define specific peripheral changes that are characteristic of this condition. OCT has also been useful in demonstrating vitreoretinal interface changes in FEVR. All of these imaging modalities are becoming more accessible and are giving us new information to better manage our patients.

**Redefining treatment algorithms:**
Who treats ROP outside of Type 1 ROP?

We looked at a large database from the i-ROP study group for reasons that babies with ROP were treated outside the usual treatment criteria. We found that children were treated with less than type 1 ROP in cases of vitreous hemorrhage, vitreoretinal traction, and temporal vessel straightening suggesting progression. About 10% of treated eyes in this study were treated for disease less than Type 1. Regarding FEVR, findings suggest that if the FA shows leakage then laser to the ischemic area should be considered. Ultra-widefield fluorescein angiography has helped define treatment guidelines for FEVR and this is another example of how treatment algorithms are changing based on imaging. Genetic testing is another issue that may impact our treatment in the future.

**Surgical innovation:**
We now have more instrumentation at our disposal for the surgical management of pediatric retinal conditions. 25 gauge+ short for ROP surgery can be helpful and the 27-gauge may allow for more predictable sutureless vitrectomy in addition to decreasing postoperative morbidity.

Although pharmacologic vitreolysis is promising, in a recent study there was no significant difference between placebo and 175 ug ocriplasmin in the production of a PVD. However, the authors of this study noted that induction of the PVD during surgery seemed to be easier in the ocriplasmin group.

Immediate sequential bilateral vitreoretinal surgery in pediatric patients can be done safely with good results and anatomic success.

**New imaging devices and techniques:**
Less expensive and integrated systems with FA, OCT, OCTA, and photos will be the future for pediatric retinal imaging. We have are starting to see new systems that are more affordable such as the FORUS system. And we also have smaller, more mobile devices such as the Visunex system. The Panocam by Visunex has a mobile handheld camera that you can take to the NICU independent of the base station and upload images to a cloud based system. The Panocam Pro will likely be available in the next year and will have FA, OCT, and fundus photography all in one unit.

Image analysis programs such as i-ROP will also be useful for disease detection and telemedicine. We’ve also created tele-education systems which have the potential to be used for training and telemedicine certification. The GEN-ROP system is an example of a digital imaging platform that can be used for tele-education.

**Take home points:**
I think we may be going back to the future since the concept of using FA and imaging for pediatric retina was introduced decades ago. What makes the current era of pediatric retina so exciting is that we have new technologies that make pediatric retinal imaging and surgery more feasible. We are now being given valuable information that we never had before and it’s important to figure out how to apply all that we’ve learned from this. We need to rethink our classification and our management of pediatric retinal diseases. We need to integrate all of these imaging devices into our practice and treatment algorithms in order to create guidelines and interventions to improve outcomes in the children we care for.

**DISCUSSION:**

**Q:** If you see a child with a complicated retinal pathology how do you approach it and what do you do?

**A:** We are fortunate to have a very good pediatric ophthalmologist who does all the screening. Do you think pediatric ophthalmologists should be doing all of the screening?

**A:** I think pediatric ophthalmologists want to screen but we also have to keep in mind that ROP is a retinal disease. ROP screening can be a source of income and hospital systems will want to pay for ROP coverage. Very often the retinal surgeons aren’t doing the screening and only called to perform surgery or laser. However, it’s
important to communicate with whoever is screening to refer patients early so not to miss advanced disease that can’t be managed appropriately.

Q: Do you use sustained delivery devices in children?
A: I usually do not. Even though this may be useful since children have a robust inflammatory response, children may also have an exaggerated pressure rise as a result of steroids. So glaucoma may become a problem.

Q: Do you think standard of care is clinical exam or imaging at bedside?
A: Having a camera to image children with ROP is incredibly useful. There is enough data out there to show that imaging is accurate and reliable. Clinical exams are not perfect and imaging is not perfect. Hospitals may be worried about the medico-legal aspects of acquiring images and storing them in the medical record. However, we do know that experts will disagree with each other on things like plus disease diagnosis and other features of ROP. Therefore, in my opinion, it’s important to be able to have the ability to do both imaging and exam by indirect ophthalmoscopy. Imaging and exam by indirect ophthalmoscopy are synergistic.

Q: What’s most interesting to me is the advent of pharmacotherapy for management. The paradigm shift is not just the imaging. It’s really the application of new treatment modalities and we’ve been far behind the curve nationally compared to our international colleagues in terms of suggesting ways to better evaluate the application of anti-VEGF or steroid therapy, but to me, this is a way that you can integrate both the imaging capabilities and the treatment options available in a fairly unique way.
A: If you’re doing anti-VEGF therapy for ROP you should have an FA.
Changing the Rules in the Management of Pediatric Retinal Disease

1. Imaging
2. Rethinking Treatment Algorithms
3. Surgical Innovation
4. New Imaging Devices, Computer Facilitated Image Analysis, Telemedicine, and Tele-Education

Rationale for Using FA for ROP

- Over 40 years of documented experience for ROP
- Potential Implications for:
  - Telemedicine Diagnosis
  - When to use anti-VEGF therapy
  - Monitoring Normal Vascular Development
  - Monitoring for "Reactivation"

Methods

- Subjects asked to indicate their diagnosis and management:
  - Zone (0, I, II)
  - Stage (1-5)
  - Plus/Pro-Plus/No Plus
  - Category (Treatment Requiring, Type A, B, None)
  - APROP

Diagnostic and Management Choices When Using FA

- Diagnosis when the consensus reference standard diagnosis was:
  - type 2 ROP
  - ROP requiring treatment
  - stage 3 disease
  - stage 2 disease
  - zone 1 ROP

- After viewing the corresponding fluorescein angiograms to each set of color fundus images, participants altered their choice of CATEGORY in 64 of 144 responses (45%)

Diagnostic and Management Choices When Using FA

<table>
<thead>
<tr>
<th>Stage</th>
<th>&quot;Plus&quot;</th>
<th>&quot;Pro-Plus/No Plus&quot;</th>
<th>&quot;Category&quot;</th>
<th>&quot;APROP&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40%</td>
<td>30%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>40%</td>
<td>30%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>40%</td>
<td>30%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>0%</td>
<td>10%</td>
<td>0%</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>0%</td>
<td>10%</td>
<td>0%</td>
<td>90%</td>
</tr>
</tbody>
</table>
Accuracy of ROP Diagnosis When Using FA

Intergrader Agreement Using FA
- Mean unweighted k statistics for each reader as compared to all other readers
- Possible clinically relevant improvement in agreement with Zone
- Statistically significant improvement in agreement of Treatment-Required ROP

Fluorescein Angiography for the Diagnosis and Management of ROP
Key Findings:
1. Improvement in accuracy of diagnosis for stage 2 or worse; stage 3 or worse; pre plus or worse, and type-2 ROP or worse.
2. Improvement in intergrader agreement for diagnosis of treatment-Required ROP.
3. Automated programs to assist in identification of Zone of ROP may be useful.

Mosaic Photography for the Diagnosis and Management of ROP
Key Findings:
1. More accurate diagnosis of clinically-significant ROP
   - Better disease and treatment (requiring ROP)
2. Improved intergrader agreement for diagnosis of clinically-significant ROP
   - More disease; stage 3 or worse.
3. No significant effect on the diagnosis of Zone

Do Mosaic Photographs Change ROP Diagnosis and Management?

Case
Ex 29 5/7 week baby born weighing 1680 grams now at 36 weeks
What's the most likely diagnosis?

1. Coats Disease
2. Aggressive Posterior ROP (APROP)
3. Familial Exudative Vitreoretinopathy
4. Oxygen Induced Retinopathy
5. Nonaccidental Head Trauma

Fluorescein Angiography and FEVR (1976)

Macular Edema and FEVR (1983)

Larger Clinical Studies: Staging System
Changing the Rules in the Management of Pediatric Retinal Disease

1. Imaging
2. Redefining Treatment Algorithms
3. Surgical Innovation
4. New Imaging Devices, Computer Facilitated Image Analysis, Telemedicine, and Tele-Education

Retinopathy of Prematurity Consensus Treatment Guidelines
- Based on the Early Treatment for Retinopathy of Prematurity (ET-ROP) study, a 2013 consensus policy statement endorsed by the American Academy of Pediatrics, American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology and Strabismus recommended treatment for Type 1 or worse ROP.

Characterizing the Frequency of and Indications for Treatment of ROP Milder than Type 1 ROP
- Retrospective review of charts and imaging from a multicenter, prospectively generated database of all infants screened for ROP at 6 major ROP centers

Implications
- In addition to peripheral staging, macular pathology seen on SD-OCT is visually significant
- Treat: CME, hyaloidal traction
- Prevent: EZ disruption
- Early detection of findings prompts widefield angiography
- Can assist in surgical planning

Indications for Treatment of ROP Milder than Type 1 ROP

<table>
<thead>
<tr>
<th>Indications for treatment of ROP milder than Type 1 ROP</th>
<th>Number of Eyes (n=100) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logistic/vegetative changes: active ROP with fellow eye being treated for Type 1 ROP</td>
<td>2 (15.0%)</td>
</tr>
<tr>
<td>Structural changes and concern for future anatomic complications: tangential traction with temporal vessel kinking</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>Structural changes and concern for future anatomic complications: steep stage 3 membranes with anterior/posterior traction</td>
<td>5 (50.0%)</td>
</tr>
<tr>
<td>Diagnose prior:臺: 未治療</td>
<td>4 (32.0%)</td>
</tr>
<tr>
<td>Persistent active ROP at an advanced postnatal age</td>
<td>3 (29.1%)</td>
</tr>
</tbody>
</table>

* Some eyes were treated for more than 1 indication
Example: Tangential Traction with Temporal Vessel Straightening

- Born 27 weeks, 950 grams
- Zone III, stage 2, plus OU with temporal vascular straightening
- Given concern for macular dragging and macular edema, treated OU with laser.

Example: Thick Stage 3 Membrane with Anteroposterior Traction AND Vitreous Hemorrhage

- Born 26 weeks, 950 grams
- Zone I, stage 3, plus OU with
  1. Vitreous and preretinal hemorrhage OS
  2. Thick stage 3 retinovascular membrane causing anteroposterior traction OS
- Given concern for anteroposterior traction causing progression to Stage 4 ROP and concern for further vitreous hemorrhage limiting diagnosable and ability to laser, treated with laser OS.

Practice Patterns in Retinopathy of Prematurity: Treatment for Disease Milder Than Recommended by Guidelines

1. In 9.5% of treated eyes in this study, experts recommended treatment for disease less than Type 1 ROP.
2. Reasons for Treatment outside of Type 1
   - Clinical and systemic; systemic intervention; retinopathy of prematurity
   - Indications for treatment outside of Type 1 ROP (in the future)
   - Indications for treatment outside of Type 1 ROP (in the future)
   - Indications for treatment outside of Type 1 ROP (in the future)
   - Indications for treatment outside of Type 1 ROP (in the future)
   - Indications for treatment outside of Type 1 ROP (in the future)
   - Indications for treatment outside of Type 1 ROP (in the future)
3. Individual clinical judgment.

Treatment of FEVR Based on FA Findings

Diversity of Retinal Vascular Anomalies in Patients with Familial Exudative Vitreoretinopathy

CHANGING THE RULES IN PEDIATRIC RETINA DISEASE – CHAN

27 Gauge

- May Allow for More Predictable Sutureless Vitrectomy
- May Decrease Post-Operative Morbidity

Pharmacologic Vitreolysis for Pediatric Retina

A RANDOMIZED, PLACEBO-CONTROLLED STUDY OF INTRAVASCULAR OCEPHALYTINS IN PEDIATRIC PATIENTS SCHEDULED FOR VITREOTOMY

Table 4. Drug-Related Adverse Events

<table>
<thead>
<tr>
<th>Category/Preferred Term</th>
<th>Placebo (n = 8)</th>
<th>Olinsol (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Any allergic event</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any study drug event</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Any injection event</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any experimental event</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any hospitalization</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any withdrawal event</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1. 24 eyes randomized in the study
2. No statistically significant difference between placebo and 115ug epoetin alfa
3. No statistically significant difference in AEs

Immediate Sequential Bilateral Vitreoretinal Surgery (ISBVS) in Pediatric Patients

- Anatomic success 89.8%
- Globe salvage rate 96.0%
- Higher stage of disease resulted in longer operative times
- Coular adverse events
  - 2 eyes from different patients - vitreous hemorrhage (36%) – no cases of endophthalmitis, hypotony, or choroidal hemorrhage


Changing the Rules in the Management of Pediatric Retinal Disease

1. Imaging
2. Redefining Treatment Algorithm
3. Surgical Innovation
4. New Imaging Devices, Computer Facilitated Image Analysis, Telemedicine, and Tele-Education

Imaging and Informatics for ROP (i-ROP) Collaborative Group

- Computer Based Image Analysis for ROP
  - Potential implications for delivering care in the developing world and improve access to care
- Disease prediction models
  - Identification of genetic risk factors for ROP
  - Quantitative image traits
  - Environmental risk factors

Global Education Network for ROP (GEN-ROP)

1. Digital Imaging for Pediatric Retina
2. Telemedicine and Technology
3. Tele-Education
   - Challenges in ROP education in developing and middle income countries e.g. Armenia, Mongolia, Thailand, Vietnam, Brazil, China
   - Tele-Education can improve diagnostic accuracy for pediatric retinal disease.


With new technology, is it now time to rethink our CLASSIFICATION and MANAGEMENT of ROP and other PEDIATRIC VITREORETINOPATHIES?

1. Imaging
   - Integrating FA, OCT and other imaging techniques
   - Redefining our classification of pediatric retinal disease and ROP
2. Redefining Treatment Algorithms
   - Know the rules but clinical judgement critical
3. Surgical Innovation
   - “Smaller is better”
   - Pharmacologic vitreolysis
   - Immediate Sequential Bilateral Vitrectomy Surgery (ISBVS)
4. New Imaging Devices, Computer Facilitated Image Analysis, Telemedicine, and Tele-Education

According to the revised FEVR Clinical Staging System proposed by Tresle et al., laser to retinal nonperfusion and extraretinal or intraretinal vascularization as demonstrated by FA should be considered for all of the following stages except:

<table>
<thead>
<tr>
<th>Stage</th>
<th>FA Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>25.6%</td>
</tr>
<tr>
<td>2b</td>
<td>27.1%</td>
</tr>
<tr>
<td>3b</td>
<td>31.5%</td>
</tr>
<tr>
<td>4b</td>
<td>35.1%</td>
</tr>
<tr>
<td>5b</td>
<td>35.1%</td>
</tr>
<tr>
<td>6b</td>
<td>35.1%</td>
</tr>
</tbody>
</table>

In a recent study by Yonekawa et al. on immediate sequential bilateral vitreoretinal surgery for pediatric patients, which of the following was not found to be true:

1. Pediatric success was 60%
2. The most common immediate post operative complication was hypotony
3. Ocular leakage was over 30%
4. Longer surgeries were correlated with higher stage of ROP

Going Back to the Future

In a recent study by Gupta et al., the following % of cases of treatment requiring ROP were treated for ROP milder than type 1 ROP:

<table>
<thead>
<tr>
<th>Stage</th>
<th>CD Before</th>
<th>CD After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.0%</td>
<td>77.4%</td>
</tr>
<tr>
<td>2</td>
<td>29.3%</td>
<td>70.7%</td>
</tr>
<tr>
<td>3</td>
<td>29.3%</td>
<td>70.7%</td>
</tr>
<tr>
<td>4</td>
<td>38.5%</td>
<td>61.5%</td>
</tr>
<tr>
<td>5</td>
<td>20.9%</td>
<td>80.1%</td>
</tr>
</tbody>
</table>

What’s the most likely diagnosis?

- Coats Disease: 0.0%
- Aggressive Posterior ROP (APROP): 81.5%
- Familial Exudative Vitreoretinopathy: 18.5%
- Oxygen Induced Retinopathy: 0.0%
- Nonaccidental Head Trauma: 0.0%
Macular Atrophy in Anti-VEGF Treatment

GIOVANNI STAURENGHI, MD

SUMMARY
Anti-VEGF is the treatment for many retinal and choroidal diseases. It is clear that the correct use of these drugs can improve visions in conditions where the stabilization of vision was considered a big success before the anti-VEGF era.

Clinical trials demonstrate the efficacy and shows in the two/three years that there are not important side effects.

One of the most reported is macular atrophy observed in patients with choroidal neovascularization secondary to age-related macular degeneration.

There are two different theories:

- A direct effect of the drug on choroidal vasculature
- A normal evolution of age-related macular degeneration

The talk will show the pro and con of the two theories.

NOTES
This presentation is about macular atrophy in the Harbor study. Atrophy was divided into adjacent and non-adjacent, which roughly correlate to those related to CNV and ones that are not. The lesions were assessed by color fundus photography and fluorescein angiography, and the reading center analyzed the images. This is important as the best ways to analyze geographic atrophy are infrared and autofluorescence, followed by OCT. The Harbor study seems to indicate that monthly injections caused more GA, but the greatest number of patients to develop geographic atrophy was those treated in the PRN group and received less injections. It also demonstrates that atrophy is not dose-dependent as the 0.5mg group developed more atrophy than the 2.0mg group. In looking at risk factors for geographic atrophy, we noticed that patients with subretinal fluid seem to have less GA.

The rates of GA were similar at 2 years between CATT, Ivan and Harbor. This suggests that clinical data supports the development of geographic atrophy from anti-VEGF therapy. Additionally, some lab results seem to support this.

Before discussing any of the cons to this argument, I want to introduce the RAP lesion. RAP lesions can be diagnosed via a multi-modality approach. On a color photo you may only see a flame hemorrhage in the macular area, while stereo imaging on FA and ICG will show the lesion floating between the retinal and choroidal vessels. Additionally, you will see leakage on the ICG, and this is the only time CNV leaks on ICG.

On an OCT when you see an intraretinal cyst without SRF, you have to think about RAP. You will also see the pigment epithelial detachment under the fluid. Dye studies will show a hot spot in the center of the PED. Indirectly, PEDs associated with RAP lesions may flatten after a single injection of anti-VEGF. This is because there is no CNV present in the PED, only fluid. Two other indications for RAP lesions are retinal-choroidal anastomosis with or without an RPE tear and the presence of reticular pseudodrusen in the fellow eye.

Reticular pseudodrusen are particularly important because 62% of RAP lesions have reticular pseudodrusen. These lesions are best identified on FA and infrared. Color pictures only detected these in 18% of cases. Therefore, the Harbor study will likely be missing many reticular pseudodrusen because it used only color photos and FA. In 2 studies (Uedda-Arakawa and Ravera), the presence of reticular pseudodrusen in patients with RAP lesions was 83% and 87%. The study by Bailey Freund’s group showed that about 34% of CNVs are RAP lesions. This information correlates nicely with the percentage of patients with geographic atrophy in the CATT, IVAN, and Harbor studies. Is it possible that these studies may have been looking primarily at RAP lesions?

This brings up 2 important points. The CATT study shows that RAP lesions have a greater correlation with GA. Additionally it was noted that less subretinal fluid was noted in RAP lesions. Lesions with more subretinal fluid are less likely to have geographic atrophy and also less likely to have RAP lesions. It seems that there is a relationship between RAP lesions, geographic atrophy and reticular pseudodrusen. This information suggests that CNV differentiation is crucial in determining atrophy.

