Dear Aspen Retinal Detachment Society 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 three young, talented, rising retinal stars – Dr. Daniel Learned, Dr. Thanos Papakostas and Dr. Jack Stringham – 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 Drs. Learned, Papakostas and Stringham, and to all of you for contributing to the intellectual vibrancy of ARDS. We hope you will find this booklet interesting, and of value to you in the care of your patients.

Please join us March 3-7, 2018 for the 46th 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

GENENTECH, INC.

for their generous contribution toward the production of these meeting notes.
ARDS 2017

PROGRAM

Sunday

MARCH 5

4:00-4:20 PM
Treatment of DME and DR: A Paradigm Shift
Pravin U. Dugel, MD

4:20-4:35 PM
Discussion

4:35-4:55 PM
Outcomes with As-Needed Aflibercept in the VISTA Extension Study: ENDURANCE 1 Year Results
Charles C. Wykoff, MD, PhD

5:10-5:30 PM
Reoperations in Vitreoretinal Surgery
Hugo Quiroz-Mercado, MD

6:15-6:35 PM
The Potential of Stem Cells Based Therapies for Retinal Diseases
Mark S. Humayun, MD, PhD

6:50-7:30 PM
PANEL 1: Advanced Management of Diabetic Macular Edema
Moderator: Pravin U. Dugel, MD
Panelists: Mark S. Humayun, MD, PhD
Hugo Quiroz-Mercado, MD
Charles C. Wykoff, MD, PhD

Tuesday

MARCH 7

4:00-4:20 PM
Common Infectious Posterior Uveitides
Debra A. Goldstein, MD

4:35-4:55 PM
Toward More Precise Subretinal Therapeutic Delivery: New Techniques and Instrumentation
Allen C. Ho, MD

Wednesday

MARCH 8

4:00-4:20 PM
Retinopathy of Prematurity and Associated Diseases
Hugo Quiroz-Mercado, MD

4:35-4:55 PM
Role of Vitreoretinal Surgery in Patients with Choroidal Melanoma
Ivana Kim, MD

5:10-5:30 PM
3D Viewing and the Future of Vitreoretinal Surgery
Allen C. Ho, MD

6:15-6:35 PM
Masquerades of Posterior Uveitis
Debra A. Goldstein, MD

6:50-7:30 PM
PANEL 3: Surgical Approaches, Advanced Viewing and Instrumentation. Case Presentation
Moderator: Allen C. Ho, MD
Panelists: Ivana Kim, MD
Hugo Quiroz-Mercado, MD
Timothy G. Murray, MD, MBA
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Detroit, MI

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Phoenix, AZ

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Mexico City, Mexico

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Retina Consultants of Houston
Houston, TX
Taylor Smith & Victor Curtin 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. Kugel, 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
2017  Gary W. Abrams, 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
2017  Mark S. Humayun, MD, PhD

Exhibitors

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Treatment of DME and DR: A Paradigm Shift

PRAVIN U. DUGEL, MD

SUMMARY

New data suggests that roughly half the patients with DME treated with anti-VEGFA mono therapy do not respond satisfactorily. Recent analyses of the DRCRnet Protocol I (the EARLY study) will be presented to enable clinicians to identify such inadequately responsive patients. In addition, alternative treatment strategies for such patients will be discussed. Finally, drugs in the pipeline for DME and DR will be presented.

NOTES

Dr. Dugel started by stating what he would like to do in his talk is to help the audience think about the patient that they are going to see next week with DME and perhaps think about DME in a different way.

These are the two key questions that were addressed, and Dr. Dugel explained that he would like to answer them with a fair amount of data.

1. Are there DME patients who do not respond well to anti-VEGFA mono therapy?
2. How do we identify this “resistant” DME patient population?

To answer the first question – first we need to consider how well does anti-VEGFA mono therapy work? It appears to work well. And not only does it work well but it modifies the disease in a significant number of our patients. We know this from the data in studies like RISE and RIDE. So what’s the problem? A few years ago Dr. Dugel was involved in a CMS database study where they looked at codes in a large volume of patients and asked how often does anti-VEGFA mono therapy actually “cure” the patients. They matched up the codes for three years in a row and the data showed that there is a group of patients that do remarkably well with anti-VEGFA mono therapy. But there’s also a group of patients that you have to keep on treating continuously. So how do we identify which group a patient falls into and that is the second question that Dr. Dugel aimed to address.

So is there any confirmatory data? If you go back and look at protocol I, there’s a post hoc analysis of protocol I that was performed, and indeed they found exactly the same thing i.e. there are approximately 50% that respond well and 50% who need ongoing treatment. So is the response to anti-VEGF therapy related to the number of injections? If you give them more injections will they do better? This does not seem to be true. The people that did the worst in protocol I also received the most injections. So there is more to this than just giving more injections.

The next question is, “Is it the disease itself that causes this heterogeneity to the response to treatment?” If you go back and look at the RIDE and RISE data, why is it that after 24 months, when these patients are then switched to receive Ranibizumab, that they never seemed to catch up? Dr. Dugel noted that there is no clear explanation for this and that this finding has been shown in other studies as well. Why is it that if the “switch” happens at about a year, as is true in the RESTORE study, they did catch up. The timing doesn’t necessarily matter but the question to ask is, “Is there a window or inflection point in which something happens whereby another process other than the process that is controlled by VEGFA comes into play?” Is the inflammation that occurs in diabetes implicated here? We know that inflammation is important in the pathogenesis of diabetic macular edema specifically and we’ve seen this in numerous studies where there is great correlation between the amount of cytokines in the eye and the amount of diabetic retinopathy. In fact, there seems to be a significant correlation between the amount of inflammation, the severity of diabetic retinopathy, and the amount of fluorescein that is seen to leak in diabetic macular edema.

When you go back and look at the literature, there is evidence that inflammation plays a role in this. Although we know that vascular permeability is important throughout the process, it’s possible that we have a disease where it is VEGFA driven in the beginning, then inflammatory driven afterwards. Perhaps there is an inflection point where the disease goes from being primarily permeability driven to inflammatory driven and we can’t tell the difference because phenotypically they look exactly the same. And maybe this is why patients respond so differently to anti-VEGFA mono therapy.

Do we have other data with steroids to support this? If you look at the Iluvien studies, the results support that a in some patients there is a transition in DME that occurs. This is not a hardwired transition point but a continuum of disease that is individualized for each patient and the clinical trial data suggests that this occurs around two years.

Back to the key questions: are there DME patients who do not respond well to anti-VEGFA mono therapy? Yes. How do we identify these patients? How does this information help in our clinics next week? Dr. Dugel discussed a post hoc analysis of protocol I, where they looked at the raw data and asked the question of when
can they identify, after three injections, who will respond and who will not respond to anti-VEGFA monotherapy. The study pooled the prompt laser and deferred laser patients together. Overall, they looked at 340 patients and classified patients and stratified them into groups that gained 5 letters or less of vision, between 5-9 letters of vision, and greater than or equal to 10 letters of vision. After three injections 40% of patients had less than a 5-letter improvement. It's important to understand that this is a very biased patient population. These patients are motivated and self-selected to come in every four weeks for three years. These are not necessarily like the patient that is seen every day with DME.

In this analysis, those who responded well after three injections with 10+ letter improvement gained an average of 16.5 letters at one year. For the group that gained less than 5 letters after three injections, they had a mean improvement of -0.3 letters following three injections and even after being injected every four weeks for a year the improvement was 2.8 letters. The intermediate responders who gained between 5-9 letters after three injections had a mean visual improvement of 6.9 letters at twelve weeks and at one year, with injections every four weeks, they still only gained 8.2 letters of vision.

Looking at a graph of the data, Dr. Dugel stated that it reminded him of swim lanes, i.e., they do not cross. The findings appeared to be consistent for three years; groups never crossed. So after three injections it seems that you can predict which patients are going to respond, and maybe can predict who will not respond well even with very aggressive therapy.

Dr. Dugel emphasized that a key point of his talk is that the long-term response to anti-VEGFA monotherapy may be predicted after three injections. Alternative therapies with different modes of action may be considered in inadequately responsive DME patients after three injections. However, it’s very important to understand that what has not been demonstrated is whether or not a different therapy will somehow do better.

We should consider a different physiology for this subset of patients but all of this is based on visual acuity. So the study also decided to look at OCTs to see if they can classify patients by OCT as well as by visual acuity. They decided to determine who was responsive to anti-VEGFA therapy based on a 20% reduction in central retinal thickness. There were 335 eyes that qualified for this study. They classified patients as follows: limited response if the response was less than 20% reductions in central retinal thickness or as having a strong response if there was ≥ 20% reduction in the central retinal thickness after three injections.

What they found was that 35% of patients had a limited early anatomic response after three injections and that 65% had a strong early anatomic response. The eyes with the limited early anatomic response were less likely to obtain a 20% reduction in central retinal thickness over the duration of the study, which was for three years. Based on the visual acuity and the anatomic response after three injections they were able to predict how well a patient was likely to do throughout the three-year study.

Interestingly when they looked at the relationship between the OCT data and the visual acuity, there was a trend between association but this was not statistically significant. Regardless, this raises another question regarding whether or not OCT is a good biomarker for these chronic patients as OCT may be very good at determining permeability but isn’t necessarily effective in evaluating inflammation and other disease processes. The study then looked more closely at the limited response group by OCT and categorized them into a group of slow responders and a non-responder group. 70% of these patients qualified to be in the non-responder group. This non-responder group was determined after just 3 injections and was not likely to have an anatomic response even if they come in every four weeks for an injection for three years.

In conclusion, a strong early central retinal thickness response was associated with greater long-term BCVA improvement; after controlling for cofounders this trend remained but the relationship was no longer statistically significant. This metric of anatomic response, measured at one time point, has previously shown an inconsistent association with BCVA response. Early central retinal thickness response was significantly associated with long-term central retinal thickness response in unadjusted and adjusted analysis. A limited early central retinal thickness response did not preclude later anatomic improvement; however, this improvement was slow to develop. In eyes with limited early central retinal response at week 12 with ranibizumab, adjunctive anti-DME therapies with alternative modes of actions may be considered to maximize the potential for timely patient benefit. Although there appears to be a patient population that does not respond to anti-VEGFA monotherapy, it is still not clear what therapy these poor responders will benefit from.