What about dose-dependence? There was no dose dependence shown. The graph or dose and frequency of injections (monthly vs PRN dosing) shows that there was less GA in the PRN group, which goes counter to information discussed about the amount of subretinal fluid and presence/development of GA. It is possible that there were more RAP lesions in the monthly injection group than in the PRN group. In a different study using FA, OCT, or color photography for CNV type assessment, there was a wide difference in the percentage of RAP lesions in each arm of the study despite randomization. This simply shows it is easy for there to be an unbalanced distribution of RAP lesions in different arms of clinical trials.
Have you ever seen GA in a patient being treated with an anti-VEGF agent for diabetic retinopathy?
I have not. Why not? Age does not seem to be the defining difference because the average age of patients in the RISE and RIDE studies were 62 and 65, respectively, and GA was still not demonstrated. This suggests that GA maybe more of a disease-related process and not a result of the treatment.

It seems that the presence of a RAP lesion suggests development of GA in 2-3 years. Does anti-VEGF increase the speed of development? We don’t know. There is probably a thinner choroid in patients with reticular pseudodrusen and that may interfere with appearance of GA.

In order to better determine this information using the Harbor study, we need the baseline CNV characteristics.

**DISCUSSION**

**Q/C:** The concept that anti-VEGF injections create macular atrophy and vision loss is bad because there’s more risk of visual loss by not injecting anti-VEGF.


All three studies showed that patients who had more injections also had better visual outcomes.

**A:** I agree. Anti-VEGF has not caused visual loss.

**Q:** You feel confident that you don’t have any vision loss?

**A:** I think there is a larger risk of losing vision by undertreating than causing visual loss by treating regularly.

**A:** The Harbor study shows that despite development of geographic atrophy, you have improving visual acuity. It depends where the lesion is.

**A:** If you get atrophy but you get better vision, does your patient care? No. Geographic atrophy outside of the lesion progresses in people whether they have neovascularization or not and progresses just as much regardless of treatment.

**Q:** Proliferative diabetic retinopathy didn’t exist until after the development of insulin because all the diabetics died before they got proliferative diabetic retinopathy. Then people were concerned that insulin was creating proliferative retinopathy. How will we ever tease out whether anti-VEGF therapy prolongs the course of the disease and as a consequence of that beneficial effect, we are seeing manifestations such as geographic atrophy versus its directly causative damage to the RPE.

**A:** Right. We see more macular atrophy the more you treat because you see less disciform scarring. If patients are developing geographic atrophy outside of the lesion, I don’t think that you should stop treating the neovascularization because there is no data to show an effect. Secondly, discontinuing treatment because of a concern for the atrophy allows for increased scar formation.

**Q:** We know that RAPs don’t involve the central fovea. What do the trials show about central atrophy progression?

**A:** RAP lesions are perifoveal most of the time. You can see central involvement with more advanced cases when it connects with a type 1 or type 2 choroidal neovascularization.

**Q/C:** Looking at the CATT raw data shows that the development or progression of geographic atrophy mirrors that of the fellow eye. Letters to the editor and the responses by the CATT team agree with the presenter.

**A:** Agreed. The presentation or understanding of the raw data may have been misrepresented.

**Q/C:** Similarly, patients with complex disciform lesions may develop an RPE tear, but this tear is a natural phenomenon. We persist in treating to try to control the underlying neovascularization.

**Q:** Monthly 0.5mg doses gives more VEGF suppression than PRN 2.0mg dosing because there is only a small difference in ½ life.

**Q:** Why do those treated less frequently have more atrophy?

**A:** Maybe it is due to other underlying factors. The presence of subretinal fluid may have protective effects in identifying the underlying atrophy. PRN dosing is performed in situations when fewer injections are required. With fewer injections it’s more likely to see the atrophy because the SRF leaves more quickly so visualization is easier.

**Q:** With atrophy progression do you continue to treat?

**A:** I believe that the data we have today shows the treatments are beneficial. I will treat but without activity would consider treat and extend.

**Q/C:** You can see atrophy as the subretinal fluid goes away. If you think about getting a PRN dosage, when there is fluid, you’re less likely to see the atrophy. This seems to be the case in both the Harbor and the CATT trial.
C: Geographic atrophy as measured by the reading center in the CATT trial seemed to indicate that it comes and goes. It is possible that this was related to the presence of subretinal fluid because we know that atrophy doesn’t disappear.

Q: You showed that there’s an association between intraretinal fluid and atrophy. As I understand it, you explained that the atrophy is due to the presence of RAP lesions. I wonder if as photoreceptors degenerate in the macula, you could lose the blood retina barrier allowing fluid to migrate into the retina. Could that be an explanation?

A: I do not believe that all atrophy is due to RAP lesions. I think reticular pseudodrusen is the key issue. Unfortunately, clinical trials have not used infrared or autofluorescence, which are the best ways to evaluate for the presence of reticular pseudodrusen. We also need to examine the fellow eye. Intraretinal cysts may be present in normal choroidal neovascularization. If these eyes develop atrophy, it may be due to reticular pseudodrusen as opposed to a RAP lesion.

Q: Do you advocate infrared in all patients?

A: Absolutely. If you use a Heidelberg machine, you always have an infrared with your OCT.
MACULAR ATROPHY IN ANTI-VEGF TREATMENT – STAURENGHI

Methodology for Measuring Macular Atrophy

The Challenge
- No consensus methodology for assessing already in this setting
- May be difficult to quantify statistically with obscuring features from CNV lesions

Measuring Atrophy in HARBOR
- Posterior analysis
- 17,000 images to be graded by masked graders at baseline, 3-month, 12-month, 18-month, 24-month
- 2 observers for FA and FAF
- Includes atrophy immediately within, adjacent and non-adjacent to CNV lesions

In PRN Arms, More Frequent Injection Does Not Appear to Be Associated With Higher 2-Year MA Rates

Monthly PRN
- 0.5 mg
- 2.0 mg

Percentage of Eyes With MA
- At baseline
- At 2 years

Do Dose & Regimen Impact Atrophy Rates?

Higher doses of Ranibizumab may be associated with higher risk of MA

Risk Factors in HARBOR: Baseline Retinal Anatomy

Lesser Risk
- Bl. Cyst Yes vs No
- Bl. Fellow Eye MA Yes vs No
- Bl. BRF Yes vs No
- Bl. CIV Sis (2 DA increased)
- Bl. PED Thickness (100 µm increase)
- Bl. SW Thickness (100 µm increase)
- Bl. Classic vs Occult
- Bl. SCP Yes vs No
- Bl. SRF Yes vs No

Greater Risk
- Higher risk of developing MA with cysts, fellow eye, MA at baseline

An essential role for RPE-derived soluble VEGF in the maintenance of the choriocapillaris

Clinical and experimental observations indicate a role for VEGF specifically the retinal pigment epithelial (RPE) layer in the maintenance of the chorocapillaris. The VEGF-A protein may be an autocrine factor guiding RPE maintenance in the etiology of choroid atrophy. The chorocapillaris mediates the maintenance of the neurosensory layer and choroid.
RAP
Retinal Angiomatous Proliferation

<table>
<thead>
<tr>
<th>Anti-VEGF Treatment cause Macular Atrophy</th>
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<tbody>
<tr>
<td><strong>Pro</strong></td>
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<tr>
<td>1 data from clinical trials</td>
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<tr>
<td>2 data from lab</td>
</tr>
</tbody>
</table>
The Incidence of Neovascular Subtypes in Newly Diagnosed Neovascular Age-Related Macular Degeneration

JINH J. JUNG, CHRISTINE Y. CHEN, SARAH MILLER, ROBERTO GALLEGOS-TOLEDO, HUNA XU, MARCELA MURGUIA, SOUHITI RODORI, AND K. BAILEY FRYNIS

choroidal neovascularization, respectively. With FA+OC, 30.0% (65/218), 99.0% (218/220), and 99.0% (220/220) were type 1 (sub-retinal pigment epithelium), type 2 (subretinal), type 3 (intraretinal), and mixed neovascularization (CNV), respectively.

Outcomes in Eyes with Retinal Angiomatic Proliferation in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)

Table 1: Pro and Con Outcomes of Groups Based on Summary of Randomized Allophylus Proliferation (n = 156)

<table>
<thead>
<tr>
<th>Pro</th>
<th>Con</th>
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</thead>
<tbody>
<tr>
<td>1. data from clinical trials</td>
<td>1. CNV type differentiation (RAP)</td>
</tr>
<tr>
<td>2. data from histopathology</td>
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</tbody>
</table>

Rates of Atrophy in Ranibizumab-Treated Eyes Similar in CATT, IVAN, and HARBOR

Among study eyes with no detectable atrophy at baseline

- CATT: 25% at Month 2, 25% at Month 5, 9% at Month 9, and 21% at Month 18
- IVAN: 25% at Month 2, 25% at Month 5, 9% at Month 9, and 21% at Month 18
- HARBOR: 25% at Month 2, 25% at Month 5, 9% at Month 9, and 21% at Month 18
Intravitreal Afibbercept Injection in Diabetic Macular Edema Patients with and without Prior Anti–Vascular Endothelial Growth Factor Treatment

Outcomes from the Phase 3 Program

Elena V. Di, MD,1 Quan Dang Nguyen, MD, MSc,1 Robert Vajifdar, MD,1 Alphonso J. Belen, MD, MD, F3, Andrea Gibson, PhD,1 Nanette Juong, OD,1 Yohosato Sio, FMD,1 David S. Boyer, MD

Table 1. Baseline Demographics and Characteristics of Patients from the VIBEX Study

Intravitreal Afibbercept Injection in Diabetic Macular Edema Patients with and without Prior Anti–Vascular Endothelial Growth Factor Treatment

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</thead>
<tbody>
<tr>
<td>1. data from clinical trials</td>
<td>1. differentiation CNV/PRP</td>
</tr>
<tr>
<td>2. data from histopathology</td>
<td>2. not dose-dependent</td>
</tr>
<tr>
<td>3. Anti-VEGF in diabetic patients</td>
<td>3.</td>
</tr>
</tbody>
</table>

### Missing point

- Data from Harbor and other studies of CNV type classification
- Growing speed analysis
- Why RAP is strongly related to macular atrophy

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### But....

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### Macular Atrophy in Anti-VEGF Treatment – Staurenghi

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### Retina

#### Choroidal Changes Associated with Reticular Pseudodrusen

| Gonzalez A. et al., | Lee J. et al., | Rainiero Forte | Sethiha F. | Huang E. | Seidel E. |

### Retina

#### Reticular Pseudodrusen in Early Age-Related Macular Degeneration Are Associated With Choroidal Thinning

| Asadi-Azizi | Mari E. | Szauter T. | Harold A. | John C. | Montesano |

**Conclusion:** CT was thinned throughout the macula in the RPD group as compared with the non-RPD group. The current analysis supports an association between RPD and a thinned choroidal layer and is consistent with a choroidal etiology of RPD. CT may be integral to understanding RPD and may be helpful in forecasting AMD progression 60K.
Healthcare Policy and Payment in 2020

DAVID W. PARKE, II, MD

SUMMARY
Payment follows policy. And policy follows politics. Politics pertaining to healthcare policy have been driven ‘top-down’. And they have been primarily driven by twin goals of increasing access to care (increasing the percentage of Americans with at least catastrophic health care coverage) and decreasing the aggregate cost of care.

In order to achieve these seemingly contradictory goals, the optics have led to the following assertions and assumptions:
• Coordinated care will lead to less expensive, duplicative, and unnecessary care and will save money that can be spent on increasing access.
• Coordinated care means primary care-led care systems
• Care systems need to be integrated horizontally and vertically into large systems
• Payment for care needs to be made with providers at risk
• Payment for care should be bundled to disease or episode of care
• Payment for care should be based primarily on the time needed to render that care

The policies that followed on these assumptions include such acronyms as:
• Value-based care
• Value-based modifiers
• Patient-Centered Medical Homes (PCMH)
• Accountable Care Organizations (ACO)
• Merit-based Incentive Payment Systems (MIPS)
• Alternative Payment Models (APMs)

As a generality, ophthalmologists are in a unique position in the physician world. The eye care pyramid depends less on primary care physicians than most other specialties. We are not attractive to integrated systems. (We don’t fill hospital beds, use expensive imaging systems, or use ICUs.) We do high-volume, low cost per episode of care work. We are an island. Yet we will be subject to the same regulations as primary care or as hospital-intensive proceduralists. For most, this means surviving (and thriving) in the MIPS world.

NOTES
Review of Terms
MIPS: Merit-Based Incentive Payment System is a new program that combines parts of the Physician Quality Reporting System (PQRS), the Value Modifier (VM or Value-based Payment Modifier), and the Medicare Electronic Health Record (EHR) incentive program into one single program based on quality, resource use, clinical practice improvement, meaningful use of certified EHR technology.

APM: Alternative Payment Models provide alternative methods for provider reimbursement, in place of the traditional volume-based Medicare FFS (Fee for Service) structure. Among AMPs are: Bundled Payments or lump-sum incentive payment, P4P (Pay for Performance), and PCMH model (Patient-Centered Medical Home).

SGR: Medicare Sustainable Growth Rate is a method/formula used by CMS to control spending by Medicare on health care providers’ services.

MACRA: Medicare Access & CHIP Reauthorization Act of 2015, designed to help the transition towards the goal of paying for value and better care. It also makes it easier for more health care providers to successfully take part in our quality programs in one of two streamlined ways: (1) Merit-Based Incentive Payment System (MIPS), (2) Alternative Payment Models (APMs)

CMS: Center for Medicare and Medicaid Services is an agency within the US Department of Health & Human Services responsible for administration of several key federal health care programs such as Medicare (the federal health insurance program for seniors) and Medicaid (the federal needs-based program), Children’s Health Insurance Program (CHIP), the Health Insurance Portability and Accountability Act (HIPAA), and the Clinical Laboratory Improvement Amendments (CLIA).

Medicare ACO: Accountable Care Organizations are groups of doctors, hospitals, and other health care providers, who come together voluntarily to give coordinated high quality care to their Medicare patients. The goal of coordinated care is to ensure that patients, especially the chronically ill, get the right care at the right time, while avoiding unnecessary duplication of services and preventing medical errors. Medicare offers several ACO programs:
• Medicare Shared Savings Program: A program that helps a Medicare fee-for-service program provider become an ACO. Apply Now.
• Advance Payment ACO Model: A supplementary incentive program for selected participants in the Shared Savings Program.
The MIPS path, or the merit-based incentive payment system, was designed to incentivize quality over quantity in healthcare. The Physician Quality Reporting System (PQRS) was introduced to collect data on certain quality measures and report them to CMS. The Medicare Access and CHIP Reauthorization Act (MACRA) repealed the SGR and introduced the MIPS pathway, which fundamentally changed the Medicare payment system. MIPS performance periods are based on the performance 2 years prior.

The MACRA legislature repealed the sustained growth rate but fundamentally changes the way Medicare determines and updates payments to physicians. The change in the following 4 years will be bigger than the change experienced in 1970s with Medicare. Macro legislation passed last year repealed the SGR and put in the global fee. Surgical bundles were maintained. If the global periods had gone away, then most surgeries would have seen a 40% cut. This fundamentally changes the way that surgeons are going to be paid. It didn’t happen because of this legislation; legislation just allowed the data extracted from the EHR system can be utilized to comply with other professional requirements such as the American Board of Ophthalmology’s MOC (Maintenance of Certification) part IV performance.

CMS reimbursement data in 2011 was about 30% fee for service, and about 68% fee for quality. In 2014 (before MACRA) there were 22% alternative payment models. That will increase by 2018 to an estimated 50% alternative payment models and 90% incentives for quality.

CMS released draft rules in April. The final issue will be in November, and data collection will begin in January 2017. The payments will be impacted in 2019. Thus, MIPS performance periods are based on the performance 2 years prior.

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The MIPS path, or the merit-based incentive payment system, is a modified fee-for-service. It takes all of the existing programs, PQRS, and value-based modifiers, and puts them all together in a single new program. Every single physician will be given a score by the feds in 2017. Based on that score, the physician will be penalized or incentivized. A higher score is going to be eligible for an incentive payment, and below the threshold for a penalty. Penalties will be assigned based on a trailing 2 year performance. The variations will be 8% delta between the worst and the best year.

Integration in health care is in process and the trend will continue for the foreseeable future. Last year there were 250 billion in pharma and biotech mergers and acquisitions, the highest ever consolidation process. This trend is not expected to slow down after elections, because it is driven by changes in business. The model, called reference based pricing, implies that insurance companies agree to set prices in a range. The difference to the charged price is paid out of pocket.

**Conclusions**

MACRA may not be ideal but alternatives could have been worse.

FFS as we knew it is gone but FFS with value and resource use modifications will continue for the foreseeable future through the MIPS pathway.

The physicians are going to be pushed by CMS to get into APM’s, but there are so many uncertainties that the future of ophthalmology practice, as well as every other specialty except primary care, will be in MIPS. The rules on APM’s may have some influence on ophthalmology practice, but not right now.

IRIS is a huge potential asset. It has the potential to be used for science, improving quality of care and also for payments.

**SELECTED Q&A**

**Q:** Do you have any insight into what happened with the PRP code? It seems like they’re really trying to change behavior by cutting it 66.6% and making the global period only ten days. It’s a dramatic cut.

**A:** The cut occurred because they took away the global. If you took out the post-operative visits, that’s what happened.

**Q:** Let’s stop doing it as much. It seems like a behavior changer. It’s so dramatic.

**A:** Quite frankly, one can make a strong argument, and we tried to make an argument, that this wasn’t good for patients.

**Q:** Is there any discussion about allowing Medicare to negotiate drug prices?

**A:** Yes, there is discussion. Will there be more of a discussion? That’s where my crystal ball gets really foggy. When you look at the lobbying power inside the beltway, the entire house of medicine is a very small fraction of the healthcare insurance industry. You’ve got a lot of forces at play here. I think it’s going to get a lot of talk because it’s a big political issue, but absolutely nothing is going to happen until well after the elections.
Q: Question for you on the provider side. There’s a lot of consolidation on the payer side, but in many cities including New York, there’s this rush by healthcare systems to control lives. In New York, we basically have four healthcare systems that 30 million people are going to fall under. How is that going to impact in terms of payment both to physicians and care for patients?

A: That’s a great question. Do I have another half-hour? First of all, you guys in New York go from one system to another all the time. You’re seeing a consolidation in many specialties, much more than ophthalmology. We are still, if you rank all the specialties in medicine, probably the most decentralized, disaggregated group of people, which is one of our strengths in many respects. We are certainly seeing aggregation on the provider side, particularly on the facility side. That’s really what’s driving it.

As the chief medical officer of a 12 billion dollar hospital system said to me, “Listen, if my CEO gives me 300 million bucks to go out and buy some hospital practices for our system, the last practice I’m going to buy is an ophthalmology group” because they don’t have any halo effect on the system. Ophthalmologists aren’t putting people in ICU’s, using expensive hospital imaging, filling hospital beds or even using the ORs (frequently opting for ASC centers instead). A CMO wants as many interventional cardiologists and neuroradiologists as possible and ophthalmologists are just about dead last on the list. That does give us some advantage because we can negotiate the relationship with those systems.
SGR Repeal—a Faustian Bargain

- +0.5% updates for 5 years
  - Proposed
  - Actual was -0.26% in 2016
  - Replaced reduced included target for reductions and budget neutrality
- Surgical bundles maintained
  - Avoid 40% out
  - Bill to be studied and likely to be a difficult process

MACRA

- Repealed the sustainable growth rate (SGR) methodology
- Fundamentally changes the way Medicare determines and updates payments to physicians—continue movement of physicians out of traditional FFS
- Incentivizes development and participation in Alternative Payment Models (APMs)
- Establishes Merit Based Incentive Program (MIPS)

CMS Reimbursement Data

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<thead>
<tr>
<th>Historical Performance</th>
<th>Goals</th>
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<tbody>
<tr>
<td>2011</td>
<td>2014</td>
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<tr>
<td>68%</td>
<td>65%</td>
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<tr>
<td>30%</td>
<td>35%</td>
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<tr>
<td>2018</td>
<td>2019</td>
</tr>
<tr>
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<td>65%</td>
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</table>

MIPS Performance Periods

Payments Adjusted According to Performance 2 Years Prior

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<tr>
<th>Period</th>
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<td>Value Performance Year</td>
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<td>Value Performance Year</td>
<td>10%</td>
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FFS ➔ MIPS ➔ APM

MIPS Overview

- Merit Based Incentive Payments System
  - Impacts begin January 1, 2019 (based on 2017 performance)
  - Raters the status
  - Attempts to measure MD performance, not including “art of medicine”
- Consolidates and replaces existing incentive programs
  - PQRS, MU, VBM
- Incentives would be based on composite score for each professional

MIPS Incentives—How much is at stake?

- Composite scores
  - At threshold (not yet defined): no adjustment
  - Higher scores, incentive payment
  - Below threshold: penalty
- Maximum adjustment factor
  - 2016 ± 4% Based on 2017 performance
  - 2017 ± 5% Based on 2018 performance
  - 2018 ± 7% Based on 2019 performance
  - 2019 ± 10% Based on 2020 performance
- Additional MIPS adjustment (up to 10%) possible for exceptional performance from 2019-2024 (don’t count on it)
MIPS Performance Category Weighting
- Quality measures: 30% (50% - 2019, 45% - 2020)
- Resource use: 30% (10% - 2019, 15% - 2020)
- Clinical practice: 15%
- MU – EHR: 25% (15% if 75% qualify)
- Weights change over time
  - When 75% of EPs achieve MU, its weight could be reduced to 15% to emphasize other categories.

Risks
- Can you meet participation thresholds?
- Will APM payments be adequate to cover services that patients need?
- Will risk adjustment control for variable risk?
- How will attribution work and how will ‘other costs’ be controlled?
- What kind of withhold will work with quality measures?
- How much will managing an APM cost?
- After investment can you meet participation thresholds?

Ophthalmology’s Hope—IRIS
- “The Secretary shall encourage the use of qualified clinical data registries in carrying out this subsection…”
- IRIS Registry will continue to support quality reporting.
- Academy is advocating tighter alignment of IRIS with MIPS as one means of participating successfully.

What ARE classes of APM’s?
- Accountable Care Organizations (ACO’s) under MSSP
- Patient-Centered Medical Homes
- Payment for a High-Value Service (hip replacement)
- Condition-Based Payment for Physician Services (heart failure)
- Multi-Physician Bundled Payment (heart transplant)
- Physician-Facility Procedure Bundle (eyectomy)
- Warranted Payment for Physician Services (cost name it)
- episode Payment for a Procedure (trachectomy)
- Condition Based Payment (total costs) (AMD)
- Combinations of the above

Lest You Think ACO’s aren’t getting traction….
- Total of 434 Medicare ACOs in 2016
- Covered lives grew from 5.9 M in 2014 to 8.9 M in 2016
- 25% earned a “bonus”
- 9 of 32 Pioneer ACOs remain

Alternative Payment Models (APM’s)
- Incentive for development and participation in Alternative Payment Models (APMs):
  - 5% bonus 2019-2024, 0.75% update after
  - Exemption from MIPS penalties
  - BUT—Must demonstrate that providers have ‘greater than nominal financial risk’ (yet to be defined)
  - BUT—25% (2019-20) to 75% (2025) of practice revenues or patient volume must come from APMs (not FFS) to be eligible for bonus
  - AND—payment to an entity, use certified EHR; report quality measures

ACO’s are very complex
- Track 1: single-sided risk, prospective assignment (80% of ACOs)
- Track 2: two-sided risk, prospective attribution
- Track 3: two-sided risk, prospective attribution, higher sharing rate with caps
- Next Generation: two-sided risk, prospective attribution, 10-15% lives
- Category (by payment structure):
  - Category 1: FFS with no link to quality
  - Category 2: FFS with link to quality (VBM)
  - Category 3: APM built on FFS
  - Category 4: population based payment
And not all ACO’s are APM’s

**DAILY NEWS**

**CMS Indicates ACOs Must Accept Penalty Risk To Be Alternative Pay Models**

February 3, 2016

- If Trulka accounts for 30% of ACOs and they don’t qualify for APM, it’s hard to see how CMS gets 90% of payments into APM by 2018

Integration in Health Care

(24% of total U.S. deals as of October 2015)

- $2350B in pharma and biotech M&A
  - Highest ever
- $229B in hospital M&A over past 3 yrs
  - Highest ever
- Aetna/BlueCross and Anthem/Cigna tie-ups ($110BB) leave 3 U.S. health insurance companies
- Walgreens/Rite Aid creates entity with 13,000 U.S. locations
  - Walgreens and CVS both over $100BB in revenue

Will This Change after the Elections?

Is Ophthalmology Too Small to Matter?

- Ophthalmology has two of the “Top Twenty” diseases on total cost basis for CMS:
  - Cataract
  - Glaucoma
- If CMS included outpatient drug costs, we’d have four, including:
  - AMD (2 year cost is $7k - $8k/patient, drug-dependent)
    - Every 10% change in drug utilization saves $200-$600 per year
  - Diabetic retinopathy

The Future: What do purchasers want?

- Better value: quality/cost
- Better ways/measures to assess value:
  - Outcomes, Patient Report Outcomes (PRO’s), patient experience, appropriateness
  - Better data to populate these measures
  - Registries, patient-generated data
  - Transparency: price and quality
  - Payment models that support quality, affordability, and accountability
  - Better collaboration among all stakeholders

Conclusions

- MACRA was a ‘deal with the devil’ — but the alternatives were worse:
  - Continued FFS, no global fees, little opportunity to impact specialties
- FFS is as we know it is dead, but FFS with value and resource use modifications will continue for foreseeable future
- We will be pushed to APMs — but too many uncertainties:
  - ACOs will expand...but it’s hard to see how you interface with ACS...15% failures
  - Academia believes most ophthalmologists will do better with MIPS
  - But we will monitor and model APMs — work with House of Medicine
- IRIS is a huge potential asset — evidence of meeting MIPS components
  - Need to get better written into regulations and evolving legislation
Regarding Accountable Care Organizations (ACO), which of the following is correct:

1. They are not funded and organized by physician groups
2. They require a minimum of 50,000 enrolled patients
3. They exist in both the commercial and Medicare worlds
4. They are rapidly going away

Under Merit-based Incentive Payment Systems (MIPS):

1. Payment will be based solely on cost savings and quality
2. Bonuses will be less than with APMs
3. The Secretary of HHS is mandated to keep the payment methodologies (e.g., cost versus quality) unchanged for three years
4. Measurement of EHR use is going away
TAYLOR SMITH LECTURE

Impact of Recent DRCR.net Randomized Clinical Trial Results on Managing Diabetic Retinopathy in 2016

NEIL M. BRESSLER, MD

SUMMARY

Several recent publications by the NIH-sponsored Diabetic Retinopathy Clinical Research Network have had a profound impact on considerations in the management of diabetic retinopathy. A comparative effectiveness trial (Protocol T) evaluated aflibercept, bevacizumab, and ranibizumab for diabetic macular edema (DME) within a randomized clinical trial. The results showed that, on average, all 3 agents caused improvement of visual acuity, although there was a significant interaction of the initial visual acuity on the outcomes. When visual acuity (Snellen equivalent) was 20/50 or worse, aflibercept, on average, was superior to ranibizumab or bevacizumab, with no increased safety concerns. When visual acuity was 20/32 to 20/40, no substantial difference in average visual acuity outcomes was identified.

Another trial (Protocol S) compared ranibizumab to panretinal photocoagulation (PRP) for proliferative diabetic retinopathy. Anti-vascular endothelial growth factor (anti-VEGF) visual acuity outcomes were no worse than (non-inferior to) PRP but resulted in substantially less average visual field loss, far fewer vitrectomies, and less likelihood of developing DME for which anti-VEGF treatment would be indicated among eyes without such DME at the time of initiating treatment for PDR. Treatments typically involved 6 monthly treatments with one exception (no DME and visual acuity 20/20 for DME cases, or no PDR for PDR cases) and then no additional treatment if the DME or PDR no longer was improving, but resumption of anti-VEGF treatment if DME or PDR worsened after it was withheld. Visits doubled to 2 and then 4 months starting in the second year after initiating therapy if DME or PDR remained stable in the absence of anti-VEGF treatment.

NOTES

The DRCR network came to be because of CDC data that demonstrated more than 25% of people in the US in 2010 were obese. Additionally, 10% of people over 18 had DM.

We were not paying attention to the dietary habits of the country, and we did not know the deleterious effects of fast food at the time. Many people went before Congress to secure funds to care for diabetic patients. Congress provided 150 million total and 5 million to NEI to create a network. The network was designed to test new therapies rapidly, and this was done by involving people across the country. About 1/3 of every retina specialist in the nation have been involved at some point. The goal was from concept to starting the trial should be less than 1 year.

The network has done numerous trials. Protocol S was designed to examine if anti-VEGF could be used instead of PRP. Why consider alternative? There has been 40 years of good treatment with PRP. Well, PRP is inherently destructive, people lose their peripheral field, their night vision is affected, and it may exacerbate their DME. We know that 5% of the people still develop severe vision loss and go on to vitrectomy. In Protocol I, it was noted that some people receiving anti-VEGF for DME did not have a progression of the retinopathy. Protocol I was comparing corticosteroids and laser, laser alone, and anti-VEGF (ranibizumab) therapy. It showed that ranibizumab was superior to either corticosteroids with laser in yellow, or laser alone in purple. Worsening was determined by the need for PRP, new VH, and worsening NV requiring additional PRP. It was proposed that while giving anti-VEGF (not only in the monthly treatment format) the progression of PDR was limited. By year 3 there was on average only 1 injection per year.

The primary question was, could you give anti-VEGF instead of PRP for proliferative retinopathy, and at least not have worsening? Once it was determined that the vision wouldn’t be worsened, there were many secondary questions that became important. Are there benefits to considering anti-VEGF therapy (like preservation of visual field)? Would you perhaps prevent macular edema among those eyes that don’t have it? Would you reduce the number of vitrectomies?

We took people who had proliferative retinopathy and randomly assigned them to either PRP or anti-VEGF with ranibizumab. We had excellent follow-up for about two years. The patients who received anti-VEGF had a median number of 22 visits over the 2 years, while those treated with PRP inly had a median of 16 visits. Why is that? The people in the laser group were seen and followed at four-month intervals, but some developed DME, which required more frequent follow-up. What were the results of the study? The vision after anti-VEGF injections was not inferior to PRP. In fact, the vision was better after 2 years. It also reduced the incidence of DME. There was far less peripheral visual field loss and the patient required fewer vitrectomies.
The visual acuity was very good initially in both groups (20/32), and the rate of high risk PDR was about 40% in both groups. About 20% of people had DME requiring treatment. Those in the anti-VEGF group were treated as scheduled because the injection covers both the retinopathy and the DME. Those patients in the PRP group also received anti-VEGF treatment for the DME component of the disease.

If the neovascularization increased at follow-up, after you completed the PRP, you had to add more PRP. The PRP was completed in one visit in more than half of patients. Some of them did half of the PRP and returned with vitreous hemorrhage, preventing completion of treatment. We still are not able to identify which patients will need additional treatments based on any baseline characteristics.

About 35% of patients had DME at baseline, but some were 20/20 and did not require any treatment. In the anti-VEGF group, everyone received 6 initial injections unless they had complete resolution of the PDR. Injections were stopped at the 6-month mark if the patient stabilized (no progression of the NV). If there was continued improvement, injections were continued until the benefit stopped. If things started to worsen again, the injections were restarted. There was a median of 9 injections in year 1 and 5 in year 2 for those with DME. In the eyes without DME there was a median of 7 injections in year 1 with 6 being given in the first 6 months. There was a median of 3 additional injections in the 2nd year.

Only 6% of patients in the injection group required PRP, which was indicated in patients that had NV growth or bleeding despite persistent injections. Eight of the 12 patients that required laser treatment had the laser done in the OR with endolaser.

The vision did not worsen in the PRP group. In the anti-VEGF group, the vision initially improved, but did not retain that improvement at 2 years. Overall, there was no worsening of vision in the anti-VEGF group compared to the PRP group. Interestingly, the combination of laser and anti-VEGF did worse in DME patients than just doing anti-VEGF alone. In the anti-VEGF group, the visual acuity improved in patients without DME. This most likely means that some patients had subclinical DME so the injections would actually be treating the DME there also. Development of DME with vision loss was 3 times more likely in the PRP group than the anti-VEGF group (28 vs 9).

This study demonstrated that peripheral vision was lost in the anti-VEGF group. It was significantly less than the peripheral vision lost in the PRP group though. Patients often don’t notice this loss in peripheral vision, but it is real vision loss. Another complication noted in the PRP group was that there was a three-fold increase in vitrectomy in the PRP group compared to the anti-VEGF group (15% vs 4%). There appeared to be no difference in systemic effects between the two treatment groups.

What are the advantages of having PRP treatment? It can typically be completed in 1 to 2 sessions and is often long lasting. However, 40% of patients needed additional PRP after initial completion at a median of 7 months. It costs less than multiple anti-VEGF injections, and there is no risk of endophthalmitis. The advantages of anti-VEGF is the superior visual acuity, less visual field loss, reduced development of DME, and reduced need for vitrectomy. It is unknown if the 0.3 mg dose would work as well, but the 0.5 mg dose was used because of Protocol I. In patients who already have DME, anti-VEGF treatment is required and the addition of laser treatment seems to worsen the outcome.

Protocol T 2-year data
At 1 year, all 3 injections worked well to prevent DME, but aflibercept had a stronger effect than bevacizumab or ranibizumab in eyes with worse visual acuity. The injection regimen consisted of 6 injections (if perfect only 4), which were eventually withheld once the edema was stabilized. After withholding treatment, restarting the treatment was performed with change in vision or worsening DME. The number of visits started to decrease in the 2nd year as did the number of injections. However, the number of treatments were the similar between the different drugs. It is important for the patients to know that 1st 2 years are critical to disease stabilization. By 2 years, aflibercept no longer had an advantage compared to ranibizumab, only compared to bevacizumab. This was also true of those with vision worse than 20/50. The benefit of aflibercept over ranibizumab was no longer seen, while the benefit over bevacizumab remained. There were no other differences appreciated at 2 years looking at the other pre-specified subgroups.

Difference in systemic effects? In those who had a prior MI/stroke there was a bigger difference between the agents with ranibizumab being the worst. Based on previous studies using ranibizumab and evaluated other APTC events, it seems that this is an outlier (same as the control group in protocol I). This is something to pay attention to in future studies, but chance is currently the best explanation.

Based on cost effectiveness and quality studies there is a battle to determine what the best treatment should be in certain situations. There is an incremental cost and effectiveness ratio that’s about five or six times what we typically accept as a reasonable increase in cost. Unless the cost comes down, there will be a collision of the patient/doctor relationship. This will be discussed at a future time.
DISCUSSION

Q: Since this data was presented, there’s a lot of anxiety in using mono-therapy anti-VEGF medication because of crunch syndrome. What is your perspective on that?

A: I think it’s like geographic atrophy with anti-VEGF. Progression of the traction detachment after anti-VEGF in a patient with severe proliferative retinopathy is the natural history of a disease. We have no evidence to support that crunch occurs. We have another trial where we had vitreous hemorrhage precluding placing PRP. We randomly assigned them to anti-VEGF or saline injection. We didn’t see a difference in the progression of traction detachments.

Q/C: I’d be interested in how far this has penetrated. How many of you have begun treating your proliferative patients with anti-VEGF medications?

Q: I live in a rural state with a lot of under insured patients who tend to have poor follow up. What do you recommend in that kind of scenario?

A: About 40% of people who get PRP are going to need more laser and may end up needing vitrectomy. Anti-VEGF is an alternative therapy, but not a superior one. You really have to make your judgment based on the patient. Maybe you can make the case that it’s better for DME, preserves their visual field, and leads to fewer vitrectomies. Maybe that is enough to get the patient to come in. Maybe PRP is better, but some of the laser patients will end up with vitrectomy and LP vision because they didn’t come in either.

We have a number of patients of with highly complex uveitis that live in northern Maine. Some of these diseases are really not compatible with living seven hours from a major medical center.

Q: Do you always inject patients that have a tractional detachment with active new vessels prior to vitrectomy?

A: No.

Q: Do you think some of the crunch cases may have been filtered out of the study because patients with pre-existing traction retinal detachment were not included in the study?

A: I think crunch does happen, but I think it happens more often if you don’t give the anti-VEGF because of the following. None of the patients in the study had macular TRDs, but in protocol I, some of the eyes did have extramacular traction detachments. The eyes injected with anti-VEGF were not more likely to progress compared to the control group. We saw very few traction detachments that went on to vitrectomy (4/5% were for vitreous hemorrhage without traction detachment). The data suggests that crunch happens more often in the absence of anti-VEGF.

Q: The results of the PDR study are really predictable. I think most of us would have said that if you keep anti-VEGF in the eye for two years, you’ll suppress or regress neovascularization and spare visual field.

A: There was no anti-VEGF after month six for most of these eyes, just so you realize. It’s gone in thirty days. We didn’t keep injecting.

Q: I understand, but you’re continuing injections for two years with decreasing frequency as needed. I would have said that was fairly predictable, the big question though is what happens after that if you try to stop injections. My concern about that is we have a very long track record with PRP. We know that these patients, once you regress neovascularization with laser, are rock solid 10, 15, 20 years down the road. We don’t know what will happen with these patients who have a great result with anti-VEGF for a year or two and think their disease is cured.

A: Absolutely. Anti-VEGF is an alternative therapy to consider. If you choose PRP, you’re choosing peripheral visual field loss, more vitrectomies, and an increased chance of developing DME if you don’t have it to begin with. I’m anticipating that PDR could rebound, but it didn’t from month 6 to 24. It didn’t so far. Now we’re going to follow these eyes up to five years, which may change our conclusions.

If you start a patient right now on it, you’re not going to harm them for two years. When you need to know what to do for year three, you’ll have the five-year results.

Of course the other thing we need is the cost analysis. We are currently conducting a cost analysis based on the pricing of aflibercept, bevacizumab and the ranibizumab and considering the vitrectomies, the visual field loss, and the DME developing that you have to treat anyway.

We will repeat this again with the five-year data and see what it shows.

Q: How many of the diabetics who entered the study with proliferative retinopathy will be alive at five years? What’s the rate of mortality?

A: I don’t know. This is the highest mortality rate among all the protocols because proliferative retinopathy brings with it a lot of unfortunate myocardial infarctions, strokes, disability, and death.
Taylor Smith Lecture – ARDS 44th Annual Meeting: Aspen, CO
Impact of Recent DRCR.net Randomized Clinical Trial Results on Managing Diabetic Retinopathy in 2016

Neil M. Bressler, MD
The James P. Duke Professor of Ophthalmology
Chief, retina division – Wilmer Eye Institute
Johns Hopkins University School of Medicine & Retina – Baltimore, MD

Financial and Other Disclosures*

- Dosing of aflibercept, bevacizumab, ranibizumab, triamcinolone (and other intravitreal corticosteroids) may not be according to local labels
- Data from IRB-approved human research is presented

I have the following financial interests or relationships to disclose:

- AAMA – Ophthalmology Editor-in-Chief
- Bayer Healthcare Pharmaceuticals Inc.
- Genentech, Inc.
- Luminis
- NIH – DRCR.net Network (Past Chair)
- Novartis Pharma AG
- Regeneron Pharmaceuticals, Inc.
- The EMMES Corporation – Chair of NEDDSM

*JAMA has determined that none of the authors listed above have a financial relationship with any entity, in any amount, that produces or supplies materials or services that could in any way affect the objects of the authors or JAMA.