There is also a continued issue with nomenclature because phenotypically it all looks the same. If you think about two oncologists talking to one another they never say that “Mrs. Smith” has breast cancer. Instead they say that “Mrs. Smith” has stage 2A breast cancer so that the oncologist will know exactly what “Mrs. Smith” has...
in order to guide the diagnosis, the prognosis, and treatment. But that's not the way we talk. We say “Mrs. Smith” has DME but we have no idea where in the continuum “Mrs. Smith” is. Dr. Dugel then commented that he believed that once we fix the nomenclature and can classify and stage DME in a similar way that oncologists have classified disease they deal with, then ophthalmologists will have the appropriate therapeutic interventions needed for specific stage of disease. It's not that one drug that is better than another but what drug is appropriate for that stage of disease.

DISCUSSION

Q: Question | C: Comment | A: Answer

Q: Great talk, I appreciate the balance in that you stated that we don’t know which drug to switch them to. So what drug do you start with? And which drug would you switch a non-responder to?

A: An anti-VEGFA is my drug of choice but to be clear we have not said that one drug is better than another but what this has taught me is that after a certain number of injections, and with little improvement, we should consider a different pathophysiology.

Audience poll: Which anti-VEGF agent do you start with? Bevacizumab ~1/3 raised hands, Ranibizumab ~1/3 raised hands, Aflibercept ~1/3 raised hands.

Q: Whenever I hear this talk and this concept I do agree that there are eyes that have the primary problem of inflammation as opposed to being VEGF driven, but I do not believe that there is a multifactorial physiologic switch. I don’t believe there is any evidence to support that. So, what evidence is there that something changes?

A: Extremely fair comment. When I talk about a multifactorial switch I am referring to the continuum of the process of permeability to inflammation. So you’re right, there probably is not a switch, but it appears to be a continuum, a balance between permeability and inflammation. Maybe you’re right and that calling it a switch may be the wrong term for what is occurring. But it appears to be a continuum of the process.

C: You could always make the argument for changing to a different anti-VEGF agent and there is good data in the literature that when you switch, you can get added efficacy, and I see that all the time. I think that’s the main concept. There’s no rationale in evoking a different pathophysiology.

The other thing is that there have been a lot of studies that have looked at inflammation. Even the DTRS looked at Aspirin use and then we used triamcinolone. All those things show the failure of efficacy.

A: We are not promoting any specific product. This data is basically saying there is a patient population that may require something in addition. That’s all it is. I stopped twice in my talk. Twice. Twice to say, “What I’ve done is to tell you there’s a differential patient population.” What I’ve not done is say that one drug is better than the other.

A: The point of the talk is to say, look, you’re able to sit there with a patient and say, “You know what, based on data,” and this is real data, “This is how I think you’re going to do.”

Q: This is one great thing about this meeting, which is the back and forth we can have with each other. It’s great. Similar to what oncologists might say, which is if it was BRCA positive or BRCA negative, I’d like to hear your take on what genotype may play in this kind of decision.

A: You’re exactly right. I don’t think there should be any trial that’s done in diabetes or AMD where genetic typing is not done. Ultimately, I think that’s exactly going to be the answer. We’re just not there yet.
New Treatment Strategies in DME

Pravin U. Dugel MD

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Pravin U. Dugel: Financial Disclosures

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Amirco (C, S)
ArieOx (C, S)
Avanir (C)
Beavert & Lamb (C, S)
Cleared
Bionuclei (C)

Digisight (C, S)
Dose Medical (C, S)
Genentech (C, S)
GlaxosmithKline (C, S)
Lilly (C, S)
Linsomed (C, S)
Lux Biotechnology (C, S)
Neurotech (C, S)
Neuros (C, S)
Otsuka (International) (S)
Owens (C, S)
Optoro (C, S)
Ophtos (C, S)
Ophtos (C, S)
Oasis (C)

CRA (C)
Permacel (C)
Regeneron (C, S)
Roth (C, S)
Sensor (C, S)
Shire Human Genetics (C, S)
Smith, Biontech (C, S)
Theramune (C, S)
Topcon (C)
TeoVision (S)

How Well Does Anti-VEGF Monotherapy Work for DME?

RISE/RISE extension: long-term data demonstrate need for early treatment to optimize VA gains

Mean BCVA achieved and maintained with ranibizumab PRN treatment up to 54 months

Well ... What’s the problem?

Key Questions

1. Are there DME patients who do not respond well to anti-VEGF monotherapy?
2. How do we identify this “resistant” DME patient population?

Key Questions

1. Are there DME patients who do not respond well to anti-VEGF monotherapy?

Patients Exhibit a Variable Therapeutic Response Over the 3 Year Period

- Approximately 50% of patients are treated successfully, but approximately 50% have DME that persists despite treatment
Are there confirmatory data?

### Patients Can Be Categorized Based on Their Anti-VEGF Response

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early and Consistent</td>
<td>Improved at the 16-week study visit but not at both the 33-week and 1-year study visits</td>
<td>143</td>
<td>49.7%</td>
</tr>
<tr>
<td>Early but inconsistent</td>
<td>Improved at the 16-week study visit but did not improve at the 33-week and/or 1-year study visits</td>
<td>43</td>
<td>14.9%</td>
</tr>
<tr>
<td>Slow and Variable</td>
<td>Did not improve at the 16-week study visit</td>
<td>36</td>
<td>12.3%</td>
</tr>
<tr>
<td>Non-Responder</td>
<td>Did not improve at the 16-week, 33-week, or 1-year study visits</td>
<td>66</td>
<td>25.0%</td>
</tr>
</tbody>
</table>

- After 3 anti-VEGF injections by week 16, it is clear if the patient is a responder or a variable non-responder.

### Patients Exhibit a Variable Therapeutic Response Over the 3 Year Period

- **14.9%** + **12.5%** + **25.9%** = **53.3%**

- Approximately 50% of patients are treated successfully, but approximately 50% have DME that persists despite treatment.

### Summary

Two populations emerge from the CMS evaluation:
- Clear anti-VEGF responders constitute approximately 50% of patients
- Variable or no anti-VEGF response is seen 50% of patients

This finding is corroborated by a recently published post-hoc analysis of the protocol I subjects treated with anti-VEGF therapy for DME.

### Is It Something About the Disease Itself?

### Patients Receiving Rbz Late in Disease Course Do Not Experience Same Benefit As Those Treated Early
The Role of Inflammation in DME

What is the scientific evidence?

Inflammation in the Progression of Diabetes

Pathophysiological Pathways

Stage of Disease

At risk (NIDT1)
Prediabetes (G21, 1BG)
Diabetes
Diabetic Vasculopathy

Aqueous Humor Inflammatory Cytokines Are Elevated in Diabetes

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<tr>
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<th>Control (n = 102)</th>
<th>Diabetes (n = 136)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>IL-1β</td>
<td>8.0 (0-104)</td>
<td>10.0 (0-104)</td>
<td>&lt;.005</td>
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<td>IL-6</td>
<td>13.5 (0-50)</td>
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<td>IL-8</td>
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<td>8.0 (0-74)</td>
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<td>MCP-1</td>
<td>70.5 (7-811)</td>
<td>385.5 (57-2568)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VEGF</td>
<td>66.0 (11-676)</td>
<td>262.0 (26-1868)</td>
<td>&lt;.001</td>
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</tbody>
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Increased Cytokine Levels in DME With More Leakage

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Control (n = 102)</th>
<th>Diabetes (n = 136)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>MCP-1</td>
<td>1284.5</td>
<td>2174.5</td>
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<tr>
<td>VEGF</td>
<td>1122</td>
<td>1322</td>
<td>&lt;.005</td>
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<td>IL-6</td>
<td>244</td>
<td>532</td>
<td>&lt;.005</td>
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<tr>
<td>ICAM-1</td>
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<td>60</td>
<td>&lt;.005</td>
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<tr>
<td>PEDF</td>
<td>0.002</td>
<td>0.002</td>
<td>&lt;.005</td>
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</table>

Role of Inflammation in DME

Early focal leakage • Diuzel leakage • Fibrosis • Pigmentary changes • Loss of photoreceptor cells

Multifactorial Switch

DME

Vascular Permeability

Inflammation

Vascular Permeability

TABLE OF CONTENTS NEXT TALK
The FAME Phase 3 Results also Support a Transition Around 2 years

FAME: Algorithms for Calculating Duration of DME

- Primary algorithm resulting in a median duration of 3 years
  - (year of randomization) - (year of diagnosis) + 1
  - The + 1 in the formula was included to ensure no patients had a duration of 0 years; however, it may have impacted the precision of the calculation
- Secondary algorithm resulting in a median duration of 1.73 years
  - ((dd/mm/yyyy of randomization) - (dd/mm/yyyy of diagnosis))
  - FDA preferred algorithm

≥ 15-Letter Improvement in BCVA, Median Duration of DME 1.73 Years

Key Questions

1. Are there DME patients who do not respond well to anti-VEGFA monotherapy?
2. How do we identify this “resistant” DME patient population?