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 Years or older

Diabetic Retinopathy Clinical Research Network (DRCR.net)

- Established in 2003 through a cooperative agreement with the National Institutes of Health of the U.S. Department of Health and Human Services
- Objective: Develop and operate a collaborative network to facilitate multicenter clinical research on diabetic retinopathy including proliferative retinopathy, diabetic macular edema and associated conditions, which are the leading and growing causes of vision impairment and blindness in the U.S. and throughout the world.

Impact of DRCR Network Trial Results on Treatment of Proliferative Diabetic Retinopathy

Completed DRCR.net Protocols

DRCR.net Protocols Enrolling or in Follow-up

Published online November 13, 2015

Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com

The JAMA Network
**Background**

- PDR treatment over last 4 decades has been panretinal photocoagulation (PRP)
  - Substantially reduces risk of severe vision loss, but...
  - Inherently destructive
  - Adverse effects
    - Peripheral visual field loss
    - Night vision loss
    - Exacerbation of pre-existing DME
  - Not perfect: 5% severe vision loss (worse than 5/200 at 2 consecutive visits) despite PRP
- Anti-VEGF, when given for DME, decreases risk of diabetic retinopathy worsening and increase chance of improvement

**Completed DRCR.net Protocols**

**Mean Change in Visual Acuity (Letters)** at Follow-up Visits

**Cumulative Probability of Worsening of Retinopathy for Eyes with PDR at Baseline**

**Primary Question**

- Is visual acuity using ranibizumab for PDR *not worse than* treatment with PRP at 2 years?
  - Non-inferiority margin of 5 letters

**Secondary Question**

- Are there potential benefits of ranibizumab on:
  - Vision throughout follow-up (area under the curve)
  - Peripheral vision
  - Macular edema
  - Incidence of vitrectomy

**Conclusions**

Ranibizumab injections for Proliferative Diabetic Retinopathy....

- No worse than (not inferior to) PRP for visual acuity at 2 years
- Superior vision over the course of 2 years (area under the curve)
- Reduces the incidence of DME
- Less peripheral VF loss
- Fewer vitrectomies
- No major safety differences from PRP identified except one case of endophthalmitis

**Randomization**

Participants with PDR:
- N = 304
- Eyes: N = 394

Baseline Ranibizumab Group N = 191
- PRP Group N = 203

2-Years Excluding Death
- N = 166 (84%)
- N = 166 (84%)

2-Years Excluding Death
- Median (Quartiles) No. Visits over 2 years
  - N = 22 (18, 24)
  - N = 15 (9, 22)
Some Key Ocular Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab Group (N = 191)</th>
<th>PRP Group (N = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean visual acuity letter score (~Snellen Equivalent)</td>
<td>75 (20/32)</td>
<td>75 (20/32)</td>
</tr>
<tr>
<td>20/25 or better</td>
<td>46%</td>
<td>46%</td>
</tr>
<tr>
<td>High risk PDR to advanced PDR</td>
<td>38%</td>
<td>37%</td>
</tr>
<tr>
<td>OCT* CST &lt; 250 μm</td>
<td>66%</td>
<td>67%</td>
</tr>
<tr>
<td>Presence of central-involved DME with VA loss*</td>
<td>22%</td>
<td>23%</td>
</tr>
</tbody>
</table>

* OCT values are Triton time domain equivalents.

---

**PRP Group PDR Treatment Schedule**

- Prompt PRP- Initial
  - 1 to 3 sittings within 8 weeks of randomization
  - Standard laser full session = 1200 to 1600 burns
  - Automated pattern full session = 1800 to 2400 burns

- Ranibizumab required for eyes with central-involved DME causing vision loss at baseline.

- If the size or amount of NV increased following initial completion of PRP, then additional PRP could be given.

---

**PRP Group Initial PRP**

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete PRP</td>
<td>98%</td>
</tr>
<tr>
<td>Performed in 1 Sitting</td>
<td>54%</td>
</tr>
</tbody>
</table>

---

**PRP Group Additional PRP**

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes given additional PRP (after completing initial PRP)</td>
<td>45%</td>
</tr>
<tr>
<td>Distribution of timing to additional PRP</td>
<td>~7 months</td>
</tr>
</tbody>
</table>

---

**Ranibizumab Group Treatment for DME**

- Required at baseline for study eyes with central-involved DME with vision loss of 20/32 or worse

<table>
<thead>
<tr>
<th>Timing of first ranibizumab injection for DME</th>
<th>Overall (N = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>47%</td>
</tr>
<tr>
<td>Baseline</td>
<td>35%</td>
</tr>
<tr>
<td>Follow-up</td>
<td>18%</td>
</tr>
</tbody>
</table>

---

**“Ranibizumab Group” – Year 1 PDR Treatment Schedule**

- 6 initial injections q4 weeks
  - One exception: if no neovascularization (NV) at 4-month or 5-month visit, then injection withheld

- Starting at 6-month visit:
  - Inject if NV improved compared with any previous 3 consecutive visits where injection given
  - Withhold injections if NV stable over previous 3 consecutive injections
  - After injection withheld, resume injections if NV worsens

---

**PRP Group # of Ranibizumab Injections**

<table>
<thead>
<tr>
<th>Eyes With Baseline DME (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to 1-year Visit (Max possible ≥ 13)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Mean</td>
</tr>
</tbody>
</table>

Note: 97% of protocol-required injections for PDR were given

---

**Ranibizumab Group # of Ranibizumab Injections**

<table>
<thead>
<tr>
<th>Eyes With Baseline DME (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to 1-year Visit (Max possible ≥ 13)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Mean</td>
</tr>
</tbody>
</table>

Prior to 2-year visit (Max possible ≥ 28)

<table>
<thead>
<tr>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Note: 97% of protocol-required injections for PDR were given
Ranibizumab Group

# of Ranibizumab Injections

<table>
<thead>
<tr>
<th></th>
<th>Eyes With Baseline DME (N = 36)</th>
<th>Eyes Without Baseline DME (N = 133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to 1-year Visit (Max possible = 13)</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Mean</td>
<td>8.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Prior to 2-year visit (Max possible = 26)</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Mean</td>
<td>13.3</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Note: 97% of protocol-required injections for PDR were given.

Mean Change in VA

- 2-Year Adjusted Mean Difference: +2.8
- 95% Confidence Interval: (-0.5, +5.0)
- Lower bound of the 95% CI of 0.5 letters was greater than the non-inferiority limit of -0.8 letters.

Area under the Curve Analysis

- Adjusted Mean Difference over 2 years (AUC): +4.2
- P-value: < 0.01
- 95% Confidence Interval: (1.3, +5.4)

Mean Change in Visual Acuity: Eyes "Baseline DME"

- 2-Year Adjusted Mean Difference: +3.0 letters
- 95% Confidence Interval: (-0.4, +1.3)

Mean Change in Visual Acuity: Eyes Without "Baseline DME"

- 2-Year Adjusted Mean Difference: +1.4 letters
- 95% Confidence Interval: (-1.5, +4.4)

Note: All charts and data are based on clinical trials and do not reflect individual patient outcomes.

*1 met failure criteria, 1 with chair approval, 1 without chair approval, 5 during vitrectomy (e.g., via endolaser), and 1 by non-study physician.
**Mean Change in Visual Acuity Stratified by Baseline DME**

- **With “Baseline DME”**
  - Mean Visual Acuity Change:
    - Ranibizumab Group: 7.0
    - PRP Group: 1.8
  - *Outlying values were truncated to 3 SD from the mean

- **Without “Baseline DME”**
  - Mean Visual Acuity Change:
    - Ranibizumab Group: 12
    - PRP Group: 0.5

**Systemic Adverse Events**

<table>
<thead>
<tr>
<th>ATPC Events</th>
<th>2-Study Eyes</th>
<th>One Study Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ranibizumab</td>
<td>PRP</td>
</tr>
<tr>
<td></td>
<td>Group N = 102</td>
<td>Group N = 114</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Vascular/Unknown Death</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Any ATPC event</td>
<td>8%</td>
<td>9%</td>
</tr>
</tbody>
</table>

*Best-estimate Tripod Collaboration defined events, occurring at least once through 2 years

**Advantages of PRP**

- Typically completed in one or two visits
- Often long-lasting effect requiring no additional treatment
  - However, in this study approximately 45% given additional PRP at median time ~7 months
- May cost less than multiple ranibizumab injections
- No risk of endophthalmitis
- No risk of systemic exposure to anti-VEGF

**Advantages of Ranibizumab**

- Mean change in VA from baseline to 2 years no worse than with PRP
- Superior mean visual acuity over course of 2-years (area under the curve analysis)
- Much less visual field loss, on average
- ~3-fold less frequent development of DME with vision loss needing anti-VEGF anyway
- ~3-fold less chance of vitrectomies
- PRP rarely needed for failure of anti-VEGF effect
- * Maybe can be used in eyes with media opacities that might preclude PRP treatment (not tested in this trial)
- * Unknown if similar outcomes with 0.3-mg ranibizumab or other anti-VEGF agents (bevacizumab or aflibercept)

*Not tested in DRCR Network Trial

**Potential Impact of Co-existing DME when Initiating Treatment of PDR**

- When **DME is present** and treatment with an anti-VEGF agent planned, PRP may be unnecessary in most cases provided that patient expected to be compliant with follow-up
- When **DME is not present**, ranibizumab is more effective than PRP in preserving central and peripheral vision, avoiding vitrectomy, and avoiding DME development, but cost, compliance with follow-up, and patient preference need to be considered
Main Outcome
Change in visual acuity at 1 and 2 years adjusted for baseline visual acuity using the intent-to-treat principle
-Visit were every 4 weeks during year 1 and 4 to 16 weeks during year 2, depending on treatment course
-Starting at the 6-month visit, focal/grid laser treatment was administered if DME persisted and was not improving
-Participants unmasked to treatment group following the publication of the primary results; though discouraged, decision could be made at that time to switch to a non-study anti-VEGF agent
-Doses: aflibercept 2.0-mg; bevacizumab 1.25-mg; ranibizumab 0.3-mg

Ocular Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Aflibercept (N = 224)</th>
<th>Bevacizumab (N = 218)</th>
<th>Ranibizumab (N = 218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median visual acuity</td>
<td>69 (20/40)</td>
<td>69 (20/40)</td>
<td>68 (20/50)</td>
</tr>
<tr>
<td>letter score (Snellen Equivalent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean OCT CST* (μm)</td>
<td>387</td>
<td>376</td>
<td>390</td>
</tr>
<tr>
<td>Any Prior Focal/Grid Laser</td>
<td>36%</td>
<td>39%</td>
<td>37%</td>
</tr>
<tr>
<td>Any Prior Treatment with anti-VEGF</td>
<td>11%</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Phakic</td>
<td>74%</td>
<td>73%</td>
<td>79%</td>
</tr>
</tbody>
</table>

*Time domain (StratusIII) equivalent

Randomization
Randomly Assigned Eyes (one per participant): N = 660

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Aflibercept (2.0 mg/0.05ml) N = 224</th>
<th>Bevacizumab (1.25 mg/0.05ml) N = 218</th>
<th>Ranibizumab (0.3 mg/0.05ml) N = 218</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year (excluding deaths)</td>
<td>95%</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>2-Years</td>
<td>90%</td>
<td>85%</td>
<td>88%</td>
</tr>
<tr>
<td>2-Years (excluding deaths)</td>
<td>91%</td>
<td>90%</td>
<td>91%</td>
</tr>
</tbody>
</table>

# of Visits in Year 2* (Completers Only)

<table>
<thead>
<tr>
<th></th>
<th>Aflibercept N = 201</th>
<th>Bevacizumab N = 185</th>
<th>Ranibizumab N = 192</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>9.4</td>
<td>9.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Median (25th, 75th percentile)</td>
<td></td>
<td>10 (6, 12)</td>
<td>10 (7, 12)</td>
</tr>
</tbody>
</table>

*Protocol required monthly visits in year 1 for all 3 groups
DME Treatment: Anti-VEGF
(Completers of the given visit only)

<table>
<thead>
<tr>
<th></th>
<th>Afibercept</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Global P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Injections: Median (25th, 75th percentile)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>9 (8, 11)</td>
<td>10 (8, 12)</td>
<td>10 (8, 11)</td>
<td>0.045*</td>
</tr>
<tr>
<td>Year 2</td>
<td>5 (2, 7)</td>
<td>6 (2, 9)</td>
<td>6 (2, 9)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

NOTE: P-values adjusted for baseline visual acuity and multiple comparisons

TAYLOR SMITH LECTURE: IMPACT OF DRCR.NET RESULTS – BRESSLER

Mean Change in Visual Acuity Over 2 Years
Full Cohort

Mean Change in Visual Acuity Over 2 Years
Baseline Visual Acuity 20/32 to 20/40

Mean Change in Visual Acuity Over 2 Years
Baseline Visual Acuity 20/50 or Worse

Mean Change in Visual Acuity Over 2 Years
By Baseline Visual Acuity Subgroup

DME Treatment: Laser
(Completers of the given visit only)

<table>
<thead>
<tr>
<th></th>
<th>Afibercept</th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>Global P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one focal/grid laser</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>37%</td>
<td>56%</td>
<td>46%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Year 2</td>
<td>20%</td>
<td>31%</td>
<td>27%</td>
<td>0.046*</td>
</tr>
<tr>
<td>Over 2 Years</td>
<td>41%</td>
<td>64%</td>
<td>52%</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Discussion

At one year:
- All three anti-VEGF agents are effective treatments for DME causing vision impairment.
- When initial visual acuity loss is mild, on average, there is little difference in visual acuity.
- At worse levels of initial visual acuity, aflibercept is more effective at improving vision.

Discussion

At 2 years:
- Vision gains were seen with all three drugs at 2 years, with reduced number of injections and lasers in year 2.
- When initial visual acuity loss is mild, on average, there is still little difference in visual acuity.
- At worse levels of initial visual acuity, aflibercept was more effective at improving visual acuity versus bevacizumab, but not ranibizumab.

Discussion

- Few eyes in any group lost substantial amounts of visual acuity.
- In year 2, ~half the number of injections were indicated per protocol as in year 1 in each group.
- Cumulative number of injections was similar across all groups.
- Similar to year 1, laser treatment was indicated per protocol less frequently in the aflibercept-treated eyes in year 2.
- Since focal/grid laser to persistent DME after the 24-week visit was a protocol-defined part of the treatment regimen, it is not possible to separate the effect of macular laser from the anti-VEGF treatment on the VA and thickness outcomes after the 6-month visit.

Discussion

- Pre-defined systemic APTC rates were higher in the ranibizumab group.
  - Consisting of more non-fatal strokes and vascular deaths in the ranibizumab group.
  - Although P-values increased slightly after adjusting for a history of prior stroke or MI and other potential confounders, this did not alter the results substantially.
- These findings have not been demonstrated consistently in previously reported clinical trials.

2 Year APTC Event Rates Across DME Studies of Anti-VEGF Agents

The 12% rate of APTC events in ranibizumab participants in the current study appears to be an outlier relative to other trials, including DRCR.net Protocol I, where the percentage was 7% with high overlap in DRCR.net clinical centers.

Additionally, across multiple retinal diseases, a meta-analysis from Thulliez et al did not identify an increased risk of major cardiovascular or hemorrhagic events with ranibizumab compared with control.

The inconsistencies in the totality of evidence creates uncertainty as to whether there is a true increased risk of APTC events with ranibizumab at this time.

Impact of DRCR Network Trial Results on Treatment of Proliferative Diabetic Retinopathy

Impact of DRCR Network Trial Results on Treatment of Proliferative Diabetic Retinopathy
Conclusions

- PRP effective for PDR over last 4 decades; remains effective in 21st century
- Ranibizumab for PDR is at least as good as (non-inferior to) PRP for visual acuity at 2 years
  - Ranibizumab: an effective alternative to PRP for PDR
  - No substantial safety concerns for at least 2 years
  - May be the preferred initial treatment approach for some patients, for example, those who have both PDR and DME
- Additional analyses planned, including cost-effectiveness
- Longer follow-up should determine whether effects sustained through 5 years

Impact of DRCR Network Trial Results on Treatment of Diabetic Macular Edema

Right eye: 20/63
Left eye: 20/20

Conclusions

- Vision gains at 2 years were seen in all 3 groups with ~half the number of injections, slightly decreased frequency of visits, and decreased amounts of laser in the 2nd year
- Among eyes with better VA no differences in 2-year vision outcomes identified
- Among eyes with worse baseline VA:
  - Afibercept, on average, had superior 2-year VA outcomes compared with bevacizumab, although the difference was diminished
  - The VA difference between afibercept and ranibizumab that was noted at 1 year had decreased at 2 years.
  - The implication of the increased rate of APTC events with ranibizumab found in the current study is uncertain due to inconsistency with prior trials, warranting continued evaluation

Typically in the DRCR Network treatment algorithm of anti-VEGF for PDR or DME, how many monthly treatments of anti-VEGF injections are given for PDR or DME before withholding therapy if the PDR or DME resolve or reach a point of stability (i.e., persistent PDR or DME, but no longer improving following an anti-VEGF injection):

<table>
<thead>
<tr>
<th>Month</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>3</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Which of the following had an impact on whether afibercept was superior to bevacizumab or ranibizumab in a comparative effectiveness trial comparing all 3 for DME in the DRCR Network?

1. Visual acuity at the time of initiating therapy
2. Phakic status
3. History of prior anti-VEGF therapy
4. Prior laser treatment for DME

<table>
<thead>
<tr>
<th>Month</th>
<th>Q1 Before</th>
<th>Q1 After</th>
<th>Q2 Before</th>
<th>Q2 After</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>91.5%</td>
<td>0.0%</td>
<td>4.3%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Which adverse outcomes were more likely with anti-VEGF than PRP for treatment of PDR in the DRCR Network study comparing these therapies?

1. Visual field loss
2. Development of DME for which anti-VEGF therapy would be indicated among eyes without DME when initiating treatment for PDR
3. Vitrectomy
4. None of the above - all were more likely with PRP

<table>
<thead>
<tr>
<th>Month</th>
<th>Q2 Before</th>
<th>Q2 After</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>1.4%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

DRCR.net: What’s on the Horizon?

For the Next Decade... Stay Tuned for:
- 1-year Results from Protocol VI Observation with Deferred Anti-VEGF vs. Focalgrid Laser with Deferred Anti-VEGF vs. Prompt Anti-VEGF for DME with Very Good VA (2017)
- 5-year Results from Protocol 6 (2018)
- Wide-field Imaging Studies (Protocol AA), Genetic Studies, Prevention Trials (Protocol WI), Vitrectomy vs Anti-VEGF for VH from PDR (Protocol AB) and More (2019 and 2020)
Endophthalmitis: Real World Cases for the Vitreoretinal Surgeon

HARRY W. FLYNN, JR., MD

SUMMARY

Vitreoretinal surgeons usually manage patients with endophthalmitis. Injecting intraocular antibiotics and using vitrectomy in selected cases are part of routine care by retinal specialists. Treatment now is performed on an outpatient basis and systemic antibiotics are optional but can be considered in more advanced cases.

The Endophthalmitis Vitrectomy Study (EVS) was a landmark study (1991-1994) showing better visual outcomes using PPV (compared to tap and inject) in patients with light perception visual acuity from endophthalmitis after cataract surgery. Newer studies have validated the EVS in terms of the effectiveness of pars plana vitrectomy for eyes with more advanced visual loss. Even though presenting visual acuity is better than light perception, many vitreoretinal surgeons appropriately consider the use of vitrectomy in eyes with more advanced inflammation or in eyes with more virulent organisms demonstrated on the initial tap and inject procedure.

Based on the specific etiology of the infection, the causative organism can often be predicted:

2. Delayed-onset pseudophakic endophthalmitis: P. acnes.
4. Post-traumatic endophthalmitis: bacillus species
5. Endogenous endophthalmitis: candida species
6. Intravitreal injection related endophthalmitis: staphylococcus and streptococcus species.

The use of silicone oil can be considered in more advanced endophthalmitis cases. Although there are limited studies on the use of silicone oil, oil may reduce rates of postvitrectomy retinal detachment or phthisis bulbi. Because of the high rate of complex retinal detachment with PVR in eyes with open globe injuries, silicone oil can be often considered in this setting. Silicone oil does not support the growth or microbes and therefore will reduce ongoing proliferation of microbes during the postoperative course. Antibiotics can be used intraoperatively and postoperatively in these silicone oil cases.

NOTES

Why do we get these cases? They always seem to come to retina on Friday and for some reason it comes to me. It’s because many of these cases are best treated with vitrectomy and because we are used to administering intravitreal injections.

We can classify endophthalmitis by etiology:

The most common type, by far, is post-operative. The most likely organism in acute onset post-operative endophthalmitis following cataract or other types of surgery is coagulase-negative Staph or Staph Aureus. Gram negatives are less common. With delayed onset endophthalmitis after cataract surgery, P. acnes is the most common, but coagulase-negative Staph and fungi are on the list also.

With filtering blebs, you can get Strep., Haemophilus, or any of the Staphylococcus species. With trauma, we think of Bacillus, as well as many Staph. species.

With keratitis, we think of very bad things, such as Pseudomonas or fungi. With intravitreal injection, we think of nasopharyngeal bacteria, such as Strep. or Staph. Finally, with endogenous endophthalmitis occurring in patients with indwelling catheters, we often think of Candida, Staph. aureus, or the gram-negatives.

I’ll show some cases.

1. Relatively quiet eye with a hypopyon, some fibrin in the pupil and HM vision. Treat as an outpatient with a tap and inject.

2. This case is a little more advanced. A MSSA case also treated with a tap and inject. This case also had a good outcome, but it was limited by chronic ongoing inflammation. In general, I recommend 6 months of topical steroids.

3. This is a MRSA case that was resistant to 4th generation fluoroquinolones. Intracameral injection of moxifloxacin would have made no difference. Even with intracameral vancomycin, we do not know what the outcome would have been. This case had a recurrence and after vitrectomy had a bad outcome with corneal edema and hypotony.

4. This case had a complicated cataract surgery with retained lens fragments. The ACIOL is visible as is a very injected eye. This patient underwent a vitrectomy and intravitreal antibiotics. They grew our coagulase negative Staph. I usually do not recommend removing the IOL at the time of the original surgery. I will consider it if they have a recurrence of if there seems to be a resistant organism in the capsular bag.
5. This patient appeared 1 day after cataract surgery and grew out Serratia from the vitreous biopsy. It can happen very early on (1st day isn’t a surprise always).

When do we decide to do vitrectomy? My bias is if it’s a bad case PPV is the initial recommendation. The disadvantages are that it may cause an RD, suprachoroidal hemorrhage or anesthesia-related risks. I recommend small gauge surgery with a syringe connected to the instrument and immediately passing the initial specimen off the field directly to the microbiology lab. I take out the cannulas, and go ahead with an injection of the intravitreal antibiotics at the same time.

In the outpatient setting, I use a retrobulbar block. I do use a speculum. I like to use a 23-gauge butterfly needle because I can see the aspirate coming up the clear tubing, and I can see when I’ve got a satisfactory specimen. Then, I can pull out, and administer the antibiotics.

The endophthalmitis vitrectomy study (EVS) is probably the best study we have. It is a multi-center prospective study that excluded patients with co-morbidities like severe AMD, glaucoma, and severe corneal edema. The eyes were randomized to treat them with vitrectomy or vitreous tap and the technique goal was to remove 50% of the formed vitreous. There was no attempt to peel epiretinal membranes, or do peripheral based shaving, or any other techniques. No removal of posterior cortical vitreous either.

In EVS, if patients had hand motion vision, or better, there was no difference in the final visual acuity between vitrectomy and tap and inject. It’s important to recognize that this study did not say you cannot do a vitrectomy. It just said the results are equal. This leaves discretion to the physician. I will sometimes do a vitrectomy for a patient with HM vision or better if it’s a bad case or I may tap and inject in the clinic and do the vitrectomy the following day in the operating room.

Now, regarding the treatments that are administered, you can see in the EVS that vancomycin and amikacin were the antibiotics of choice. Compared to what we use now, which is vancomycin and ceftazidime. Steroids were not used in the EVS, but they are recommended at this point. Subconjunctival cases can be eliminated in many cases, but I still use them in some complicated cases.

What about retinal detachment in the EVS? They were similar in the 2 groups.

What about small gauge surgery? I think in the future, we will consider using 27-gauge surgery more and more in these cases, so we can get in and out quickly with the least trauma to the sclera and the vitreous base. I would recommend that you consider using a 6 mm infusion cannula to make sure you get through that vitreous base, and can satisfactorily have infusion into the vitreous cavity and not into the suprachoroidal space.

Silicone oil is our friend in some of the bad cases. It may preserve the globe.

There are very few reports of small gauge surgery in endophthalmitis. This is a study of 21 patients, and looking at the efficacy of 23-gauge surgery. You can see visual acuity improve in about 2/3 of patients, but this is improvement to ambulatory vision. This is not really reading vision.

ADDITIONAL CASES:
Here’s a P. acnes case that has intracapsular white material, 20/400 vision, had been treated with topical and intravitreal antibiotics, and did not respond. We did vitrectomy, cleaned out the capsule, grew out P. acnes, and had a favorable return in vision.

This is a case of Acremonium who resembled P. acnes, but had a recurrence after our initial vitrectomy and intracameral antibiotics. The patient was re-treated and had a favorable outcome after removal of the capsular bag and the IOL when the reinfection occurred.

This is a case of blebitis being treated with topical Vigamox by glaucoma service. I gave the patient subconjunctival lidocaine, and then I administered 25 mg of vancomycin right up next to this bleb. Her management is still ongoing.

Here’s an example of a patient who comes in with a bleb infection. I did a vitrectomy, injected Subconjunctival and intravitreal antibiotics and preserved the crystalline lens. The vision eventually came back to 20/50 visual acuity. I showed this case because in phakic patients, particularly glaucoma patients, there’s a dilemma about what to do with the crystalline lens. We have a couple of publications on this showing that if the infection does not invade the capsule, and that these eyes can be left phakic by the vitrectomy surgery.

Should we do vitrectomy on everyone? There are no randomized prospective trials, but the paper by Busby et al out of Wills demonstrated better outcomes in patients who had initial vitrectomy.

What about glaucoma filtering tubes and implants? This is another ongoing dilemma, whether you have to take the tube out. In general, we do take the tube out but leave the reservoir in place. We have a paper in press of 13 cases. The most common organism in our series was Staphylococcus epidermidis. In prior series, it’s been often Streptococcus. You see the outcomes are relatively poor. Only 5 eyes at 20/200 or better visual acuity, and 5 eyes were eviscerated or enucleated. You get bad organisms, and have bad outcomes.
What about endogenous fungal endophthalmitis? This was a lady with a history of indwelling catheters for chemotherapy treatment. I took her to vitrectomy, left the crystalline lens in place, and administered intracocular amphotericin B. I usually recommend voriconazole for a case like this. After cataract surgery she improved to 20/25.

This is another case of Candida. This patient had a vitrectomy and removal/debridement of the white ball, and came back to satisfactory vision.

This is an example by keratitis-associated endophthalmitis. The fungus was growing into the cornea and iris, and there was a retinal detachment in the back of the eye. She had a full vitrectomy, then I injected a full dose of amphotericin B and a full dose voriconazole with the goal of globe salvage.

What about silicone oil? Silicone oil does not support the growth of bacteria or fungi, so organisms can’t proliferate into the vitreous cavity. The Europeans use it a lot more than we do. The real dilemma is what is the proper dose of intravitreal antibiotics or anti-fungals in an air-filled or silicone-filled eye. I think the safest thing to do is to use half dose, and we’ve done that and gotten away without toxicity, but there’s no answer to that question.

What about trauma? Early vitrectomy is best way to avoid endophthalmitis for an intraocular foreign body. In an army-based series, the open globe injuries were closed immediately then the patient was sent to another country for definitive treatment (removal of the intraocular foreign body). There were no cases of endophthalmitis, with delays in removal of up to 21 days.

A few years ago, there was an epidemic of endophthalmitis associated with a compounding pharmacy that had contaminated product. Multiple patients developed endophthalmitis, and the pharmacy was shut down.

There’s a center in South Florida that started giving intravitreal stem cells that were obtained from a biopsy of abdominal fat. They had a formula for turning that into stem cells, and they started injecting patients in a trial that was advertised on clinicaltrials.gov.

Here are 3 cases of bilateral same day injections. This resulted in terrible vision and a toxic reaction associated with preparation technique. Legal action is underway.

The last issue is these patient with hemorrhagic occlusive vasculitis that may follow intracameral antibiotics. There may be a delayed-onset of the vasculitis of up to 10 days, but that may be problematic when cataract surgeries are often done only 1-2 weeks apart.

**DISCUSSION**

**Q:** Do you have any guidelines for when to inject again? What would the timing of that be? Are there types of infection, like fungus, where you routinely inject a series of times?

**A:** Often times, patients are doing better on the day after treatment. You can look for retraction of fibrin in the anterior chamber. There’s usually some re-absorption, or change in the hypopyon. You can also look at ultrasound. If I get a bad organism like Strep, or a gram-negative, I’m going to go back in with a vitrectomy early. That’s sort of an overview of your question.

**Q:** Typically, if you’re going to re-inject, what’s your interval to re-injection?

**A:** It again depends on the organism and the severity of the appearance. I would say I’m not hesitant to use vancomycin again in 24 hours.

**C:** I think that more eyes are harmed by re-injection than are helped by re-injection. In rabbit studies, some of the retina was killed when intravitreal antibiotics were repeated after 48 hours. It is important to note that we were looking at aminoglycosides and earlier cephalosporins.

If I have a really bad case, I’m wondering if I’m missing that this is actually getting better by not getting worse, and I should ride it out. I often give a lot of steroids or I’m going to go back with a vitrectomy if needed.

For the really bad cases that had the correct initial management (vitrectomy, antibiotics etc) but continue to progress, the salvage rate with repeat vitrectomy and repeated antibiotics is really poor.

**Q/C:** I usually recommend intensifying the topical anti-inflammatories, and watching to see if you need to do a vitrectomy.

**A:** Right.

**Q/C:** I think we agree on that.

**A:** I don’t like systemic steroids because of the side effect profile like worsening of diabetes, and other things.

**Q:** The EVS talked about using IV antibiotics, and did not recommend it. That came out of the experience from Iraq where they used fourth generation fluoroquinolones (Colyer et al. Ophthalmol. 2007;114.1439-47) What do you think about that approach?

**A:** Well, I don’t use them very much. Our microbiology lab has demonstrated that coagulase-negative Staph has about 60% resistance to fourth generation fluoroquinolones.

**Q/C:** I think that more eyes are harmed by re-injection than are helped by re-injection. In rabbit studies, some of the retina was killed when intravitreal antibiotics were repeated after 48 hours. It is important to note that we were looking at aminoglycosides and earlier cephalosporins.

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**A:** Well, I don’t use them very much. Our microbiology lab has demonstrated that coagulase-negative Staph has about 60% resistance to fourth generation fluoroquinolones.
Q/C: I appreciate the EVS, but was the LP versus non-LP vision a pre-specified end point?
A: It was not at the pre-specified endpoint

Q/C: If I think the eye needs to go to vitrectomy, and it’s 20/800, we’re going to vitrectomy.
A: Absolutely. If a patient comes in too late to bring the case to the OR that night, I would tap and inject them, and schedule them for the next day. If they come in, and they’re doing better, you cancel the surgery.

Q/C: Has anybody seen the hemorrhagic occlusive vasculitis happen from another intracameral antibiotic during cataract surgery? I saw one.
A: I haven’t seen one.

Q/C: Moxifloxacin was used intracameral, and the patient was under topical. He had two vitrectomies before the cataract surgery. He was about 54 and vitrectomies were done. Not by us, I saw him for a second opinion.
A: I think you should report the case to the ASRS.
Q/C: I already have.

Q: What are your final comments on the use of intracameral antibiotics prophylactically during cataract surgery?
A: I do not recommend their use.
Acute-onset Endophthalmitis

- VA LP
- VA 20/50
- PPV, IOAB
- Serratia

PPV for Endophthalmitis

- Controversy regarding which patients will benefit most from PPV
- PPV typically reserved for patients with more advanced disease
- Benefits of PPV:
  - Reduces intravitreal load
  - Obtains adequate material for achieving a positive culture
  - Improved visualization to assess severity and extent required
- Disadvantages of PPV:
  - Retinal detachment
  - Choroidal hemorrhage
  - Operating room setting
  - Anesthesia related risks

Outpatient clinic tap & inject procedure

Endophthalmitis Vitrectomy Study (EVS) (1990 – 1994)

- 420 patients with acute-onset endophthalmitis followed for 9 months
- Endophthalmitis within 6 weeks of cataract surgery or secondary IOL implantation
- Randomized to:
  - PPV or vitreous tap
  - +/- systemic antibiotics
  - cefazol & amikacin

EVS Results

- If VA ≥ HM
  - No difference in final VA with PPV vs. Tap/Inject
- If VA < LP
  - PPV had better outcomes:
    - 3x increase of achieving 20/40 or better VA (33% vs 11%)
    - 2x increase of achieving 20/100 or better VA (56% vs 26%)
    - 56% decrease of severe visual loss: less than 5/200 (20% vs 47%)
Regimens for treatment of Acute-Onset Postoperative Endophthalmitis Following Cataract Surgery

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EVS regimen</th>
<th>Current regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous anti biotics</td>
<td>Vancomycin 30 mg IV</td>
<td>Vancomycin 30 mg IV</td>
</tr>
<tr>
<td>Intravenous anti biotics</td>
<td>Cefazolin 1 g IV</td>
<td>Cefazolin 2.2 g IV IV</td>
</tr>
<tr>
<td>Ocular topical anti biotics</td>
<td>Tobramycin 8 mg</td>
<td>Tobramycin 8 mg</td>
</tr>
<tr>
<td>Ocular topical anti biotics</td>
<td>Dexamethasone 0.1%</td>
<td>Dexamethasone 0.1%</td>
</tr>
</tbody>
</table>

Retinal Detachment in the EVS study

Rate of RD based on initial procedure

<table>
<thead>
<tr>
<th>Initial Procedure</th>
<th># of Patients</th>
<th>Retinal Detachment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitrectomy</td>
<td>203</td>
<td>10 (0.05)</td>
<td>.05</td>
</tr>
<tr>
<td>Tyvek</td>
<td>205</td>
<td>13 (0.05)</td>
<td></td>
</tr>
</tbody>
</table>

- The incidence of RD after endophthalmitis treatment were similar in the PPV & Tap/Inject groups.
- The overall incidence of RD was 8.3%

Small gauge PPV for Endophthalmitis

- Retrospective study, 21 patients
- Jan 2010 – June 2014
- Surgical efficacy and timing of 23G PPV

- Medical outcomes: 20/20 vision in all patients
- Visual acuity improved in 16/21

Endophthalmitis often treated with PPV

- Chronic/delayed-onset endophthalmitis
  - P. acnes
  - Fungal
- Blob-related endophthalmitis
  - Streptococcal
  - Hemophillus influenza
- Endogenous endophthalmitis
  - Candida
  - Acremonium
- Trauma-related endophthalmitis
  - Bacillus species
  - Listeria

Small gauge vitrectomy

- Chen in 1996 — First described sutureless PPV
- Fujii/De Juan in 2002 — Developed 25G Transconjunctival system
- Eckardt in 2005 — Introduced 23 G Transconjunctival PPV

Advantages:
- Decreased postoperative complications
- Decreased operating time
- Decreased hole formation
- Less patient discomfort
- Decreased complications

Delayed-onset Endophthalmitis

VA 20/400
PPV, IOAB
P. acnes

Post EVS Era

- Current PPV options in management:
  - Small gauge surgery
  - Intravitreal infusion cannula
  - Silicone oil

P. acnes Endophthalmitis

VA 20/400
Post PPV, Plaque coverage
P. acnes
Long term follow-up VA 20/30
Delayed-onset Endophthalmitis

Blebitis

Bleb-Associated Endophthalmitis

Endophthalmitis Associated with Glaucoma Drainage Implants

ENDOPHTHALMITIS: REAL WORLD CASES – FLYNN, JR.

* Results:
  - 13 patients (intra-ocular antibiotics - all eyes)
  - Intraocular implantation in 8 eyes
  - Recent implant placement or intraocular injection in 5 eyes
  - The most common organism: Staphylococcus epidermidis (5 eyes)
  - Pre-infection visual acuity - range 20/30 to 1/200
  - Visual acuity at last follow up was the following:
    - VH: 20/300
    - IF: 20/30
    - HM: 20/200
    - 20/2000: 5 eyes

Endophthalmitis Associated with Glaucoma Surgery

Endogenous Fungal Endophthalmitis

VA = 20/400
PPV, Amphi-B
VA = 20/25
Candida
Endogenous Fungal Endophthalmitis

VA = 20/400
PPV, Ampho-B

VA = 20/50
Candida

Post-Traumatic Endophthalmitis

Past and Current Controversies
- Time to initial dose and ID/BF removal
- Use of intravitreal antibiotics
- Selection and duration of systemic antibiotics
- ID/BF placement changes with trauma-induced changes

IOFB & Endophthalmitis: Role of PPV

- Retrospective, non-comparative, interventional case series
- 29 eyes of 27 US military soldier with a mean of 6 months of follow-up

Silicone oil in Endophthalmitis

In Vitro Antimicrobial Activity of Silicone Oil Against Endophthalmitis-Causing Agents

2007
- Median time to IOFB removal was 21 days (mean, 18 days; range, 2-61 days)
- Mean preoperative visual acuity was 20/60
- No cases of endophthalmitis, stromal bullae, or sympathetic ophthalmia
- Poor visual outcome and perioperative complications rate are related to extensive intraocular injury
- Timing of strabismus did not correlate with visual outcome

Silicone oil in Endophthalmitis

Persistently Vitreous Culture-Positive Exogenous Bacterial Endophthalmitis

- Mean follow-up: 28.7 months
- Clinical symptoms were
  - After cataract extraction (3/21, 51%)
  - After glaucoma surgery (6/20, 30%)
- Visual Acuity
  - Mean visual acuity: 2.20 (0-7.04) LogMAR (range 0.0-0.7)
  - Mean final visual acuity: 1.00 (0-1.2) LogMAR (range 0.0-1.2)
Endophthalmitis: Real World Cases for the Vitreoretinal Surgeon

- Postoperative:
  - Acute onset postoperative endophthalmitis:
    - Coagulate (-staphylococci), acinetobacter, streptococcus species, gram negative bacteria
  - Delayed onset (chronic) endophthalmitis:
    - P. aeruginosa, propionibacterium (staphylococci, fungi)
  - Congenital filtering bleb associated endophthalmitis:
    - Streptococcus species, hemophilus influenza, staphylococcus species
  - Post-traumatic: Bacillus species (20-40%), staphylococcus species
  - Keratitis associated: Pseudomonas, staphylococci
  - Intravitreal injection associated: Staphylococcus/synechococcus
  - Endogenous: Candida species, s. aureus, gram-negative bacteria

Questions

Regarding the Endophthalmitis Vitrectomy Study, which statement is correct?