Summary

- These results support that in some patients a transition in DME occurs
  - This transition occurs on a continuum, unique for each patient
  - Clinical trial data supports that 2 years is an important inflection point for the population as a whole
- Results from multiple phase 3 clinical trials in DME support the observation of a differential need for therapy in the chronic DME population

Patients Exhibit a Variable Therapeutic Response Over the 3 Year Period

- Approximately 50% of patients are treated successfully, but approximately 50% have DME that persists despite treatment
Long-term Response to Anti-VEGF Therapy for DME Can Be Predicted After 3 Injections — An Analysis of the Protocol I Data

Pravin Dugel, Joanne Campbell, Nancy Hulekasrip, Sallard Kiss, Anat Lowenstein, Albert Augustin, Julia Ma, Allen Ho, Valshini Patil, Scott Whitcup, Victor Gonzalez

DATA AND METHODOLOGY

Dataset: DRCR Protocol I
- Pooled Ranibizumab plus Deferred Laser and Ranibizumab plus Prompt Laser Study Arms

Post-hoc assessment by observed Week 12 BCVA response
- Long-term BCVA response out to 3 years (LOCF)
  - Mean BCVA change from baseline
  - ≥10 and ≥15 letter improvements from baseline

DRCRnet Protocol I Study Population

<table>
<thead>
<tr>
<th>Sample size at baseline</th>
<th>RAN + Deferred or Prompt Laser</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Sample size at baseline</td>
</tr>
<tr>
<td></td>
<td>BCVA observed at 12 weeks</td>
</tr>
<tr>
<td></td>
<td>CRT observed at 12 weeks</td>
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</table>

Stratification into 3 cohorts at 12w
- 6 Letters Improvement
- 5-9 Letters Improvement
- 10 Letters Improvement

Response after 3 Injections Predicted One Year Acuity

<table>
<thead>
<tr>
<th>Mean BCVA Change from Baseline</th>
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<tbody>
<tr>
<td>0.8</td>
</tr>
<tr>
<td>1.0</td>
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<tr>
<td>1.2</td>
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</table>

Conclusion

- Post-hoc analysis of DRCRnet Protocol I data shows that BCVA response after 3 anti-VEGF injections (at 12 weeks) is a strong predictor of long-term BCVA response
- Early response remains a significant predictor of long-term behavior even after adjusting for baseline characteristics
**Key Points**

- This is the first analysis to demonstrate that long-term response to anti-VEGF therapy in DME can be predicted after 3 injections.
- Additional therapies with alternate modes of action may be considered in inadequately responsive DME patients after 3 injections.

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**Assessing the Association between Early Anatomic Response and Long-term Outcome with Anti-VEGF Therapy in Diabetic Macular Edema – A Post Hoc Analysis of Protocol I**

Pravin U. Dugel, 1,2, Joanna Campbell, 1 Sulakshana Kas, 3 Anat Lowenstein, 2 Vanessa Shiff, 1 Jeff Lui, 1 Nancy M. Heikelamp, 1 Albert J. Augustin, 1 Allen C. Ho, 1 Victor H. Gonzalez, 2 Scott M. Witkin. 1,2,3

1 Department of Ophthalmology, Jules Stein Eye Institute, University of California Los Angeles, CA, USA; 2 Medical Retinal Research, Inc., White Plains, NY, USA; 3 Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA.

**Methods**

Dataset: DRGCR.net Protocol I
- Pooled ranibizumab + prompt laser and ranibizumab + deferred laser treatment arms.

Post hoc assessment by observed anatomic response at Week 12:
- Long-term visual acuity response out to 3 years (LOCF)
  - Mean BCVA change from baseline at Weeks 52, 104 and 156.
  - Long-term anatomic response out to 3 years (LOCF)
  - Proportion of eyes with <20% and ≥20% reduction in CRT at Weeks 52, 104 and 156.

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**THE ASSOCIATION BETWEEN EARLY AND LONG-TERM ANATOMIC RESPONSE REMAINED STATISTICALLY SIGNIFICANT EVEN AFTER ADJUSTING FOR POTENTIAL CONFounding FACTORS**

<table>
<thead>
<tr>
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<th>Multivariate Logistic Regression* on 20% CRT Reduction</th>
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<tbody>
<tr>
<td></td>
<td>At Week 52</td>
<td>At Week 156</td>
</tr>
<tr>
<td>Parameter</td>
<td>Odds Ratio (95% CI)</td>
<td>P-Value</td>
</tr>
<tr>
<td>&lt;20% CRT reduction at Week 12</td>
<td>0.13 (0.07-0.24)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- Eyes with <20% CRT reduction at week 12 were less likely to see ≥20% CRT reduction at years 1 and 3.

---

*Excludes: Active Age, Gender, Base CRT, Baseline CRT, Baseline CRT + ranibizumab injections at week 52/104.

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**Table of Contents**

- Long-term Anatomic Response in Eyes Categorized by Early Anatomic Response at Week 12
- One-Third of Eyes Had a Limited Early Anatomic Response at Week 12
- Eyes with Limited Early Anatomic Response Were Less Likely to See 20% Reduction from Baseline in CRT over the Study Duration
CONCLUSIONS

- A strong early CRT response was associated with greater long-term BCVA improvement; after controlling for confounders, this trend remained but the relationship was no longer statistically significant.
- This metric of anatomic response, measured at one timepoint, has previously shown an inconsistent association with BCVA response.

- Early CRT response was significantly associated with long-term CRT response in unadjusted and adjusted analyses.
- A limited early CRT response did not preclude later anatomic improvement; however, this improvement was slow to develop. In eyes with limited early CRT response at week 12:
  - Only 31.4% converted to show a strong response at year 1
  - ‘Trials’ non-responders’ were less likely to develop a strong CRT response over years 2 and 3 than those who subsequently showed a strong response at week 52 (slow responders).

KEY POINTS

- Early CRT response to ranibizumab is a significant prognostic indicator of medium- to long-term anatomic outcome in DME.
- For eyes with limited early CRT response to ranibizumab, alternative anti-DME therapies may be considered to maximize the potential for timely patient benefit.

Key Questions

1. Are there DME patients who do not respond well to anti-VEGFA monotherapy?
2. How do we identify this “resistant” DME patient population?

Role of Inflammation in DME

- Early focal leakage
- Diffuse leakage
- Fibrosis
- Pigmentary changes
- Loss of photoreceptor cells
- Multifactorial switch

VEGF-Mediated Vascular Permeability
VASCULAR PERMEABILITY

INFLAMMATION
Outcomes with As-Needed Aflibercept in the VISTA Extension Study: ENDURANCE 1 Year Results

Charles C. Wykoff, MD, PhD

Purpose: To investigate the long-term dosing requirements of patients managed with aflibercept for center-involved DME causing visual acuity loss.

Methods and Results: All patients completing the phase 3 VISTA trial at 4 clinical trial sites in 3 states were offered enrollment in the phase 4 ENDURANCE extension study. Sixty patients enrolled in ENDURANCE. All patients received aflibercept in the presence of clinically relevant DME, inclusively defined as DME limiting visual function per the treating investigator in attempt to assess real-world aflibercept use. Main outcome measures were mean aflibercept injections given through month 12 (M12), proportion of patients receiving no aflibercept, and the role of macular laser in decreasing treatment burden among patients requiring on-going treatments.

A mean of 4.5 aflibercept treatments were administered through M12. Eighteen (30%) patients required no aflibercept. BCVA gains achieved during VISTA were maintained and stable with individualized dosing during ENDURANCE, fluctuating by less than 1.5 mean letters at any given time point. Likewise, mean central retinal thickness remained relatively stable during ENDURANCE. Thirty-seven (62%) patients met macular laser criteria at a mean of 19.5 weeks with no significant difference in the frequency of aflibercept treatments before or after macular laser.

Conclusion: Vision gains achieved during the 3-year VISTA trial were maintained through 12 months of the ENDURANCE extension study with a reduced treatment frequency, with 30% of patients receiving no IAI. No significant reduction in IAI frequency was observed after macular laser application.

Notes: Dr. Wykoff discussed the results of the ENDURANCE study, an extension study following VISTA. More specifically, his group determined whether the efficacy and safety achieved with 2 mg intravitreal aflibercept injections for diabetic macular edema during the phase III VISTA DME trial were maintained with individualized, as-needed treatment, as part of a Phase IV, multicenter, open-label extension study.

He presented an example of a patient receiving multiple injections after two or three years of injections with an improvement in the vision from 20/80 to 20/32. Dr. Wykoff made the point that despite the good outcomes, the frequent visits and injections pose a burden to the patients as well as to the healthcare system. He later on summarized the injection number in various landmarks trials such as Protocol T, Protocol I and the open label extension study following RISE and RIDE pointing out that there are major differences in long-term injections needed given the complex retreatment algorithms in the second half of the trials.

ENDURANCE was a phase 4 open label study designed to assess the need for ongoing aflibercept in this VISTA population, essentially in the fourth year of treatment. All patients at the four clinical trial sites listed here were offered the opportunity to enroll in ENDURANCE, and 67% of eligible patients chose to enroll.

During ENDURANCE, patients were retreated PRN with two milligrams of aflibercept in the presence of clinically relevant DME. Visit intervals were prescribed according to protocol and if specific criteria were met, macular laser was applied in an attempt to see if that could help decrease treatment burden in this population. The primary end point was the number of aflibercept injections administered and secondary endpoints were vision and retinal thickness as measured by the OCT.

Clinically relevant DME was DME limiting visual function per the treating investigator. Subsequently, Dr. Wykoff presented some cases of clinically relevant DME. During ENDURANCE, patients were initially seen every month and if no aflibercept was given over three visits, the intervals increased to eight weeks. Again, if no aflibercept was given at three more visits, the interval was extended to 12 weeks.

At baseline, ENDURANCE patients were about three years older, had gained about ten letters of visual acuity, and had lost about 190 microns of central retinal thickness. During ENDURANCE, 10% of patients discontinued the trial during the first year, and 4% of scheduled visits were missed.

Visual acuity outcomes achieved during VISTA were then stable and maintained during the subsequent one year of ENDURANCE, with mean visual acuity fluctuating by less than a letter and a half at any given time point. Outcomes during ENDURANCE were not dependent on the original VISTA randomized arm, and they were not dependent on the need for re-treatment during ENDURANCE.

So, during ENDURANCE, the majority of patients demonstrated stable vision fluctuating by less than five letters at any given time point. About 15% of patients...
gained substantial vision at some time point, and 15% lost substantial vision. Most of these were due to cataract, either cataract extraction or cataract progression. The anatomic gains achieved were then stable and maintained during ENDURANCE, fluctuating by less than about 30 microns in any given time point.

How many injections did it take with aflibercept to maintain these gains that we achieved during VISTA? 30% of patients did not receive any additional aflibercept dosing, and the other 70% received at least one injection with a mean injection frequency of four and a half shots over the fourth year after randomization into VISTA.