- a) The rates of retinal detachment were similar in the vitrectomy and tap and inject groups
- b) During vitrectomy, removal of the posterior cortical vitreous was recommended
- c) Intravitreal steroids were administered in all cases
- d) Removal of the intraocular lens was recommended

Correct answer: a

Questions

Regarding the treatment of endophthalmitis using vitrectomy, which statement is correct?

- a) Small gauge vitrectomy has been shown to have better outcomes compared to standard 20 gauge PPV
- b) Silicone oil can be considered in more severe cases
- c) Prophylactic 360-degree endolaser treatment is always recommended
- d) Removal of all epiretinal membranes is recommended during initial treatment

Correct answer: b

Questions

The most frequent organism isolated during vitrectomy may be predicted by the etiology of infection. The following pairing of etiology with organism is correct in all except one:

- a) Delayed onset post-cataract endophthalmitis - P. aeruginosa
- b) Trauma related endophthalmitis - bacillus species
- c) Bacteremia related endophthalmitis - streptococcus
- d) Endogenous endophthalmitis - staphylococcus epidermis

Correct answer: d
A Controlled Comparison of the Intravitreal Dexamethasone Implant vs. Intravitreal anti-VEGF Injections for Diabetic Macular Edema

TAREK S. HASSAN, MD

SUMMARY
Treatment of chronic DME with anti-VEGF injections may require a lengthy course and ultimately produce suboptimal results. It has become increasingly accepted that there are two pathophysiologic pathways that contribute to DME formation, the VEGF-mediated pathway (treated with anti-VEGF medication) and the inflammatory pathway (treated with corticosteroids), and each may be approached independent of one another.

We report a prospective trial that compared a series of three monthly intravitreal ranibizumab injections to the single intravitreal injection of the dexamethasone implant, performed by random assignment in matched eyes of the same patients, to assess the short term differences between the two treatments.

Eleven patients (22 eyes) were assessed. All had matched eyes with respect to VA, central macular thickness, and amount and type of prior intravitreal anti-VEGF treatment. Patients had stable, well-controlled blood sugars. One eye of each patient continued ranibizumab monthly X 3 and the other received the one time injection of the dexamethasone implant without additional ranibizumab.

At month 4, we found equal VAs and degree of improvement between each group but the eyes receiving the dexamethasone implant had significantly greater reduction in central macular thickness. Patiens were given a choice as to their continued treatment and 8 of the 11 patients chose to continue to have the dexamethasone implant placed in both eyes.

We demonstrated that in matched eyes, there was a greater reduction in DME in those that had their treatment changed to the dexamethasone implant than in those that continued with their monthly ranibizumab therapy.

NOTES
Treatment of chronic DME
Chronic DME is one of most difficult diseases for us to take care of because we have so many treatments to choose from, now that we have to figure what it is that we want to use, and when we want to use it. DME is also very recalcitrant, and we have to figure out ways to manage patients that don’t respond. The main stream approach for chronic diabetic macular edema is largely the use of anti-VEGF therapy. We’re often faced with a situation where a patient is seen, probably less often than as guided by our pivotal trials, and they have variable amounts of waxing and waning responses to our anti-VEGF therapy. Diabetic macular edema is most likely a mixed mechanism disease and we have to look at our treatment paradigms as such to try to determine what’s best for our patients.

Anti-VEGF drugs bind diffusible VEGF, prevent receptor binding of VEGF, so that the cascade of events that give diabetic macular edema is prevented. The RISE/RIDE and VISTA studies have shown us the success of this medication. There are also studies looking at DME treatment with steroids. The Meade trial was a phase three trial looking at the 0.75 mg dexamethasone implant known as Ozurdex. That, too, showed statistically significant improvement of vision, reduction of central macular thickness in these types of chronic diabetic macular edema eyes. In the FAME Trial longer acting steroid implant is the fluocinolone implant that showed a statistically significant improvement of vision, and reduction of central macular thickness at a two year time point.

Mixed mechanism of DME
The pathophysiology of DME ranges from the anatomic defect of the tight junctions, to various enzymatic and cytokine activities that contribute to the edema. Anti-VEGF agents treat one of a whole cascade of events that can go on to cause diabetic macular edema. With steroids, additional anatomic and physiologic changes in DME are impacted. There is basically an anti-VEGF and an anti-inflammatory pathway.

Treatment paradigm considerations
Some eyes with DME actually have vitreous traction and a vitrectomy would potentially be a good treatment option in this subset. Other eyes may have peripheral ischemia identified on wide field angiography and applying PRP may be useful in these patients. For obvious non-central microaneurysms focal laser as per the ETDRS may be considered. For other types of DME the question becomes do we use anti-VEGF or steroids or a combination of both.
After three months of treatment, we see that both groups results assessed at three subsequent visits. Implant, and no other treatment. Patients were then continued with three monthly doses of ranabizumab, the other eye got only one injection of the dexamethasone implant. All were type II diabetics. The average HbA1c 62 and no one had had a prior history of dexamethasone implant.

Our series
Prospective trial comparing intravitreal ranibizumab to intravitreal dexamethasone in a consecutive series of matched eyes in the same patient. Both eyes of each patient had multiple prior anti-VEGF injections on a q4-6 week schedule with moderate success, stable vision, but persistent DME. We assessed in the short term the response of simultaneously treating each eye, one with the continued therapy and the other with a dexamethasone implant.

We had 11 patients, 22 eyes, again matched within patient. All had the same stage of diabetic retinopathy, equal amounts diabetic macular edema, and symmetric treatment histories. They were fairly consistent in their anti-VEGF therapy and they had a similar persistence of DME. There were 4 men, 7 women, with a mean age was 62 and no one had had a prior history of dexamethasone implant. All were type II diabetics. The average HbA1c was 6.5. The mean number of anti-VEGF agent injections, prior to entering the trial, in both eyes was 9.

The mean vision was equal in both groups. One eye continued with three monthly doses of ranibizumab, the other eye got only one injection of the dexamethasone implant, and no other treatment. Patients were then assessed at three subsequent visits.

Results
After three months of treatment, we see that both groups had visual acuity improvement, 20/50 to roughly 20/37 in each group. We can see that, after month three, the central macular thickness was reduced, significantly more in the dexamethasone group than in the ranibizumab group. Intraocular pressures were slightly higher in the dexamethasone implant group than in the ranabizumab group. Interestingly, eyes that had been getting consistent ranibizumab therapy, with the vigilance of the study, did get somewhat better on the same treatment. Both eyes typically got better with less macular edema however the dexamethasone eyes had a more pronounced, faster response.

At the conclusion of the trial patients had a choice of what treatment they wanted to continue. Eight of the 11 patients said that they wanted the dexamethasone implant. Eight of the 11 wanted the Ozurdex in both eyes. Two of them wanted to stay on the same regimen of getting ranibizumab in one eye and dexamethasone in the other. Two eyes in the dexamethasone group had IOP elevations over 30. One of these eyes was started on drops, and both had normalized pressures by three months. There were no complications in the ranibizumab group.

Study Limitations
While the study is internally controlled in patients with symmetric disease that all had the exact same prior treatment exposure and diabetic status, this is a relatively small series with somewhat short follow-up. Only two drugs were compared.

Conclusion
This series clearly demonstrates that there is a differential in response to intravitreal injections depending on the target mechanism being attacked; either anti-VEGF or anti-inflammatories. Dexamethasone leads to improvements in eyes that are not optimally responsive to anti-VEGF therapy. If you look at matched eyes in the same patient in a controlled environment, both anti-VEGF and anti-inflammatories improved vision and reduced macular edema. In both situations, the diabetic macular edema came back as soon as the medications were gone.

The vigilance of frequent follow-up even helped the anti-VEGF arm that wasn’t responding as well as before. Again, there are numerous cytokines that have been identified that play a role in DME and may be more responsive to steroids rather than just anti-VEGF agents. Chronic DME should be attacked through different mechanisms. It’s important to note that steroids have also been shown to reduce the severity of diabetic retinopathies. Now we have two mechanisms, both of which modulate the actual disease. Combination therapy with anti-VEGF and long term steroid therapy may be the optimal treatment approach to DME.
DISCUSSION

Q: Now that we have longer term, sustained release steroids, is that your next clinical trial?

A: The key is that the complication profile is acceptable for a trial. If we’re comfortable that patients won’t have a pressure spike than a fluocinolone acetonide implant may be ideal for this.

C: (comment) I believe we have overstated concerns that removing vitreous will inhibit intravitreal anti-VEGF or dexamethasome. I don’t let that influence a vitrectomy decision for me any longer.

C: We have protocol U which we’re trying to get going. It’s been slow in recruitment, I guess because anti-VEGF has worked so well. We don’t have that many chronic DME patients. They often get better after three injections.

Q: Studies have suggested anti-VEGF is protective against non-perfusion. Do you prefer to use the cortico-steroid combination with an anti-VEGF due to these potential vascular benefits of the anti-VEGF, more than steroids?

A: Yes, I believe you need both. I like to give anti-VEGF every few months.

Q: I think we all agree that for eyes that are not responding to anti-VEGF, there’s a strong rationale for moving on to steroids, potentially a combination. My question relates to the dexamethasone implant, as opposed to triamcinolone. There have been a lot of claims that there are significant advantages to the dexamethasone implant but it is about ten times as expensive. We’ve had a lot of discussion at this meeting about the cost of the drugs that we’re giving. My question is what do you feel like you’re getting for the extra ten times cost?

A: I believe it is a longer duration of effect up to about three to four months. Also I believe the intraocular pressure rise problems that we see in the major trials using the dexamethasome implant are significantly less. We need more comparative data and cost analysis. Another thing to remember is that triamcinolone combinations are different. It’s a question that has to be answered by each physician, looking at their experience. We’re having that discussion with minimal data, and most of the data is your clinical experience, or my clinical experience. Even when the numbers are fairly large, it’s still not as compelling as what we would like to see in a randomized clinical trial. We need more data but most of our clinical trials have industry support and you see why this issue is not likely to have this level of support. That’s where the DRCR, to me, can really step in and make a difference for us.
DEXAMETHASONE IMPLANT VS. ANTI-VEGF INJECTIONS FOR DME – HASSAN

DME Treatment: Anti-VEGF Agents

Pathophysiology of DME: Rx with anti-VEGF

DME Treatment: Anti-VEGF Agents: Very Successful

Pathophysiology of DME: Rx with Steroids

DME Treatment: Steroids: Dexamethasone implant... >15 letter gain

Treatment Paradigm: Considerations

DME Treatment: Steroids: Fluocinolone implant... >15 letter gain

74 y.o. Pseudophakic, no Sx, VA = 20/30
2014 ASRS PAT Survey: N=805

How would you treat DME refractory to laser and ranibizumab?

- Intravitreal corticosteroids
- Intravitreal anti-VEGF
- Combined therapy

11 patients (32 eyes) vs. DEXA
- Matched eyes within each patient
- same stage of diabetic retinopathy, equal DME
- Symptomatic treatment history
- Consistent anti-VEGF therapy

Demographics:
- 4 men, 7 women
- Mean age: 62 y.o. (range, 51-84)
- All Type 2 DM
- 8 pseudophakic, 4 phakic eyes
- Mean DME FU before entering trial: 19 mos. (range, 5-69)
- Fatty stapes, well controlled BB

We persevere with treatment:
We know benefits result from long-term therapy
We switch to make it better...

When to switch anti-VEGF agent?
When to switch to something else!

Ranibizumab: Example of resolution
Dexamethasone: Example of resolution

FIELD TREATMENT: Decisions on the MECHANISM of DME
DEXAMETHASONE IMPLANT VS. ANTI-VEGF INJECTIONS FOR DME – HASSAN

OUR SERIES: Management of DME
OVERALL RESULTS: EQUAL...

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab Eye</th>
<th>Dexamethasone Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, Mean VA</td>
<td>20/85</td>
<td>20/80</td>
</tr>
<tr>
<td>After month 1, Mean VA</td>
<td>20/125</td>
<td>20/90</td>
</tr>
<tr>
<td>Baseline, Mean CMT</td>
<td>421 microns</td>
<td>461 microns</td>
</tr>
<tr>
<td>After month 1, Mean CMT</td>
<td>372 microns (-47)</td>
<td>316 microns (-105)</td>
</tr>
<tr>
<td>Baseline, Mean IOP</td>
<td>16.9 mm Hg</td>
<td>17.2 mm Hg</td>
</tr>
<tr>
<td>After month 1, Mean IOP</td>
<td>16.1 mm Hg</td>
<td>19.0 mm Hg</td>
</tr>
</tbody>
</table>

EXAMPLE 1... Both ↓ DME, Dex more + faster

OUR SERIES: Management of DME
MONTHLY VA RESULTS

![Graph showing logarithmic VA results]

PREVIOUS TALK

EXEMPLARY RESULTS... Both ↓ DME, Dex more + faster

OUR SERIES: Management of DME
MONTHLY CMT RESULTS

![Graph showing microns results]

When active, DEX eyes with greater DME reduction: significant at month 2

OUR SERIES: Management of DME
MONTHLY CMT RESULTS

![Graph showing area between the curves]

At Month 4: Treat per patient choice
- 8/11 patients wanted dexamethasone OU
- 1/11 stayed with same regimen
- 1/11 switched treatment between the eyes
  - 1x panretinal
  - 2x wanted ranibizumab OU

Complications:
- 2 DEX eyes had IOP > 30 (at 1 visit only)
- 1 at month 2, 1 at month 3
- 1 started on drops
- Both normalized IOP by month 3

OUR SERIES: Management of DME
Considerations after the trial...

EXAMPLE 2:
AT MONTH 4 → Received DEX in previous Ranibizumab Eye

PREVIOUS TALK
DEXAMETHASONE IMPLANT VS. ANTI-VEGF INJECTIONS FOR DME – HASSAN

**Ozurdex leads to improvements in eyes NOT optimally responsive to anti-VEGF therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean-BSD Corrected Visual Acuity (ETDRS)</th>
<th>Mean-Central Focal Thickness (µm)</th>
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<tbody>
<tr>
<td>Tzanet et al., 2015 P = 321 Baseline Month 3</td>
<td>0.36 X 0.38 LogMar; 0.44 X 0.38 LogMar</td>
<td>532 ± 12.6 mm; 356 ± 6.8 mm</td>
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<tr>
<td>Landi et al., 2015 P = 158 Baseline Month 2</td>
<td>0.26 X 0.25 LogMar; 0.33 X 0.33 LogMar</td>
<td>305 µm; 305 µm</td>
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<tr>
<td>Ramadan et al., 2016 P = 119 Baseline Month 1</td>
<td>0.67 X 0.37 LogMar; 0.38 X 0.39 LogMar</td>
<td>350 ± 21.5 mm; 330 ± 19.5 mm</td>
</tr>
<tr>
<td>Bozic et al., 2014 P = 9 Baseline Month 1</td>
<td>0.94 X 0.33 LogMar; 0.36 X 0.36 LogMar</td>
<td>521 ± 22.1 mm; 516 ± 22.1 mm</td>
</tr>
</tbody>
</table>

**Steroids attack soluble cytokines in DME**

- Cause numerous pathophysiologic changes

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Capillary Degeneration</th>
<th>Pericyte Loss</th>
<th>Permeability</th>
<th>Inflammation</th>
<th>Neovascularization</th>
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<tr>
<td>VEGF</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

**Study Limitations**

- **POSITIVE:**
  - Externally controlled
  - Bypass patients with systemic disease
  - Placebo treatment evaluated controlled
  - DM status controlled
  - Follow-up controlled
  - Adherence to protocol controlled
  - Patient samples, etc.
  - Consecutive series

- **NEGATIVE:**
  - Small samples
  - Short follow-up
  - Other drugs not compared: antibiotics, blood pressure, angiomatosis

**OUR SERIES: Management of DME**

Conclusions...

- **CEAND DEMONSTRATES:**
  - Differences in response to minimal injections vs. total varying mechanisms that cause DME
  - Anti-VEGF vs. Inflammatory
  - Matched eyes in the same patient
  - Controlled
  - Anti-VEGF action at ranibizumab + anti-inflammatory action of dexamethasone – BOTH improve VA and reduce DME
  - DME recurred after both medica caused
  - Dexamethasone (2 wk-3rd month)
  - Ranibizumab (10-4-8 weeks)

- **HOWEVER:**
  - Patients with persistent DME, stable on anti-VEGF therapy + improved more in the eye started on dexamethasone injection vs. the other eye getting anti-VEGF
  - With only 1 dexamethasone injection vs. 3 ranibizumab injections
  - Reduction in GDM – greater throughout for significant at month 2

**The pathogenesis of diabetic macular edema is:**

1. Exclusively mediated by increased levels of VEGF
2. Exclusively mediated by increased levels of inflammatory cytokines other than VEGF
3. Is likely mediated by neither mechanism
4. Is likely mediated by both mechanisms

**An improvement in diabetic retinopathy severity scores is seen after long-term, consistent treatment with:**

- Ranibizumab
- Corticosteroids
- Neither
- Both

**When patients with matched bilateral disease are given the choice of treatments, the majority will choose:**

1. Treatment with anti-VEGF medications preferentially
2. Treatment with corticosteroids particularly the dexamethasone implant, preferentially
3. Treatment with both at the same time
4. Treatment with neither at any time

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188 ASPEN RETINAL DETACHMENT SOCIETY MEETING NOTES 2016
Myopic Traction Maculopathy: Mechanisms and Treatment

MARK W. JOHNSON, MD

SUMMARY
Myopic traction maculopathy (MTM) is an extensive schisis-like thickening in the outer retina of highly myopic eyes with posterior staphyloma. In addition to the outer schisis-like thickening, there may be other findings, including inner retinal fluid, foveal detachment, and lamellar or full-thickness macular hole. This disorder occurs in a substantial portion of patients with pathologic myopia. The pathoanatomical features have been characterized since the advent of optical coherence tomography (OCT) and intuitively suggest a gradual stretching or splitting of the retina over time, likely caused by relative tautness of the inner retina compared with the outer retina within the concavity of the posterior staphyloma.

The precise cause of traction is still debated. Some authors argue for a preretinal structure, such as a remnant cortical vitreous layer after PVD or obvious epiretinal membrane (ERM). Others have argued that MTM is caused by something intrinsic to the retina, such as the internal limiting membrane (ILM) or the stiffness of retinal arterioles. There is good evidence that the cause of the inner retinal noncompliance in MTM is not uniform but varies from one eye to another. At least four major traction mechanisms have been identified:

- Vitreomacular traction (associated with perifoveal PVD)
- Remnant cortical vitreous layer (vitreoschisis during PVD)
- Epiretinal membrane
- Intrinsic noncompliance of the ILM

Although successful surgical repair can be tailored to the specific pathologic mechanism(s) operating in a given eye, wide ILM peeling, possibly with a foveal sparing technique in selected eyes, is the surest way to resolve all possible traction mechanisms. Anatomic and visual results are generally favorable.