At the end of one year of ENDURANCE, 52% of patients were at a visit interval of 8-12 weeks and about half of patients were at monthly visits. During ENDURANCE, 62% of patients met eligibility for macular laser after a mean of 19 and a half weeks, and 68% of these received a mean of 1.7 macular laser sessions. The annualized aflibercept injection frequency both before and after macular laser was 8.2 versus 7.8, a difference of injection frequency of 0.4. This difference is probably not clinically relevant, and certainly not statistically relevant in this small sample. 12% of patients demonstrated progressive diabetic retinopathy, and 7% demonstrated new vitreous hemorrhages.

The most important limitation of the ENDURANCE study is the small sample size. This was only 60 patients. The study had a very structured follow-up. There was no opportunity for treatment extension. There was no opportunity for switching anti-VEGFs. And there was no opportunity for adding or switching to a steroid.

In summary, trying to combine what we have learned from both the Open-Label Extension and ENDURANCE, following ranibizumab and aflibercept dosing in the fourth year of treatment following randomization, the visual and anatomic gains achieved during the Phase III trials have been maintained. About 25% to 30% of patients may not require any additional dosing, at least in that fourth year, specifically for DME. Finally, maybe most importantly, about a third of patients are going to experience obvious worsening of diabetic retinopathy severity when you decrease the frequency substantially.

**DISCUSSION**

Q: Question | C: Comment | A: Answer

Q: I think there are a couple of things that are important that you showed there. As you know, we’ve been using the anti-VEGFs now for quite some time and I have a number of patients from some of the original trials that we did where we’ve been treating them now for probably 12 to 15 years. The good news is that, eventually, the number of injections do decrease. The bad news is that you can’t get them off the injections completely. It’s interesting because the edema eventually gets better, just like you showed in your study, and then, the severity starts getting worse.

What I do now with these patients is that I not only treat them for the DME. I follow them also for the severity of the retinopathy and if you intervene before it gets back to where the severity was when you noticed the edema, the PDR and all that doesn’t really come back to the same level. So it’s really nice to see that you showed that. This is something that we’ve been doing now with some of these patients for over a decade and they do extremely well. Maybe one or two injections a year to keep them stable.

A: I think it’s a great point. Maybe I drank the Kool-Aid too much when originally Protocol I came out and I certainly have seen my partners continue to do this in discussions with patients. It’s easy to say upfront we’re going to treat you really intensively, and then, average number of shots is going to be zero to one and you’re four and beyond, I don’t think that that’s accurate. I think these people need something on an ongoing basis if they still have diabetes. Now, certainly, if they’re cured, or they got a pancreas transplant or something else, maybe they can come off, but my patients at least are needing some frequency of ongoing dosing for disease management.

Q: Before you move on, can you comment on the laser because for me, at least in my clinical practice, I’m really avoiding macular laser because I haven’t seen that kind of positive impact in macular laser that I had hoped to see.

A: I absolutely agree. When I structured this I was trying to think of something. I kind of thought we would have a large portion of patients that needed no injections, and then patients who needed a lot of ongoing injections. That wasn’t what we found. A lot of patients needed semi-regular dosing, but not every month. And so I was hoping in those monthly patients that maybe laser would help, so it wasn’t the population I really expected. I agree. I’ve moved away almost entirely from using focal laser to treat the center-involved DME causing visual acuity loss. Now, there’s certainly some cases, the circinate rings, that may be appropriate.

Q: What I wanted to caution you is I think we’ve got to be really careful about using the number of injections as a proxy to treatment burden. People do that all the time and I don’t think that’s fair. The reason that I say that is I know that people, not you, but people get up and say, look, if we make a contract with our patient according to Protocol I and say, “If you’re willing to give me a year of your life and come in every single month and get an
injection, your injection numbers are going to go down at Year 2, 3 and 4,” and that’s right. The injection numbers do go down, but that does not mean the treatment burden goes down because they’re still seen every four weeks. The injections take a second and we just, like, throw a dart, right, that’s all it is, so I think it’s really important not to confuse injections as a proxy to treatment burden. If the patient is coming in, that’s the treatment burden.

A: I think it’s a great point. I absolutely agree and that’s why to me the most meaningful number is 23 median visits. We talk a lot about the 15 to 16 injections, that patient is coming almost monthly for two years.

C: The truth of the matter is, is that they see burden not as injection. They see burden as the visits. That’s why it still amazes me in some offices that I share patients with where they’ll bring the patient back for the second eye injection still.

Q: Great talk, Charlie. I enjoyed it. I was interested in the 30% of patients that didn’t require injections because what I tell my patients who come in really active is that if we can get you out of this really active phase without losing too much vision in 5 to 10 years, most diabetics go into a quiescent phase where they don’t need anything and they do fine. But I’ve never heard a good explanation for why that is, so I’m asking you, as well as the rest of the audience. Why is it that these diabetics go through this really active phase, and then go through this really quiet phase and for the rest of their life, they don’t become active again a lot of times?

A: It’s a great point. Certainly, we all have those nasty PDR eyes that you have full PRP and are stable for decades afterward. I don’t know, but at least in my end I think that the number of patients that requires zero treatments after a year or two is small. It’s less than 30%. In my practice, it’s maybe 10 to 20% and these patients do need ongoing management. Maybe not aggressive monthly or every other month dosing, but they do need to be followed closely for years.

Q: Last year we discussed the importance of PRP in these patients because of this concept that patients may not continue to come back for long-term follow-up. Could you comment on those patients that continue to need ongoing therapy, where some of this is their diabetic retinopathy, as much as the diabetic macular edema? Do you move to PRP in that group, and do you use wide-field fluorescein for targeted therapy? Are you going to talk about that a little bit, maybe tomorrow?

A: I use angiography a lot. I think it adds to my understanding of the disease. Lloyd Aiello has published some great work saying peripheral findings do matter in the prognosis of these patients. DRCR Network has an awesome trial that’s ongoing, looking at the value of that long-term. So, I think we’ll learn more.

In my hands, in a PDR eye, I think the anti-VEGFs work beautifully, as long as there’s no traction. But anti-VEGF therapy is not a cure, and I make sure the patients understand that. And so I do have a very low threshold to put in an anterior PRP. It’s not going to be the only treatment they ever need, but it’s a safety blanket for them in case they are non-compliant, and many times noncompliance is what got them to my office in the first place.

Q: So I know this is not part of your talk, but in my clinical algorithm I see a patient with DME on day one. I have a sense; I tell them that doing treatment early, versus maybe six months later, preserves vision or gets them better. But it seems that your data suggests that if they delayed treatment or if they had the laser to rescue it and then delay treatment for 24 weeks, they ended up with the same visual results and the same OCT results. Am I wrong in supposing that delay of therapy, of the anti-VEGF, if that’s my first-time therapy, will not leave vision on the table?

A: I agree with everything you just said. VISTA and VIVID was nice for us as a community, because they gave us a different window to look at: six months. And then, beginning at six months, if patients did poorly, they got rescued. So, it’s not exactly the same, because not everyone got transitioned over to aflibercept. And we’ve looked very closely at that population, and they did extremely well. They gained, actually more vision than the patients originally randomized to aflibercept. But remember, they lost vision before they got access to aflibercept. So in reality, they never got to where the patients originally randomized to aflibercept ended up. Now, they were a slightly different population, so it’s not a completely clean analysis.

C: So, the take-home message, for me, is that you don’t wait. If you have to wait and if there’s some reason to wait, you still have hope for your patients. But I wouldn’t want you to walk out thinking that if you’ve got a patient presenting with active DME, that you should definitely wait.

C: I don’t think it’s the comfort level of waiting, but how much pressure do you put on the patients.

A: AMD and DME, very different. AMD I think of as a relatively much faster blinding disease. The curves don’t go down immediately. They’re slow over weeks to months, but it’s a much more pressing issue to start treatment. DME, I actually rarely will start treating the first visit, regardless of how bad it is. I want the patients to buy in; I want to explain it. I want them to bring their
family back so they’ve really bought-in to this concept, that it’s long term. This is a big decision, and it didn’t start last month.

Q: So, do you let visual acuity fluctuate before to do that? If my patients come in and vision’s below 20/20, I’m treating the first time they’re in my office. If their vision’s 20/20 and you’ve got those patients that are like, “I don’t know why I’m here,” that’s the patient that I bring back. I ask them to bring back their family. I’m pushing about hemoglobin A1c control, “See your diabetologist.” But I’m still not comfortable waiting in diabetes. Though I agree I’m more comfortable waiting for diabetic macular edema than for AMD.

C: I just wanted to follow up on the comment about how we get people to be quiescent. I think all of our retinovascular diseases, whether it’s AMD, DME, or RVO, all of them are quite different. Ultimately, what we’re trying to do is to get the vessels to end up being in a quiet state. An anti-VEGF, while it’s great, is not quite getting us there, and there’s a whole field of opportunity to try and figure out how to trick the vessels into behaving again. And I think that’s the next frontier.

Q: Are there no patients for which you use LASER. You feel that DME laser is like bismuth for syphilis or something? You don’t use it at all?

A: I tend to be more of a splitter in life than a lumper. The way I split that question is that there are three kinds of DME. I’ll make this real simple. Center-involved DME with visual acuity loss, there is no role for LASER. But then the other two, I think the jury’s still out, and that’s why protocols like V are ongoing.

C: But I do think that you’ve alluded to the fact that circinate retinopathy that there are times when putting a spot of laser in can be incredibly effective.

Q: Charlie, as somebody who likes to image all my patients with multiple machines, I hate to ask this question, but wouldn’t it be just easier, just to inject all our patients every eight weeks and not do a fluorescein? The question I’m asking is, what is the number needed to harm? I think that what we’re doing is very reactionary, and there are patients who don’t need their metformin at 1,000 milligrams. They might need it at 950. But do we have too much information, and as a result, not getting the results because we’re under-treating? Because even the numbers that you showed aren’t really what we do in the real world. They’re still substantially more.

A: You’re absolutely right. I think we, as a retina community, err on the side of under-treatment, for sure. But that said, I am a big believer in individualized therapy. Three to four injections is an average, and there are patients that need a lot less and a lot more. And for those that need a lot more, I’m looking for other treatments I can do to try to decrease that burden.

C: I think that the concept of just inject on a fixed protocol for everybody, that gives me chest pain when I hear that. I think that the art of this is clinical management of your individual patient. And we have such good imaging capabilities. And if you know that 30% of your patients are never going to need to be injected again, you’re may end up treating a large number of patients that may never need to be treated.