NOTES
Myopic traction maculopathy
Myopic traction maculopathy involves extensive schisis-like thickening, primarily in the outer retina, in highly myopic eyes with posterior staphyloma. It may also involve various combinations of inner retinal schisis, foveal detachment, and lamellar or full-thickness macular holes. It goes by a number of names, the most common other name is myopic foveoschisis. It occurs not infrequently in eyes with pathologic myopia. It's generally slowly progressive, and sometimes leads to substantial vision loss. The OCT findings can be quite dramatic, appearing as if the retina is disintegrating, both the inner and outer retina, with schisis-like changes extending far into retinal periphery. Other times the findings can be subtle. The visual acuity may be quite good despite significant thickening and anatomic abnormality. There are atypical presentations as well. What appears to be a macular detachment turns out to be myopic traction maculopathy on OCT because the photoreceptor elements could be seen along RPE stretched out under the retina.

Pathogenesis
The pathogenesis of myopic traction maculopathy is not completely understood but there are important clues. The first is that it virtually always occurs within a posterior staphyloma. A second clue is that asymmetry in the posterior staphyloma gives rise to asymmetry in the macular thickening. Thirdly, a dome-shaped macula can be relatively protective. The pathoanatomy of myopic traction intuitively suggests a gradual stretching or splitting of the retina over time, likely caused by a relative tautness of the inner retina compared with the outer retina in the concavity of the posterior staphyloma. There's still debate in the literature about the precise cause of the traction.

What is the cause of inner retinal noncompliance?
Some have argued that it is always the pre-retinal structure, like a partial PVD with vitreomacular traction, a remnant cortical vitreous layer, or an obvious ERM. Others have said that it's really something intrinsic to the retina, like the ILM, or even the stiffness of the retinal arterioles. Several years ago, we published a study trying to understand what mechanisms were involved. A take home point of the study was that the cause of the inner retinal non-compliance was not uniform, and seemed to vary from one eye to another. The second take-home from this study was that surgical repair could be tailored successfully to the specific pathologic mechanism in a given eye.

Methods
This was retrospective study of consecutive patients who had undergone vitreoretinal surgery for myopic traction maculopathy. In each eye, we retrospectively identified the major traction mechanisms that were operative in that eye. Then we looked at intraoperative findings, and the response to the surgical approach.
Results
Vitreomacular traction, from partial PVD, was a factor in 50% of the eyes. In about a third of the eyes, there were no obvious pre-retinal structures of any kind, and so the traction was attributed to intrinsic non-compliance of the ILM. In 17%, there was an obvious epiretinal membrane. In another 17%, there was no epiretinal membrane clinically, or by OCT, but there was a broad layer of remnant cortical vitreous found intraoperatively. The surgery in these eyes addressed only the major traction element. The average follow-up post-operatively was 44 months. The vision improved by two or more lines in all eyes, and the retinal thickening resolved completely in 83%, and partially in the remaining. Gas tamponade was helpful only in eyes with macular hole or detachment, and didn’t seem to have much effect on the others.

Representative cases
Case 1: 52 year old highly myopic woman with macular schisis and an outer macular hole that resolved entirely after separation of the hyaloid and gas tamponade with no peeling of ILM
Case 2: 81 year old man recovered vision to 20/20 after ERM peeling with no ILM peeling. The retina was to a normal configuration
Case 3: 62 year old woman with a Weiss ring and no vitreous traction or clinically apparent ERM. At time of surgery a broad cortical vitreous layer was peeled with no ILM peeling and no gas tamponade. There is partial resolution of traction at six months
Case 4: 46 year old woman with PVD over the macula and no ERM. Dusting with triamcinolone at time of surgery did not identify any vitreous remnants but the ILM was peeled. Postoperatively the only areas of traction/thickening were at areas of arterioles where ILM was not peeled suggested that in this case the ILM was the culprit.
Case 5: 48 year old woman with vitreomacular traction from a partial PVD who recovered after separation of the posterior hyaloid and ILM peeling

Conclusions
Myopic traction maculopathy appears to be due to a relative tautness of the inner retina overlying the posterior staphyloma. The outer retina conforms to the concavity of the staphyloma, but the inner retina is unable to do so. Over time, the retina gradually stretches apart. The traction mechanisms that are responsible for this non-compliance include vitreomacular traction, a vitreo-schisis layer after PVD, frank epiretinal membrane, age-related non-compliance of the internal limit membrane, and the minor effects of retinal arterial stiffness. In eyes without preretinal traction elements, ILM peeling resolved the traction suggesting that the ILM itself may play a role. One mechanism could be that as we age many eyes develop a microscopic cellular and collagen proliferation that may not be detectable clinically, or OCT that increases the tautness or the stiffness of the ILM. In some eyes, it appears as if the inner retina is attempting to detach from the taut ILM to follow the outer retina posteriorly into the staphyloma resulting in inner retinal schisis.

Surgical repair
Surgical repair, as just illustrated, is successful when the major traction mechanisms are identified and relieved. The surgeon has two options. The minimalist approach involves identifying and resolving only the major traction mechanism and avoids complications of ILM peeling in select eyes but is unlikely to be successful in every case. The preferred approach is a comprehensive approach that addresses any pre-retinal tractional elements, but also includes ILM peeling in every case. This gives the highest single operation success rate, since the ILM itself can be a traction element. It also ensures complete removal of anything that’s sitting in front of the ILM and causing traction. Even with comprehensive surgery and peeling of the ILM extensively the resolution of macular thickening occurs very slowly in many eyes. In some eyes, resolution of the thickening occurs rapidly and reasons for this are one of the great mysteries of this disease.

So how should ILM be peeled in these eyes?
It should be peeled broadly to mirror the staphyloma margin if possible. If peeled over the fovea there is risk of inducing a macular hole so foveal sparing techniques may be used.

Role for gas tamponade?
Gas tamponade is critical in eyes with macular holes and helpful in eyes with macular detachment but may be unnecessary in other cases. Myopic traction maculopathy with the presence of a macular hole is especially challenging to treat and requires ILM peeling and gas. Once traction is removed and if the hole is still present, it is useful to wait until the retinal thickening resolves before attempting a second surgery for hole closure since the retinal thickening may prevent hole closure around the edges.
Take home points
Myopic traction maculopathy is caused by a relative tautness of the inner retina overlying a posterior staphyloma. The cause of the inner retinal noncompliance varies from one person to another. Surgical repair is typically successful when major traction mechanism are identified and relieved. A comprehensive approach that includes peeling the ILM and overlying membranes provides the highest single-operation success rate. Foveal sparing ILM peeling techniques may reduce the rate of macular hole formation. Surgical outcomes are generally excellent and long-lasting.

DISCUSSION:
Q: When do you operate on these patients (do you have a symptomatic or visual cutoff)?
A: I approach it as I would an ERM. We talk seriously about surgery when they can no longer do activities of daily living.

Q: I’m surprised that you peel over the fovea but have had no macular hole formation. What is your trick?
A: There is a higher rate of hole formation when you peel across the fovea so I tend to use gas as well when I’m worried about the fovea.

Q: What’s your approach to peeling ILM?
A: I have a preference for avoiding ICG. I do worry about toxicity. I used triamcinolone and peel ILM and any ERM component preferably as a single sheet. I have a preference for starting with a sharp instrument and just making a little cut in the ILM using a spatula to create a broad plane and then lift and peel with forceps rather than the pinch and peel technique.

Q: These are long eyes and some instruments don’t reach the retinal surface, do you use special instruments?
A: There are instruments designed for highly myopic eyes. So far I have had to use those only once. It is a risk you may not be able to quite get to where you need to be.

A: I sometimes take out the cannula or drop the pressure in eye and push the eye wall in to reach. Only once did I have to use a specially made longer instrument.

C: (guest) Macular buckling in myopic traction maculopathy. Posterior pole buckling can be used to control the posterior staphyloma. This works because there are two main mechanisms at play in these highly myopic eyes; the first is the longitudinal growth of the eye and the second is a collagen abnormality making the sclera soft and more easily deformed posteriorly. Typically, myopic degeneration is not seen until eyes are at least 27 mm long. Based on observational studies, there is virtually a linear relationship between vision loss and the length of the eye suggesting that halting longitudinal growth may minimize vision loss. Macular buckling achieves this by pushing the sclera and choroid anteriorly towards the retina, resulting in relaxation of the ILM and decreased thickening of retina. As vitreo-retinal surgeons, we think about vitreoretinal traction but what we really have is sclera-choroidal-retinal traction posteriorly that overcomes the ILM inelasticity creating the schisis cavity. Macular buckling is very successful in my practice, essentially stopping the posterior traction and the pathologic process of posterior pulling.
Myopic Traction Maculopathy
Pathogenic Mechanisms and Surgical Treatment

Mark W. Johnson, MD
University of Michigan Kellogg Eye Center

I have no relevant financial interests

Financial Disclosures

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  - OSI
  - Tyrogenex
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Myopic Traction Maculopathy

- Extensive schisis-like thickening in outer retina in highly myopic eyes with posterior staphyloma
- Findings may also include
  - inner retinoschisis
  - fovea detaching
  - lamellar or full-thickness macular hole

Myopic Traction Maculopathy

- Findings can be quite dramatic
- Apparent disintegration of inner and outer retina

Myopic Traction Maculopathy

- Schisis-like changes can sometimes extend far into retinal periphery

Myopic Traction Maculopathy

- Findings may occasionally be subtle
- This woman originally misdiagnosed by Donald Gass as non-X linked retinoschisis (ERG normal)

Myopic Traction Maculopathy

- Also known as myopic foveoschisis
- Occurs in 1% to 3% of people with pathologic myopia
- Slowly progressive, often with substantial vision loss
- Pathoanatomic features not recognized prior to advent of OCT

20/125
20/30
Myopic Traction Maculopathy

Pathogenesis

• A third clue
  - dome-shaped macula can be relatively protective
  (and macular buckling can be curative)

• Pathoanatomy intuitively suggests gradual
  stretching or splitting of retina over time
  - likely caused by relative weakness of the inner retina
  compared with the outer retina in concavity of
  posterior staphyloma
  - Precise cause of traction still debated

Myopic Traction Maculopathy

Atypical Presentation

ILM thickening (microscopic ERM?) with photoreceptor shearing in staphyloma?

Myopic Traction Maculopathy

Pathogenesis

• Not completely understood
• Important clue
  - MTM virtually always occurs within a posterior
  staphyloma

Myopic Traction Maculopathy

Pathogenesis

• Another clue
  - asymmetry in the posterior staphyloma gives rise to
  asymmetry in the macular thickening

MTM Traction Debates

What is the Cause of Inner Retinal Noncompliance?

• Pre-retinal structure?
  - partial PVD with vitreomacular traction
  - nonaneuritic vitreous layer
  - ERM

• Intrinsic retinal element?
  - ILM
  - retinal arterioles

Diversity of Traction Mechanisms in Myopic Traction Maculopathy


• Cause of inner retinal
  noncompliance not uniform
• Varies from one eye to
  another
• Surgical repair can be tailored
  successfully to the specific
  pathologic mechanism(s)
  involved
**Methods**

- Retrospective study
- Consecutive patients
  - vitrectomy surgery for MTM
- Major traction mechanisms identified
  - pre- and intra-operative findings
  - anatomic responses to tailored surgical approach

---

**Results**

**Major Traction Mechanisms**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitreomacular traction (perifoveal PVD)</td>
<td>50%*</td>
</tr>
<tr>
<td>Intrinsic noncompliance of ILM</td>
<td>33%*</td>
</tr>
<tr>
<td>Eipiretinal membrane</td>
<td>17%</td>
</tr>
<tr>
<td>Remnant cortical vitreous (after PVD)</td>
<td>17%</td>
</tr>
</tbody>
</table>

* One eye had 2 major traction mechanisms

---

**Results**

- Surgery addressed only the major traction element
  - patient requiring 2 surgeries considered to have 2 major mechanisms
- Postoperative findings
  - average follow-up = 44 mo (minimum, 6 mo)
  - VA improved by 2 or more lines in all eyes
  - retinal thickening resolved
    - completely in 63%
    - partially (at 6 months) in remaining
  - gas tamponade appeared helpful only in eyes with macular hole or detachment

---

**Illustrative Case**

**ERM**

- 62 year-old woman
  - Preoperative
    - Weiss ring
    - no clinically apparent ERM
  - Surgery
    - identified and peeled broad cortical vitreous layer
      - [no ILM peeling]
      - no gas tamponade

**Illustrative Case**

**Remnant Cortical Vitreous Layer**

- 52 year-old woman
  - Preoperative
    - perifoveal PVD
    - stage 1B MH
  - Surgery
    - separation of posterior hyaloid
    - [no ILM peeling]
    - gas tamponade

---

**Illustrative Case**

**Vitreomacular Traction**

- 46 year-old woman
  - Preoperative
    - PVD over macula
    - [no ERM]
  - Surgery
    - no vitreous remnants
    - [with transclerotomy]
    - ILM peeling
    - gas tamponade

---

**Illustrative Case**

**Intrinsic Noncompliance of ILM**

- 81 year-old man
  - Preoperative
    - Weiss ring
    - ERM
  - Surgery
    - ERM peeling (no ILM peel)
    - no gas tamponade
**Myopic Traction Maculopathy**

**Pathogenesis**
- MTM appears to be due to relative tautness of inner retina overlying a posterior staphyloma
  - outer retina conforms to concavity, but inner retina unable
  - retina stretches apart gradually over time
- Traction mechanisms responsible for noncompliance:
  - diverse
  - vary from one eye to another
  - include:
    - vitromacular traction from partial PVD
    - remnant cortical vitreous layer (after PVD)
    - ERM
    - age-related noncompliance of ILM
    - retinal arteriolar stiffness (inner mechanism)

**ILM in MTM**
How Does It Cause Traction?
- In eyes without preretal traction elements, ILM peeling resolves MTM
- Possible explanations:
  - highly elastic nature of ILM renders it taut (like a drum), resistant to permanent deformation and stretching
  - microscopic cellular and collagen proliferation develops after PVD and is not detectable clinically or by OCT
- Biomechanical rigidity of ILM increases with age
  - ILM peeling increases retinal compliance by over 50%*

*Friedenwald, et al. Retina 2006;26:905-908

**Illustrative Case**
Multiple Mechanisms (VMT and ILM)

**48 year-old woman**
- Preoperative #1:
  - VMT from partial PVD
- Preoperative #2:
  - separation of posterior hyaloid
- Postoperative #1:
  - MTM with macular detachment
  - no apparent ERM
- Postoperative #2:
  - ERM peeling
  - gas tamponade

Inner retina attempting to detach from taut ILM = inner retinal schisis

Inner retina occasionally able to separate from taut or ERM (= ILM)

**Myopic Traction Maculopathy**
Surgical Repair
- Surgical repair is typically successful when major traction mechanisms are identified and relieved
- Surgeon has two options:
  1. **Minimalist approach**—identify and resolve only the major traction mechanisms:
     - avoids complications of ILM peeling in select eyes
     - unlikely to be successful in every case
  2. **Comprehensive approach**—addresses preretal traction elements and includes ILM peeling in every case:
     - highest single-operation success rate (since ILM itself may be major traction element)
     - ensures complete removal of all cellular and vitreous components (current or future traction)
Myopic Traction Maculopathy
How Should ILM Be Peeled?

- ILM should probably be peeled broadly to near the staphyloma margins to avoid persistent traction near macular center.
- Risk of inducing macular hole if peeled over fovea (approximately 15%).
- Recommended (but challenging) technique: fovea-sparing ILM peeling*
  - Appears effective in preventing MH formation.

**Niu et al., Retina 2012, 32:830-834.

- Minimalist Approach
  - ERM peeling alone

- Comprehensive Approach
  - Broad peeling of remnant cortical vitreous layer + limited peeling of ILM

- Comprehensive Approach
  - PhM, ERM, and ILM peeling

- Comprehensive Approach
  - ERM and ILM peeling

- Comprehensive Approach
  - Resolution of macular thickening occurs very slowly in many eyes...
Myopic Traction Maculopathy
Role for Gas Tamponade?

- Critical in eyes with macular hole
- Probably helpful in eyes with macular detachment
- In other eyes
  - My experience suggests gas unnecessary
  - Retrospective, comparative case series:
    - Results of PPV, ILM peeling were same with or without gas tamponade
    - Mean time to resolution was shorter in gas-treated group (2.3 versus 4.5 months)


MTM with Macular Hole
Especially Challenging Hole Closure

Pharmacologic Vitreolysis for MTM?

- Pharmacologic induction of PVD may be helpful in eyes with selected traction mechanisms
  - vitreomacular traction (partial PVD)
  - remnant cortical vitreous layer (after PVD)
- Unlikely to be successful in those eyes in which ERM and/or native ILM play major pathogenic roles

Summary

- MTM is caused by a relative tightness of inner retina overlying a posterior staphyloma
- The cause of the inner retinal noncompliance varies from one person to another
- Surgical repair is typically successful when major traction mechanisms are identified and relieved
- Comprehensive approach (peeling ILM and overlying membranes) provides highest single-operation success rate so far
- Surgical outcomes are generally excellent and long-lasting
Which of the following tractional elements may cause myopic traction maculopathy?

1. Epiretinal membrane
2. Remnant cortical vitreous layer following PVD
3. Internal limiting membrane
4. All of the above

Surgical repair of myopic traction maculopathy is successful only when it includes wide peeling of the ILM:

1. True
2. False

Which of the following is the most common feature of myopic traction maculopathy?

1. Inner retinal schisis-like thickening
2. Outer retinal schisis-like thickening
3. Macular detachment
4. Macular hole
Medical and Surgical Management of Enhanced S-Cone

DONALD J. D’AMICO, MD

SUMMARY
Enhanced S-Cone Syndrome is an extremely rare autosomal recessive retinal degeneration with night blindness and variably progressive visual loss that was first identified in 1990. It is caused by a mutation in the rod-specific NR2E3 transcription factor leading to an overpopulation of the retina with S cones. Patients display a nummular pattern of retinal pigmentation which may be confused with retinitis pigmentosa, and also may present with a striking macular schisis. The diagnosis is confirmed by both genetic and ERG testing with the latter displaying enhanced short-wavelength sensitivity, absent rod function, and a delayed, low-amplitude 30-Hz flicker.

This presentation describes the author's experience with an affected patient who suffered visual loss in association with progressive macular schisis, and the author's attempts to medically (acetazolamide systemically and topically) and surgically (vitrectomy, ILM peeling, gas injection) arrest the schisis progression. Initial treatment with systemic acetazolamide was unsuccessful, and surgery itself was unsuccessful; however, the patient subsequently became responsive to acetazolamide systemically and topically at very low doses, and has maintained visual acuity stability with schisis collapse for several years. This patient represents the first known ILM peeling for macular schisis in this condition, and highlights the complexity of addressing the structural retinal abnormalities in association with Enhanced S-Cone Syndrome.

NOTES
This is a rare condition that is not often encountered by retina specialists.

What is Enhanced S-Cone? It’s a really rare autosomal recessive retinal degeneration that is associated with night blindness and variably progressive visual loss, identified in 1990. It includes Goldmann-Favre with the optically empty vitreous or sometimes called clumped pigmentary retinal dystrophy. The patients have a spectrum of disease, but the core findings are usually retinal changes. One that's really striking is a nummular deep retinal pigmentary lesion often located along the arcades that are sometimes mistaken for retinitis pigmentosa. They may also have macular retinoschisis, which I had never seen before this patient.