Q: The number needed to harm?

C: The number needed to harm is a number, but remember, when we harm, we harm in a huge way. It’s not like I’m thinking, “Is my harm an injection?” In my opinion the harm is that the patient is visually blinded from endophthalmitis after injection. I think that we’re all struggling with what the right answer is. So, that’s the key. That’s why we’re all here, and that’s why these discussions, I think, are much more important, almost, than any other aspect of what we’re doing. We need to take the literature and apply it to the patients we’re going to see when we’re back next week.
VISTA EXTENSION STUDY: ENDURANCE 1 YEAR RESULTS – WYKOFF

ENDURANCE
Extension Study Following VISTA

Charles Wykoff MD PhD

Disclosures

- Financial
  - Consultant – Allergan, Alimera, Bayer, Genentech, DRCR, Genentech, ONL Therapeutics, Regeneron
  - Speaking, Allergan, Regeneron
  - Research Support – Alcon, Alimera, Allergan, Genentech, DRCR, Genentech, Regeneron

- Human Subjects
  - This study is Institutional Review Board approved

- Funding: Investigator Initiated Trial
  - Grant from Regeneron
  - CERF had control on trial & is responsible for study design, data collection & analysis

![Image of study results and data charts]

![Image of tables and graphs showing study outcomes]

![Image of clinical trial data]

![Image of frequent visits and multiple injections]

![Image of retreatment algorithm for particular criteria]

![Image of Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt versus Deferred Laser Treatment: 5-Year Randomized Trial Results]

![Image of table showing DRCR Protocol-I Intravitreal injections]

![Image of chart showing outcomes with As Needed Ranibizumab after Initial Monthly Therapy]

22 ASPEN RETINAL DETACHMENT SOCIETY MEETING NOTES 2017
VISTA EXTENSION STUDY: ENDURANCE 1 YEAR RESULTS – WYKOFF

**RIDE/RISE Open-Label Extension (OLE)**

- PRN Re-Tx Criteria
  - Evidence of DME on TD-OCT
  - Worsening visual acuity 3ESE refr.
  - Visual acuity <14 letters in March 9 due to DME

- Follow-up interval:
  - 30 days for 1st visit
  - 60-90 days, investigator discretion (must Tx at visit)

- Completed VISTA = 357

**ENDURANCE**

**Methods:** Clinically-Relevant DME

- DME limiting visual function per the treating investigator

**ENDURANCE**

**Methods:** Interval & Macular Laser

- Visit Intervals:
  - Q4 week: if no aflibercept x 3 →
  - Q8 weeks: if no aflibercept x 3 →
  - Q12 weeks →
  - Recurrent CR-DME: aflibercept given and return to Q4 week interval

- Macular Laser
  - Beginning at week 12, if 2 aflibercept in 24 weeks
    - Focal to leaking microaneurysms outside of the FAZ
    - Grid to areas of diffuse leakage & areas of retinal non-perfusion outside of FAZ

**Baseline Demographics**

<table>
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<th>VISTA (n=459)</th>
<th>ENDURANCE (n=60)</th>
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<td>63.3 (55.5)</td>
<td>63.3 (48.3)</td>
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<tr>
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<td>299 (65.5)</td>
<td>29 (48.3)</td>
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<tr>
<td>Race, n (%)</td>
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<tr>
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<td>46 (76.7)</td>
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<tr>
<td>Black or African American</td>
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<td>24 (5.3)</td>
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<tr>
<td>Mean HbA1c</td>
<td>7.8</td>
<td>7.5</td>
</tr>
<tr>
<td>Mean duration of diabetes, years</td>
<td>17.1</td>
<td>20.2</td>
</tr>
<tr>
<td>Mean BCVA, letters</td>
<td>59.3</td>
<td>69.6</td>
</tr>
<tr>
<td>Senser VA equivalent</td>
<td>20/63</td>
<td>20/40</td>
</tr>
<tr>
<td>Mean CRT thickness (µm)</td>
<td>292</td>
<td>290</td>
</tr>
</tbody>
</table>

**ENDURANCE**

**Design**

- Re-Tx PRN in presence of CR-DME
- Visit Intervals according to protocol

**Endpoints**

- Primary
  - Aflibercept (intravitreal administered)
- Secondary
  - Mean change in BCVA & CRT

**Patient Retention**

<table>
<thead>
<tr>
<th>Enrolled</th>
<th>Completed 1 Year</th>
<th>Possible Visits</th>
<th>Missed Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>54 (90%)</td>
<td>666</td>
<td>29 (4%)</td>
</tr>
</tbody>
</table>
ENDURANCE: VA Outcomes

- Differences in Outcomes:
  - Original VISTA arm: P=0.73
  - ENDURANCE Re-Tx: P=0.96

ETDRS Changes

ENDURANCE: Anatomic Outcomes

How many injections to maintain visual & anatomic gains?
**VISTA EXTENSION STUDY: ENDURANCE 1 YEAR RESULTS – WYKOFF**

**ENDURANCE**

*Limitations / Challenges*

- Sample size: 357 → 60 → 54 completed 12 months (my Tx)
- Structured follow-up: no opportunity for TREX
- No opportunity for switching anti-VEGF or adding steroid
- Define DME that deserves Tx? CR-DME
  - DRCR: Complex re-Tx algorithm dependent on VA, OCT & change
  - RIDE/RIDE OLE: “Evidence of DME”

**Long-Term Tx of DME**

*OLE & ENDURANCE*

Visual & anatomic gains achieved during phase III trials maintained with individualized dosing

- 25-30% patients require no additional dosing for DME
- 3-5 mean intravitreal injections
- 20-40% patients experience worsening of DRSS
Reoperations in Vitreoretinal Surgery

HUGO QUIROZ-MERCADO, MD

SUMMARY
Reoperations are surgeries that may be unplanned return to the operating room that frequently occurs within 30 to 90 days after first surgery or planned surgery as a second step or complication after first surgery. We will discuss several approaches in several pathologies either on planned or no planned surgeries.

Association to Prevent Blindness in Mexico City is an ophthalmological referral center in which 2,400 vitreoretinal surgeries are performed annually. Based on some research and anecdotal experiences from our hospital we will discuss several approaches to resolve reoperations, ways to prevent complications, interesting cases and personal view to improve better outcomes.

Main topics will include: PPV vs SB for primary RRD, management of submacular fluid, macular folds, submacular hemorrhage during surgery, phaco-vitrectomy, MH reoperation, severe bleeding during TRD surgery, among others.

Finally I will discuss some things out of the box. Is there room for new vitreo-retinal surgeries? Can we work together with anterior segment surgeons to improve outcomes after cataract surgery?

NOTES
Dr. Quiroz-Mercado discussed the following:
1. Unplanned returns to the OR.
2. Planned or late complications that take us back to the OR.
3. Techniques to improve outcomes in selected pathologies.

Unplanned reoperations in vitreoretinal surgery can occur within 30-90 days after surgery, and this may be used as an indicator for quality of care. There are several variables that may lead to a higher chance of reoperation, one of which is the severity of pathology. It is important to periodically analyze how often and why we are returning to the OR so policies and routines can be established to prevent return trips to the OR.

Planned or late complications leading back to the OR may also occur. Silicone oil removal is an example of a planned trip whereas late complications requiring reoperation include reopening of a macular hole, recurrent vitreous hemorrhage, retinal detachment, or cataract. So how can we prevent these unplanned trips back to the OR? Embracing new techniques and developing our own techniques based on experience can help prevent unplanned trips back to the OR.

How do we prevent reoperations? We have to embrace new techniques. For example, staining ILM with brilliant blue instead of ICG. In Dr. Quiroz-Mercado’s opinion, staining with brilliant blue is totally different than staining with ICG. He stated that brilliant blue makes the ILM stiffer and better visualized, and therefore the surgery may be easier.

One way to prevent a return trip to the OR is by doing procedures in the office. Dr. Quiroz-Mercado stated that in-office fluid air exchange for the post-operative vitreous hemorrhage is a great way to save a trip to the OR. He does this by using either expansile gas or air with a 10cc syringe and the plunger at half way (5cc). That way he can draw some fluid out of the vitreous cavity and then inject gas. He’s done these in numerous settings for vitreous hemorrhages including those that have occurred after retinal detachment surgery and epiretinal membrane peels.

Other potential ways to prevent further trips to the OR is to be immediately available for our cataract surgeons. When we send them a cataract that occurred after vitrectomy, being available during their cataract surgeries may prevent a third trip to the OR for a dropped lens. Also consider performing cataract surgery at the time of silicone oil removal which again can save another trip to the OR.

Dr. Quiroz-Mercado then went on to discuss techniques that can improve outcomes in selected pathologies.

He presented a case of massive vitreous hemorrhage while performing a tractional retinal detachment (TRD) repair in a diabetic patient. The eye was full of blood and the bleeding could not be controlled. This is a difficult situation that is often encountered while doing TRD repairs. A technique he likes to use in these situations is to use PFO as a tamponade to help me obtain hemostasis. He fills the vitreous cavity with PFO and will take the patient back in about 10 days to remove the hemorrhage and finish the surgery. Other ways he deals with massive hemorrhage in a TRD is with anti-VEGF therapy. He uses it during the perioperative period. Cryotherapy at the sclerotomy can also be helpful in minimizing postoperative recurrent vitreous hemorrhage.

How many anti-VEGF treatments do you do when you have recurrent vitreous hemorrhages after doing a vitrectomy for vitreous hemorrhage? For example, after doing a vitrectomy in a PDR patient with vitreous
As for tamponades, there are times that silicone oil is preferable. He likes to use silicone oil in monocular patients thus allowing for visual rehabilitation on postoperative day one. He also uses silicone oil when there are altitude considerations or for TRDs when the patient is on blood thinners.

Dr. Quiroz-Mercado discussed another technique he uses for patients under oil who need a reoperation. He will perform a two port PPV in which no infusion is needed and all he will need is a light pipe and another instrument e.g. vitrector, forceps. He has used this two-port system to do ERM removals and recurrent retinal detachments under oil. He cautioned, however, that if you try this method you have to move your instruments very slowly in the eye otherwise you create a vacuum effect and create small bubbles that will make your view difficult.