This is a diagnosis made by ERG or genetic testing. The blue cones are in a higher preponderance so the retina is over-sensitive to blue light. The ERG shows enhanced short wave sensitivity and absent rod function. There is a delayed or low amplitude flicker.

Most of these patients have a rod specific transcription factor (NR2E3) mutation. Transcription factor error allows primitive photoreceptors to be driven into an increase in cones. Reduced rod function occurs as a result.

Example of Enhanced S-Cone ERG by Dr. Sophia Pachydkai: You can see an enhancement in blue sensitivity and decrease in rod function. The same is shown in the Vaclavik study. The normal rod response is on the bottom left. The top left demonstrates the lack of rod response. Additionally, the hyperpolarization of the S-cones is demonstrated in the upper right.

There was a 51-year-old patient who complained of night blindness since 5 years old, and he complained of progressive vision loss that began in his mid-30s. He was treated by an outside retina specialist and sent in for assistance in management. Thankfully, he had been worked up by 2 well known inherited retinal disease specialists, so his diagnosis was not in question. He had a vision of 20/200 in the right eye, and 20/80 minus 1 in the left eye. He had an interesting appearing macular schisis demonstrated on OCT. An outside physician had given him an injection of Avastin that did cause improvement. He also had a trial of oral Diamox, but it had to be discontinued secondary to significant side effects.

Fundus photos: The right eye showed pigment appearing similar to bear tracks and the left eye gave a sense of schisis with high elevation broadly throughout the fundus. In patients with pigment clumping and night vision problems, you should consider prompt testing to evaluate enhanced S-cone.

Now what? Over the next several months the vision worsened and the schisis worsened. His left eye went from 20/80 to 20/200, and the right eye was still 20/200. He had failed previous Diamox. He had failed Avastin. The patient wanted treatment, so we attempted a vitrectomy, hyaloid removal, ILM peeling and a gas bubble. Unfortunately he failed the surgical treatment.

After surgery, we decided to retry Diamox at a lower dose, especially considering the right eye was starting to worsen at this point. We went with 250 mg daily because it has been shown that a full dose is not necessary in retinal degenerations.
After 7 weeks, schisis almost completely collapsed in left eye, and he did not have any side effects. Unfortunately, he did not have any improvement in vision in the left eye. The vision in the right eye improved a little bit, but he also had some residual schisis. We then dropped the dosage of Diamox to 125 mg daily (62.5 BID), which maintained collapse of schisis in both eyes.

This syndrome was reported by originally in 1990 by Mike Marmor and others. The diagnostic clinical findings were night blindness, maculopathy and enhanced S-cone sensitivity. There is actually a post-mortem study that demonstrated extra S-cones in a cadaver eye. There are also animal models. The animal models have some flaws, but the retina in these histologic studies shows a paucity of rods and an abundance of cones. Adaptive optics would be a good tool to evaluate one of these patients.

Iannaccone reported the first use of oral Diamox in this condition, and he used 125 mg b.i.d. His patient improved from 20/200 to 20/30 with a collapse of the schisis cavity. At week 12, the vision was 20/20. He then decreased the dose to 62.5 milligrams twice a day, but added Trusopt. He was able to maintain the resolution of the schisis, and the less-affected fellow eye in this report also demonstrated improvement.

In our patient, we did the same treatment. He continues to use the Trusopt medication BID and the Diamox 62.5 mg BID. He has remained stable for years without side effects.

Was the early failure of therapy explained by the short duration, or did the surgery render the lesion Diamox-sensitive? I don’t really know. We also agree that the addition of a topical carbonic anhydrase inhibitor like Trusopt may be beneficial in these retinal degeneration cases with associated maculopathy.

**DISCUSSION**

**Q:** Have you used any of the topical carbonic anhydrases in your other patients with retinal vascular disease, in the same hope that the RPE pump function is altered?

**A:** You know, I haven’t tried that. Have you?

**Q/C:** Yes, it works.
Enhanced S Cone Syndrome

- 51 year old male with night blindness since age 5, followed by gradual central vision loss that had begun in his mid 30’s
- The patient was referred to DJD at Weill Cornell in October 2008 for management of macular retinoschisis
- He had already been given a diagnosis of enhanced S cone syndrome in 1995 after careful ERG evaluation in Boston and Texas
- On presentation in Oct 2008 he had VA of 20/200 right eye and 20/80-1 left eye

Enhanced S Cone Syndrome

- For macular retinoschisis, an outside physician had given an injection of Avastin in his left eye two months earlier with no improvement, and had also given a trial of oral Diamox 1 gram/day which was discontinued due to side effects

ERG and Genetic Testing

- ERG February 2005
- Genetic analysis May 2009
**Enhanced S Cone Syndrome**

- Over the next several months, the patient complained of worsening vision in his left eye (which decreased from 20/80 to 20/200) in association with an increasing macular retinoschisis; the right eye remained stable at 20/200
- Because of his failure with previous treatments with Diamox and Avastin, a pars plana vitrectomy with posterior hyaloid removal was performed in the left eye on June 3, 2009

**Surgical Procedure**

- During surgery, the posterior hyaloid was detached by typical soft-tipped cannula/aspiration technique
- An epiretinal membrane was noted over the peripapillary area, but it was quite strongly attached, and peeling was abandoned after several attempts
- 10% C3F8 gas was used for tamponade, and face down positioning was performed for several hours/day in a manner similar to macular hole repair

**Enhanced S Cone Syndrome**

- March 16, 2010

Unoperated OD
20/250

8 months PostOp OS
20/250

20/200 in each eye; Diamox 250 mg/day

**Enhanced S Cone Syndrome**

- May 5, 2011

OD
VA 20/150 OD and 20/200 OS
Patient has no Diamox side-effects but notes no real change in his central vision

**Enhanced S Cone Syndrome**

- June 2011 on Diamox for 7 weeks

OD
OS
VA 20/150 OD and 20/200 OS
Patient has no Diamox side-effects but notes no real change in his central vision

**Enhanced S Cone Syndrome**

- September 2011 on Diamox for 4 months

OD
OS
VA 20/125 OD and 20/200 OS
Patient has no Diamox side-effects but notes no real change in his central vision
Management of Enhanced S-Cone – D'Amico

Enhanced S Cone Syndrome

- In 2009, A. Iannaccone and coworkers reported the first use of oral Diamox with successful resolution of macular retinoschisis in a patient with ESCS
  - Using 125 mg BID, the patient improved from 20/200 to 20/30 at week 4 with collapse of large macular retinoschisis in one eye
  - At week 12, VA was 20/20
  - Dose was later decreased to 62.5 mg BID and topical dorzolamide 2% (Trusopt®) was also added with successful maintenance
  - Less affected fellow eye also had improvement

  *Iannaccone A et al. AJO 2009;147:307

Enhanced S Cone Syndrome


Enhanced S Cone Syndrome

- Intravitreal Avastin® injection had no effect on reducing the macular retinoschisis in this patient
- Vitreoretinal surgery was also unsuccessful
- Oral Diamox was subsequently able to collapse the macular lesion; the failure of an earlier Diamox treatment is probably explained by the short duration of therapy at a symptom-producing dose
- Although the result of Diamox on the lesion was dramatic, VA showed only minimal improvement
- We have added topical 2% dorzolamide Rx and also reduced the oral Diamox to 125 mg/day and been able to maintain a flat macula for >3 yrs.

Enhanced S Cone Syndrome

- Transmitted as an autosomal dominant
- Associated with absent rod function
- Associated with reduced short wave sensitivity
- Characterized by normal 30 Hz flicker

Enhanced S Cone Syndrome is:

- Transmitted as an autosomal dominant
- Associated with absent rod function
- Associated with reduced short wave sensitivity
- Characterized by normal 30 Hz flicker

Thank You!
These statements regarding Enhanced S Cone Syndrome are ALL TRUE EXCEPT:
1. Patients display retinal pigmentation that may be confused with RP.
2. If present, an associated retinoschisis typically involves the periphery.
3. A mutation is found in the rod-specific NRPE3 transcription factor.
4. The retina of affected patients has a surplus of S cones.

The macular schisis in Enhanced S cone syndrome:
1. Can be a cause of central vision loss.
2. May be responsive to carbonic anhydrase inhibitors.
3. Is not observed in all patients with this syndrome.
4. All of the above.
PANEL 3:
Practice Management 2016

MODERATOR: TIMOTHY G. MURRAY, MD, MBA
Panelists: R.V. Paul Chan, MD, Donald J. D’Amico, MD, Tarek S. Hassan, MD, Szilárd Kiss, MD

SUMMARY
Healthcare policy is undergoing rapid transformation that is directly impacting the clinical practice of the vitreoretinal specialist. This panel will discuss major shifts in coding (ICD 10), documentation (EHR focused), and compliance. Specific focus on evolving short-term strategies to enhance the practice environment will be targeted. This panel will incorporate specialists both in Academic and Private based clinical practice to more broadly address these critical issues within the context of real-world ophthalmology.

NOTES
Moderator: “The most important thing is that we’re here because we love what we do.” Physicians practice their profession not so much for the living it provides them, but for the passion of taking care of their patients.

Types of Practices
We define a small practice as 25 patients per day, a medium volume practice as 50 patients per day, and a large volume practice as 75 patients per day. Particular providers have different practices, and an academic environment makes a difference. Private practices allow the physician to be more directly involved in managing the workflow and in practice management.

Concrete example of a typical schedule in a high volume private practice: Physician in the clinic Monday and Thursday and alternates Tuesday and Wednesday, operating on an alternate Tuesday and Wednesday. Physician goes to the pediatric hospital on Friday. Clinic slots for about 75 patients, but typically sees about 80. He has a 7:30 start time working with 3 technicians in a frontloaded clinic. All patients receive photos or OCT, and everyone with a tumor gets an ultrasound.

Some providers perform intravitreal injections as needed during the clinic day and some schedule intravitreal injections for a non-clinic day. New information from the OIG tend to favor intravitreal injections on the same day, with the understanding that this can be integrated into clinical practice. About half of the physicians prepare the injections themselves, and the other half use ancillary personal (such as registered nurses or technicians) for that. Most agree that getting photos and OCTs on everybody is recommended. About 2/3 of the audience perform OCTs and 1/3 perform photographs with OCTs, sometimes supplemented with ultrasounds. To trivialize these procedures could be a disservice to the practice as the consequences of being wrong can be devastating.

The average time from check-in to check-out depends on how the practice is organized. Generally, in an academic environment, the average patient encounter time is longer, up to 4½ hours. It can be reduced to about 2 hours, as the Bascom Palmer example shows. The reason for shorter duration of visit in private practice is that the physician plays a bigger role in workflow, by taking personal interest in every aspect of the practice.

A related side issue is patient waiting time. While it may be impossible to eliminate waiting time, the patients need to be educated about the importance of the service provided and prepared to “spend the day” in the clinic. The particularities vary by practice and by workflow.

Impact of EHR (Electronic Health Records) to Practice Management
With the prevalence of Electronic Health Records (EHR), the paper is going away. It will be essentially impossible to practice in the U.S. without an EHR, in the way that the policy mandates are going.

EHRs allow for better scheduling and improved workflow. With EHR the workflow becomes more understandable so it is critical to know how to construct EHR flow paths. EHR implementations vary by practice: some have electronic health records in each room, some have imaging displayed in each room, but most have both.

Example from the panel: “I have two 32-inch monitors integrated with the EHR system so I can look at my imaging while evaluating patient. That’s ultrasound, visual field if I need it, or OCT. The small computer on the left allows me to write on the screen, so that I can do indirect ophthalmoscopy drawings if I so choose.”

One positive outcome of adopting EHR is that providers can give their patients a copy of their note at the time of their clinical visit. Some EHRs, such as EPIC, even allow patients to log on the system and extract pertinent information.

A negative of the EHRs in the US is that most of them cannot exchange information between each other. While some, like EPIC or MDI, allow providers to communicate through the system, most do not allow communication across the systems. Resolving this problem will help both the providers and the patients by improving workflow and the accuracy and availability of the data and coding.
It has been observed that EHRs have not decreased the risk of malpractice concerns, despite the expectations to the contrary. This is true especially during the transition from paper to electronic health records, a process that can introduce data errors, disturb the workflow, and be trying for providers.

Quality Metrics and Patient Satisfaction

Commonly used quality metrics could be frustrating as they do not always account for the real quality of the medical care. The measures used by various methods are sparse and do not cover the entire medical act. While the patient’s perception sometimes can be critically important, what the physicians value as quality is not what is commonly reported. As one of the participants in the panel put it: “There are comments on some of the systems that we use: how was the parking? What was the bathroom like? Not that I’m saying those things aren’t important, but I think the doctor that’s going to stick a needle in your eye should really be defining the experience for you.”

MIPS: Merit Based Incentive Payment System, is criticized because, although it is defined as a quality-based system, the real quality has a secondary role, while the emphasis is on cost.

Press Ganey scores: Press Ganey is a large company that provides about 90 percent of patient satisfaction surveys. The surveys are sent out to the patients or handed out in clinic. The response rate is generally low, sometimes 2 percent, 5 percent or 10 percent. These responses, including texts, are aggregated. There are certain metrics that a department, or an individual physician, have to meet. Many clinics assign disproportionate importance to these surveys, which may be inappropriate, for several reasons. One reason is that Press Ganey scores are assigned to a provider regardless of how few responses were received making them statistically irrelevant, or even misleading.

Another reason is that sometimes the quality of the medical act is not objectively correlated with patient satisfaction. Regardless of how comfortable the office is or how many people are floating around the office, the quality of care depends in a large measure on the medical particularities of the patient and on the dedication of the physician. Moreover, retina patients are often scared, distressed and uncomfortable, especially on their first visits. They don’t know what they have, or whether the physician is going to do something for them. One advice from a panel member is: “I am kind in my tone, and yet very direct in what I tell them…” Another reason is that in some locations, such as New York City, the patient’s experience can be intrinsically more stressful, because of external factors.

Other outlets that provide rankings or statistics, such as ProPublica, Medicare, or Iris Registry, have similar problems. In some cases there are even data errors that are hard to fix. For instance, in New York or other large metropolitan areas, doctors do not show in their databases or show with incomplete or incorrect data. An example given by a panelist describes that he is listed on Medicare as an otolaryngologist despite his efforts for more than three years to correct the problem.

Generally, while it is accepted that patients have various levels of complexity and difficulty, generic scores do not properly capture this fact. Particularly academic centers, which tend to attract more difficult patients who are disadvantaged. A notorious example, presented even in major publications such as the “Wall Street Journal” and the “New York Times” describes that a neurology group at John Hopkins ranked statistically low in ProPublica, despite the fact, argued by its chairman, that it generally deals with more difficult cases, which inevitably have worse outcomes.

Online Markers

Online markers are defined as websites that allow the public to review physicians online, such as Vitals.com, HealthGrade.com, or even Yelp.com. As these reviews are notoriously unreliable, they may influence some patients into using or not using a particular physician. Not only are these reviews not properly vetted through web governance, but also the questions themselves often have little relevance and they are often out of context. While some physicians in the panel are “a little shocked that patients will look at these ratings and make a decision,” there are certain demographics so accustomed with these tools that they rely on them. The panel identified “younger patients” and “elderly patients” as demographics prone to be influenced by online reviews.

Some physicians feel that these kind of reviews, similar to reviewing restaurants or coffee shops, commodifies retina or ophthalmology and “we are not a commodity”. However, overall the panel recognizes that this situation is here to stay, therefore physicians have to cope with this reality.

Revenues from Pharmacology-Supported Clinical Studies

The panel had been asked to clarify how the revenue from pharmacology-supported studies should be ideally distributed within a group. The consensus was that it is a complicated issue, because of the desire to keep a practice cohesive in its intent and its direction even though the physicians within the practice may not contribute to the studies equally. The solutions vary, from distributing the income equally among partners regardless of how involved in the study they are, to a scenario in which each physician receives the proceeds from his/her own clinical trials.
Configure Practice

- Medical record system
  - Paper
  - EHR
- Clinic Setup
  - Integrated intravitreal injections
  - Separate injection clinic/time

Ocular Oncology Clinic

(not the norm)

- Monday, Tuesday/Wednesday, Thursday clinics
- Slotted for 75 patients
  - Typical no-show rate 5%
- Integrated Med/Surg, integrated intravitreal injection, high volume imaging

Template/Staffing

- 7:30 am Clinic Start
  - 3 technicians
  - Front end loaded clinic - 9 patients/hour
- Tumor imaging – photo, sd OCT, digital a/b echography
- Macular imaging – sd OCT, FA/ICG

Imaging/Injection Staffing

- Two FTE dedicated photographic pods including Fundus camera and Spectralis sdOCT
- One FTE dedicated echographers
- Two FTE dedicated injection nurses (beginning at 8 am)
**Imaging Volume**
- 70 fundus photographs/SD OCT
- 45 diagnostic ultrasounds
- 5 FA/ICG studies

**Patient Focus**
- Immediately acknowledge patient and family
- Establish “rapport” early
- Fully focused on patient during in-room examination time
- Always discuss findings, diagnosis and standing (stable, active, need for treatment)

**Injection Volume**
- 2 injection rooms
- Typically 35 to 40 injections/clinic day
- Standardized documentation
- Standardized ophthalmic preparation

**Communication CRITICAL**
- EHR of complete examination and findings to referring physician and all involved clinicians
- HER note directly to patient on all visits
- Copies of imaging as requested

**Physician Resource**
- 3 exam rooms based
- Electronic imaging – all rooms
- EHR – all examinations/procedures
- E-prescribing active as of 3/2011

**Patient “Quality” Markers**
- Vitals.com
- Healthgrade.com
- Rate md.s.com
- May be manipulated by small number of patients
  - Use your satisfied patients to post comments and reviews

**“Quality” Parameters**
- Patient data including all imaging displayed on computer monitors
- Patient coordinator in room for conclusion of all exams
- In-room, real-time examination and procedure coding

**CAHPS**
*Consumer Assessment of Health Care Providers and Systems*
- CAHPS Clinician and Group (CGCAHPS) survey is a standardized tool that measures patients’ perceptions of care provided by physicians in an office setting.
- Developed by AHRQ
  - Agency for Healthcare Research and Quality
- Measures of patients’ perceptions of care including: getting appointments and health care when needed, how well doctors communicate, courtesy and helpfulness of office staff and overall rating of the doctor.
**Question 5**
I obtain imaging on essentially ALL patients to include:
1. Fundus photo/infrared
2. sdOCT
3. FA/ICG
4. OCTA
5. Both 1 and 2

**Question 6**
Electronic Display
1. I have electronic health record displayed in each room
2. I have imaging displayed in each room
3. I have both the EHR and imaging displayed in each room

**Recent reimbursement changes reflect the decreasing importance of pre-surgical and post-surgical decision making in improving patient outcomes.**
1. True
2. False
3. Are you kidding me!
4. Both 2 and 3

**EHRs have decreased the risk of malpractice concerns for the surgeon by enhancing documentation.**
1. True
2. False

**ICD 10 coding will improve patient care while decreasing administrative time for the practice.**
1. True
2. False
45th Annual
Aspen Retinal Detachment Society Meeting

March 4–8, 2017
The Viceroy Snowmass

For Information

MEDICAL CONFERENCE PLANNERS, INC.
1251 Post Road, Scarsdale, NY 10583
914-722-0664 phone
ards@medconfs.com
www.medconfs.com