There are several different techniques that can be used for reoperations for macular hole surgery. One method is stretching the retina under silicone oil, using a soft tip of forceps. Another method used is ILM peeling with a flap of temporal retina that is transposed into the hole, so when you do the fluid air exchange the flap is covering the hole.

And recently, it has been shown that autologous retinal transplantations can be done with some success. A case was presented that was published in JAMA Ophthalmology Feb. 2016 of a patient who presented with a 1100 micron hole and improved to 20/80 postoperatively following an autologous retinal transplant.

Dr. Quiroz-Mercado then continued with the topics of how to protect the retina during pars plana vitrectomy and then to surgery for central retinal artery occlusions (CRAO).

PFO has been infused during a PPV successfully in lieu of BSS. The reason behind using PFO instead of BSS is that there is increased oxygenation to the retina under PFO, and this may be neuroprotective. This may be useful in our diabetic patients, trauma patients, or our surgeries where there is extensive manipulation.

For CRAOs, Dr. Quiroz-Mercado said that he has never seen a patient improve with ocular massage. He described a patient who presented within hours of experiencing a sudden loss of vision from a CRAO and they took him to the OR. Using forceps to crush the emboli they were able to open the artery and promote reperfusion. They could see that the circulation in the retina looked much better. And all of this was done under PFO. The patient’s vision improved to 20/80. So, Dr. Quiroz-Mercado suggested that the next time you see an acute CRAO, don’t massage it, but consider immediately taking the patient to the OR.

The topic of combination anti-VEGF therapy with surgery for CNVs was discussed. Although retinal surgeons used to surgically remove CNVs, this procedure may be less common now in the era of OCT and anti-VEGF. A case was presented of a patient with CNV, the vision was 20/150, and the patient had an intravitreal injection of bevacizumab. The CNV was juxtafoveal and the membrane was subsequently surgically removed. On follow up, the center of the fovea was free of blood and the vision was 20/60. At six months follow up, the vision was 20/20.

Surgical video was shown demonstrating the removal of the CNV away from the center of the fovea. It is type II CNV. Dr. Quiroz-Mercado did not recommend doing this for all cases of CNV but did suggest considering this approach for cases of type II when they are juxtafoveal. He also recommended combining surgery with anti-VEGF therapy.

Dr. Quiroz-Mercado concluded by saying that there is room for new venues for research. We have seen how anti-VEGF has changed the way we treat AMD and diabetic macular edema. But what about retinal detachments? We still have very bad visual acuity in many cases despite good anatomical outcomes. Can we create a new drug to help these patients?

DISCUSSION

Q: Question | C: Comment | A: Answer

Q: I always learned so much from your talks. So one of the areas we don’t concern ourselves with too much but has one of the highest re-operation rates is recurrent vitreous hemorrhage after vitrectomy for vitreous hemorrhage. You mentioned cryotherapy to the sclerotomies. Do you still do cryotherapy to the sclerotomies even when we are using small gauge instrumentation? Also, when I look at these patients who I’ve already operated on and in particular the ones who’ve had anterior laser with depression, in a large percentage of the cases, I can’t find the neovascularization, so where do you treat?

A: I recommend using UBM to identify the source of the blood. I do not use cryotherapy much anymore. I used it in some cases when my patients are very sick or have kidney problems. We did a study at our hospital in which
we used UBM and we were able to locate the vessels causing the bleeding. I have not done this but you could use the UBM to locate these vessels and use cryotherapy or anti-VEGF therapy, maybe this will prevent us from needing to take our patients back to the OR.

C: I’d offer one thing that I learned and I still teach the fellows, and I agree post op vitreous hemorrhage is still a problem. I use a hypotensive test at the end of surgery shutting off the infusion, soften the eye, and then you watch. And you watch for a minute or so, and you look, and a lot of times you’ll see where bleeding is coming from and you can address it.

Q: Do you suture your sclerotomies after doing a vitrectomy for vitreous hemorrhage to prevent hypotony?

A: No, I am afraid that the suture will push out the gas and then cause hypotony.

C: Happy to see in office fluid air exchange, I feel that I can prevent going back to the OR 75% of the time with this. To do these I like to use the Alcon 25-gauge trochar without valves, and use a 30-gauge needle to inject fluid and fluid will flow right out around the needle. After the vitreous hemorrhage is sufficiently cleared at the end of the procedure the eye will be soft so then inject fluid with a 25 gauge needle to add pressure. It works beautifully.
Reoperations in Vitreoretinal Surgery

Second step (planned) or late complication

- Silicon oil removal: planned
- Macular hole reopening: complication

Reoperations in Vitreoretinal Surgery

How to prevent reoperations

- Embrace new techniques
- Create own techniques based on experience

Didier Ducorneau in France
ppv for ERM

Reoperations in Vitreoretinal Surgery

Unplanned return to the OR

- Rhegmatogenous retinal detachment
- Massive hemorrhage in TRD
- Incomplete ERM dissection
- Lens damage during ppv (June outbreak)
- RD after ILM and ERM surgery

Reoperations in Vitreoretinal Surgery

Unplanned return to the OR

- In-office air fluid exchange
- Massive hemorrhage in TRD

In-office air fluid exchange

Expansible gas or air
10cc syringe
Plunger at half way (5cc)

Massive hemorrhage in TRD

- Management during surgery
- Reoperation depending on posterior hyaloid status
- If posterior hyaloid is present early reoperation mainly with SO filled eyes

How many days can we leave PCL in the vitreous cavity?

Mid term PCL tamponade

- Trauma cases
- Severe RD
- Some TRD

AC compartmentalization

Three years PCL tamponade with
AC damage Fina VA 20/50
Normal ERG

Post operative hemorrhage in TRD

- How to prevent it during surgery
- How many anti-VEGF treatments before bringing patient back to the OR?
- Retro SO blood

URM study of new vessels at several ports
Patients under dialysis
Hemorrhage in TRD
- Prevent trans and post operative bleeding with anti-VEGF treatment
- Cryotherapy of sclerotony sites
- Transoperative PCL
- Tamponade with PCL
- Reoperation before 10 days

Lens damage during ppv
- First ppv surgery: lens damage
- Best timing for reoperation cataract surgery
- When planning cataract surgery prevent 3th reoperation by considering retina surgeon participation

Reoperations in Retinopathy Detachment Surgery
Second step (planned) or complication
- Silicon oil removal
- Macular hole reopening

Reoperations in RRD
- Pneumatic retinopexy
- PPV with and without SB
- Is it room for SB?
- Which SB? Segmental, radial, etc.

Silicon Oil removal
- Combined with phacoemulsification
- Hybrid technique with 20 port (faster to aspirate)
- Membranes are easier to remove from retina when the eye had SO several weeks
- Consider 360 laser for unseen breaks

Best technique for RRD
TRENDS IN PRIMARY RETINAL DETACHMENT SURGERY
Results of a Bipartneter Study
- Two centers study: Vienna and NY
- SB vs PPV
- Anatomical and visual outcomes comparable

Personal experience: Best VA with pneumatic, ppv than SB
REOPERATION: vitrectomized eye with SB

Techniques for reoperations
- Two-port ppv under SO
Redetachment in eyes with SO
- Two port vitrectomy (no infusion)

Silicon Oil vs Gas
- Consider only eye patients
- Consider altitude
- Blood thinners in TRD’s
- SO and ±5 disposable contact lens for immediate visual rehabilitation

Reoperations MH surgery
- ILM peeling with flap techniques
- Retina stretching under SO
- Autologous retina transplant

Can we improve outcomes in selected pathologies
- Protect retina during PPV
- Surgery for retinal artery occlusions
- Advantage on combining OCT, small gauge PPV and anti-VEGF on extraction of juxtafoveal CNV

Intravitreal fluids during PPV

Vitrectomy Under Air
Valet, Yined B, MD; Lee, Christopher J, MD; Devli, Francois MD; Holobach, Jean-Pierre MD; Section Editor(s): Williams, George A. REINA 2012;32:1062
Perfluorocarbon perfused vitrectomy

- USE of PCL infusion in lieu of BSS
  (increase oxygenation, neuroprotection ?)

Change indications for CRAO

- Nd YAG laser Embolysis or PPV arterial embolectomy

Can we indicate CNV removal on the era of new OCT technology, anti-VEGF and small gauge ?

1 week PO
VA 20/60
FUTURE

Surgery vs Molecular treatment

- Present technology is good enough to replace some procedures or combine with molecular treatment to get better outcomes?
- AMD: Laser, PDT, Translocation → anti-VEGF
- DME: Laser, pPV → anti-VEGF and steroids
- RRD: just surgery. Where is it’s molecule ???

All pathologies surgical treated should have its own molecule regardless of what good surgery is.

FUTURE

Surgery vs Molecular treatment

- Most common surgery is cataract surgery

- Are we working on “protecting” macula structures on eyes with DME and AMD in the perioperative period of cataract surgery?

- Cataract surgery in AMD and DME → Neuroprotection (new molecule)
The Potential of Stem Cells Based Therapies for Retinal Diseases

MARK S. HUMAYUN, MD, PhD

SUMMARY
The talk will cover a novel approach to transplant a stem cell derived monolayer of RPE in dry AMD. Preclinical results leading to the approval of the phase 1 study and some of the phase 1 results will be discussed.

NOTES
There are numerous ongoing clinical trials investigating the use of stem cells for retinal diseases. Current clinical trials are enrolling patients with geographic atrophy, wet AMD, retinitis pigmentosa and Stargardt’s disease. The cell source includes embryonic stem cells but also fetal tissue and adult eyecup preparations. These cells need to be cultured under a cGMP.

Dr. Humayun described the study for retinitis pigmentosa that is led by Michael Young and the company ReNeuron. It involves allogeneic retinal progenitor cells from fetal eyes that can be expanded through multiple passages differentiated into photoreceptors in vitro and in vivo. These cells when implanted in the RCS rat, the rats showed improved head tracking behavior. The method of delivery is subretinal and the clinical trial is still ongoing.

Jcyte is another retinal progenitor cell line. The method of delivery is intravitreal and no immune suppression is used. The idea is that this mechanism is neurotrophic. A current trial is ongoing. Enrollment is complete and so far, they’ve passed all four interim Data Safety Monitoring Board safety reviews.

There are great treatments for wet AMD; however, there is an unmet clinical need for patients with advanced atrophic AMD. In patients with geographic atrophy, the issue is not just with the RPE cell. Dr. Humayun noted that this is a very important consideration. The drusen accumulate in RP as we know clinically, but then the Bruch’s membrane also gets affected. The Bruch’s membrane is not what we think it is. If you were to take new RPE cells and put it on this Bruch’s membrane, they won’t do as well as it has been shown in the past.

Currently, there are efforts to maintain visual acuity with anti-complement drugs. Replacing RPE with synthetic Bruch’s membrane could improve vision. Where’s the data on that? There is a common perception that in patients with geographic atrophy the overlying photoreceptors are gone and the choriocapillaris are atrophied. But are they really gone? In patients that received an autologous RPE transplant from the peripheral retina, vision improvement has been reported in previous studies. This approach, however, did not become very popular given its high complication rates. It did serve as the proof of principle that a healthy RPE layer can improve vision in patients with advanced geographic atrophy. In addition, investigators are theorizing that a new RPE layer can restore the outer segments of the photoreceptors.

Dr. Humayun continued by elaborating on his sheet approach of delivering RPE stem cells into the subretinal space. Polarized RPE, cells with the apical surfaces up and the basal surface down, produce an enormous amount of PEDF and VEGF. Could that VEGF actually recover the choriocapillaris, which otherwise looks atrophic?

His group has created a synthetic membrane that is permanent, much like an IOL. The backside is thin like Bruch’s membrane and allows 200 kD molecules to diffuse. They also designed a special tool for the delivery of the sheet with the stem cells. This tool actually rolls it up much like a taco and it feels like an IOL injector in the subretinal space. There is no cell death or loss during the delivery.

He demonstrated the technique with a surgical video. After a PVD is induced a small subretinal bleb is created at the site of the injection and the injector unloads the sheet with the stem cells in the subretinal space. He stressed that a key step of the whole surgery is the induction of the macular detachment which has to happen slowly over 20-25 minutes. Furthermore, he showed OCT and histology data of the implant in pigs demonstrating good survival of RPE and proper placement in the subretinal space.

Phase 1/2 studies have already been initiated and are currently enrolling new patients. Dr. Humayun showed clinical and OCT data of a patient that received the RPE sheet implant. The external limiting membrane started forming in the area that received the implant and this effect was maintained until the last follow-up of the patient at 9 months after the surgery. That is in contrast to the OCATA study where the ELM never regenerated. He concluded his talk stating that photoreceptor transplantation is very challenging given the synaptogenesis problems encountered in it. On the other hand, he pointed out that the way to regenerate the outer retina is by transplanting healthy RPE as it does not require any synapses with the overlying neural tissue.
In summary, a sheet of human hESC-RPE on synthetic Bruch's membrane can be implanted and is well-tolerated in the subretinal space of animals. The RPE/membrane graft survives and performs the functions of RPE cells. Further trials are planned in humans. These trials will address key questions such as the health of photoreceptors and choriocapillaris.

DISCUSSION

Q: Nutrient transport, or oxygenation across the membrane?
A: You basically have to have the membrane be about 0.3 microns that allows about 250 kilodaltons, and so that's the key. What we couldn't do with the membrane is we couldn't make holes all the way through it. That would be the easiest way to build that membrane. The reason we couldn't do that is because the cells would go right through the hole. So, we had to create this membrane which had a flat top surface, much like you make computer chips, and that allowed the top side to be flat, and the back side to have those thinned areas.

Q: How did you make sure the sheet was implanted the right way up?
A: Very good question. So, everybody said the thing's going to flip. What we do is we make a fiduciary mark. Anytime you want to build anything like this in engineering, you basically build a fiduciary mark which has got a little "Snoopy" nose. So on the handle, when you grab it, it's got a little nose and if it's right side up the nose is always going to be this way. If it's flipped, the nose is going to be pointing downwards.

Q: Did you ever flip them?
A: Oh yeah, we flipped them! It doesn't flip with the tool. Once you get into the sub-retinal space it doesn't flip, but before that when we didn't have the tool it would flip all the time. It was challenging.

Q: Why do you put PFO in that area?
A: Because I want to flatten out the retina. I don't want to aspirate there with the fluid because you may aspirate the cells. So I put PFO on there so you don't aspirate any of the cells.

Q: That's awesome, Mark. My question comes down to the surgical technique, because we know histopathologically, in areas of atrophy, that the macula, or what's left of it, is fused. And, in some of the suspension trials that we've done, that you mentioned, when we tried to create the bleb and actually had the bleb move into the atrophic area, the bleb will either just move around the atrophy or we've created a macular hole.

Q: What gauge was the inserter?
A: That's 20 gauge. So, you can do the gauge 25 or 23, but you have to enlarge. You can't use a non-directional sub-retinal cannula, sub-retinal injector. That will always spread it either peripherally or around it, or blow a hole. So, you have to use a directional sub-retinal injector. That, we did. And then no calcium magnesium. Really important.

Q: What do the cations do?
A: We used to detach a lot of retinas, as you know from translocation and animal studies. Turns out that divalent cations, if you remove them, it sort of breaks that RPE adhesion to the photoreceptor outer segments and it's easy to remove. These people, they don't have outer segments. So, one would think that that mechanism may not apply, but I've seen that it works a little better than just using BSS plus or something.

Q: Why not use inducible pluripotent stem cell derived RPE cells? Because then you could match them with the patient and you wouldn't need immunosuppression.
A: So, the pre-matched stuff is difficult thus far. They're coming up with what's called universal cell line where they knock out the HLA antigens so it is what you were talking about. But right now, they're not there. So, if you have to do it for each patient using the Yamanaka factors or the other factors, what happens is that you have to, from a regulatory standpoint, you have to release that batch, test it. It becomes very expensive per patient. But you do avoid, obviously, the immunosuppression. But if you were to do it on every patient and use their iPS cells, it is very expensive. But if you take an iPS cell, remove the HLA antigens and make it a universal cell line, which is really hot topic right now, it might work. But let me tell you about the Riken second patient, when they use Yamanaka's from Japan, Nobel prize, the whole nine yards, iPS is king there. They had a malignant transformation on the second cell line before they injected and so they ended up stopping the study. So, those transformational factors that take those cells from dermal, or whatever cells back, are not completely innocuous.

Q: Very interesting that you've seen the regeneration of the external limiting membrane on these cases. What about the other side? Have you seen any evidence on OCT of regeneration of the choriocapillaris?
A: Great question. And we're doing that right now. We're looking right through that. And this membrane is pretty transparent so it allows us to do that.
The Potential of Stem Cells Based Therapies for Retinal Disease

Mark Humayun, MD, PhD
Corneas Regs Professor of Biomedical Sciences
Professor of Ophthalmology, Biomedical Engineering, Cell and Neurobiology
University of Southern California

Relevant Financial Disclosure

Regenerative Patch Technologies
Alcon/Novartis
Iridex
Replenish
Second Sight Medical Products
Clearside

Unmet Clinical Need

Advanced AMD

Dry (atrophic) AMD
80-90%

Wet (exudative) AMD
10-20%

Treatment Hypothesis: Replace damaged RPE on synaptic Bruch's membrane to prevent vision loss

Dramatic Visual Acuity Improvement after Autologous RPE Transplant

In-vivo imaging: Human photoreceptor mosaic using Adaptive Optics

Other Stem Cell Based Therapeutics for AMD

Therapy | Developer | Status of Previous
--- | --- | ---
Suspension RPE Cells | Advanced Cell Therapies, Inc | Phase I Complete, Three-Patient Phase II Completed
Suspension RPE Cells | Cell Cure, Inc | Preclinical/Early Phase I Indicated
Suspension Neural Progenitors | Stem Cells, Inc | Phase I Clinical Trial Initiated
Suspension Neural Cells | Janssen (JNJ) | Phase I/II Clinical Trial
RPE Cells on a Hyaluronic Platform | First Junctional Progenitor Cell (Bioengineered) | Just Filed Regulatory Documents with FDA
POTENTIAL OF STEM CELLS BASED THERAPIES – HUMAYUN

CPCB-RPE1 Cells Survive Post Transplant

Limitation of Cell Suspensions

- Human
- RPE
- DAPI

Non-human with hESC-RPE cell suspension: Poor RPE Survival

CPCB-RPE1: Why Polarized RPE on a Membrane Instead of Suspension RPE cells

Advantage Over Competitors Using Suspension RPE cells

- Polarized RPE cells
- Non-polarized RPE

- Show more neurotrophic growth factor (NGF) secretion from the apical surface
- Can integrate with PR outer segments thus promoting efficient phagocytosis of ROS
- Non-polarized RPE

Polarized RPE Secrete PEDF

Membrane support critical for polarization and function of RPE

Permeability of Parylene C

Parylene thinner than 0.65μm has similar flux and MW exclusion to both native and previously reported artificial Bruch’s membranes.

CPCB-RPE1: hESC-RPE Synthetic Substrate Patch

hESC-RPE / parylene patch in RCS rat

CPCB-RPE1 Cells Survive Post Transplant

hESC-RPE patch after transplant

40 ASPEN RETINAL DETACHMENT SOCIETY MEETING NOTES 2017
POTENTIAL OF STEM CELLS BASED THERAPIES – HUMAYUN

CPCB-RPE1 Phagocytes Photoreceptor Outer Segments in the Host Retina

- 60 days after implantation
- Phagocytes not observed in native RCS retina

Delivery of CPCB-RPE1

- Delivery in the Yucatan Pig
  - Can visualize RPE diffusion between retina and choroid
  - Peripheral Retinopathy at 3, 5 mm

Surgical Video-Implantation in Enucleated Porcine Eye

Transplant Surgical Suitability

- Pre-implantation
- Post-implantation

CPCB-RPE1 Survives in the Yucatan Pig Subretinal Space

- 3 Months after Surgical Implantation
- Infrared
- FA
- OCT

CPCB-RPE1 In the Pig Subretinal Space

- Infrared Fundus Photography, SD-OCT Imaging, and Histology After Implantation
- Good survival of RPE
- RPE migration in subretinal space
- No evidence of retinal detachments

Conclusions

- A sheet of human hESC-RPE on a synthetic Bruch’s membrane can be implanted and is tolerated well in the subretinal space of animals (transplanting differentiated RPE)
- The RPE/membrane graft survives and performs the functions expected of RPE cells
- Further tests are required to demonstrate the tolerability and functionality of this approach in patients-phase 1 studies in 2015
  - Health of photoreceptors (7 inner segment survival)
  - Health of choriocapillaris (RPE with VEGF production)

Team

Thank you for your attention
PANEL 1: Advanced Management of Diabetic Macular Edema

MODERATOR: PRAVIN U. DUGEL, MD
Panelists:
Mark S. Humayun, MD, PhD
Hugo Quiroz-Mercado, MD
Charles C. Wykoff, MD, PhD

SUMMARY
Recent studies have suggested that we are on the precipice of a monumental paradigm shift in the management of the leading cause of blindness in the world, diabetic related vision loss. This expert panel will discuss the clinical implications of recent clinical trials in the management of patients with DME and DR. Representative cases will be presented. This will be a clinical discussion emphasizing both the physiologic and logistic implications to the community physician of a strategic shift in treatment.

NOTES
Case 1: DME treatment:
55-year-old man with DME. He had 8 bevacizumab injections, still had edema. He was given 14 bevacizumab injections total, still had edema. VA was still very poor. He was then given a dexamethasone implant.
The fluid got a little bit better, but the visual acuity really didn’t change much at all after the dexamethasone implant. Now he looks anatomically better, but the vision was still poor. So while we can say that the steroid implant may have improved the anatomy, visual acuity-wise his vision really hasn’t changed a lot.

QUESTIONS:
• How do you judge “poor response” or “non-response” to anti-VEGFA monotherapy?
• Do you switch antiVEGF drugs first?
• Do you consider steroids? If so which one? Bolus? Ozurdex, Illuvien?

DISCUSSION
Q: (Moderator) How do you judge a poor response or a non-responder in your clinic patients?
A: (Panelist 1) A true non-responder is pretty rare unless you have a mechanical reason for the edema or something else. If the fluid looks the same in a month it doesn’t mean they’re a non-responder in my opinion.

Certainly a poor responder is much more common in DME. That almost always, is defined by anatomy. Sometimes you dry the retina and the vision gets better and sometimes I can’t really control that. But I can control what the OCT looks like. I do 2-4 injections. I almost always start with bevacizumab because of insurance. What I switch to is very individualized. If there hasn’t been much response I change to steroid, if there’s moderate response I switch to the same class.

Q: (Moderator) Let’s say you do 6 injections of bevacizumab and things stabilize. What do you do next? Protocol T taught us that there may be a difference between bevacizumab and the rest of the branded drugs. Do you switch to branded or go to a steroid?
A: (Panelist 2) I make sure to do an FA. If there is PDR or extensive non-perfusion I do full laser. Managing systemic disease is also key. I think steroids work very well in DME. I will switch after 3-5 injections. I have the most experience with Ozurdex. PPV is important to consider if there is traction.

DISCUSSION ON BOLUS VS DEPOT STEROIDS:
Some of the discussion points with bolus steroids included the PK of bolus injections and which has the highest and shortest peak. This is often associated with the shortest duration of action and the highest association of side effects and complications. About 50% of the audience started with bolus injections, which was surprising to some. People were comfortable with the procedure; the cost is lower and there has previously been good results with limited side effects of the medications. No one indicated that they would go to Iluvien first because of the duration of action, but 50% would do ozurdex primarily after anti-VEGF agents if they were not working.
One audience member described a technique she uses of “Slurry Kenalog”. She uses 40mg kenalog after being centrifuged and injects it through a 30 g needle. The depot stays there for months. She stated that she has only had 1 person requiring a trabeculectomy in ~8 yrs. Her average duration of action is ~8 months. (https://eyetube.net/video/uummnxen/). She said that Trisence seems to break up and does not work as well as the kenalog.

CASES ON OCTA AND OTHER IMAGING MODALITIES AFFECTING TREATMENT IN DIABETIC RETINOPATHY:
The first case was an asymptomatic physician with areas of no-flow on OCTA, but otherwise relatively normal FA and other imaging. Similarly, another patient was presented who had mild capillary drop out on FA, and much more apparent areas of no flow on OCTA.
In contrast there was a patient with 20/400 vision and moderate capillary drop out on FA and a few cysts OCT, but good flow on OCTA. He improved to 20/100 with anti-VEGF therapy.

QUESTIONS TO PANEL

- In 2017, do you routinely order a FA for a DME patient and DR patients?
- Do you routinely order an OCTA for DME or DR and how does that influence your management or follow-up?
- Finally, what do you think the role of OCTA will be in two years?

A: (Panelist 3) I don’t order FA for mild DME. Unless the vision is off or if there is NPDR and I’m looking for PDR. I do order OCTA routinely because a lot of people at my institution are showing me the benefit.

AUDIENCE RESPONSE:
How many have OCTA (30%), use it routinely (30%), and how many feel it changes management (1 person)?

DISCUSSION POINTS ON OCTA:

It is critical to get nomenclature correct when discussing OCTA and flow. The OCTA machines use a binary decision to decide if it is going to be black or depict flow. It should be termed “no flow” rather than truly being able to say “capillary drop out”. There should be better standardization between nomenclature and the company’s algorithms so there is a standard.

The panel did find benefit in OCTA. People will have it on initial exam and show the patients the extent of their disease in conjunction with the rest of the imaging.

With regards to changing management, some of the panel felt that even in asymptomatic eyes with no flow on OCTA, they would treat. They would treat even without edema to possibly have beneficial effects on vasculature loss which may be supported in the RISE/RIDE studies by decreasing vascular loss. The challenge is that currently we don’t know if it’s truly beneficial and we don’t know the end point to injecting these patients. Other people would not treat no-flow on OCTA without edema because the data is currently not there, but there was a consensus that better improvement of systemic conditions should be discussed, which will improve retinopathy as in the DCCT trial.

CASES ON HOW HAS PROTOCOL S CHANGED YOUR MANAGEMENT:

50 year old diabetic man with decreased vision OD, VA 20/80 OD. HbA1C 10.3% and uncontrolled hypertension.

The question is, how do you treat DME in a setting of proliferative diabetic retinopathy in 2017? Protocol S shows that injections are non-inferior, and patients may benefit from not having peripheral vision wiped out. However, they had to be injected every 4 weeks.

A: (Panelist 2) For PDR I start with anti-VEGF. In 3-4 months I would do laser.

A: (Panelist 1) These patients with PDR aren’t always compliant with follow-up. I wish they were. I wish they followed up with the contract. But they don’t and many times they’re in that situation because they’re noncompliant in the first place. I find it a great disservice for us to simply go to anti-VEGF without at least thinking about a potentially more permanent treatment for a patient when they might want that in their long-term life.

DISCUSSION ON PROTOCOL T

Most people felt they would do a combination of laser or injections depending on many variables including patient compliance and cost to the system. It was mentioned that patients with diabetes have on average a monthly visit with a doctor and adding scheduled injections just adds to this. Only 20% of the patients in protocol S could be extended beyond monthly visits. Most people agreed that although there is not perfect data for every given situation that they would do a combination of laser and injections in the setting of PDR and macular edema.

AUDIENCE SURVEY:

1. There is an alarming disconnect between clinical trial results and real life results. (Answer is YES). 78% of attendees answered correctly.

2. Steroid implants are a viable option for patients who do not respond to anti-VEGFA monotherapy. (Answer is YES). 100% of attendees answered correctly.
**CASE DESCRIPTION**

- 55-year-old man diagnosed with diabetic macular edema
- **Health History**
  - Patient has type 1 DM, blood sugar is not well controlled with diet alone
  - History of hypertension
- **Ophthalmology History**
  - May 12, 2012: Compliant with treatment for diabetic retinopathy
  - May 24, 2012: VA OD = OS = 20/200
  - September 25, 2012: Dexamethasone implant OD for DME
  - September 2013: Dexamethasone implant OS for DME

**Images:**
- September 10, 2012, dexamethasone implant #1, day 30
- November 19, 2012, dexamethasone implant #2, day 28
- May 15, 2013, dexamethasone implant #3, day 30

**Dates:**
- OD: July 2012, October 2012, April 2013
- OS: May 2012, October 2012, April 2013
Questions

- How do you judge “poor response” or “non-response” to anti-VEGFA monotherapy?
- Do you switch anti-VEGFA drugs first?
- Do you consider steroids?
- If so, which one? Bolus injection, azurhex, illuvien?
Questions

- Do you routinely order an FFA for DME/DR
- How does the FFA influence your management? Follow up?
- Do you routinely order on OCTA for DME/DR
- How does the OCTA influence your management? Follow up?
- What will the role of OCTA be in 2 years?

50 y.o. diabetic man with decreased vision in right eye. HgA1c 6 months ago was 10.3% and he also has hypertension

OD = 20/80

Patient received 5 ranibizumab injections
OD = 20/63
PANEL 1: ADVANCED MANAGEMENT OF DME

Resolved DME and regression of Proliferative Diabetic Retinopathy

OD Comparison

Fluorescein Angiography

Options:
1. PRP
2. Anti-VEGF
3. PPV, EL
4. Ocriplasmin

Questions

- After Protocol S, how do you manage a patient with DME+PDR?
- After Protocol S, how do you manage a patient with PDR alone no DME?)
- After Protocol S, how do you manage a patient with severe NPDR alone (no DME)?
- If you had PDR, how would you want to be treated?

No Show, Then 16 Months Later

Questions

- How do you determine "compliance??"
- Is it time to consider primary PPV for some PDR patients?

Proliferative Diabetic Retinopathy

PRP vs Anti-VEGF vs PPV
There is an alarming disconnect between clinical trial results and real life results:

1. Yes
2. No
3. Not my problem

Mean: 1.6
Total: 42

93.1%
38.1%
4.9%

1. Yes
2. No
3. Not my problem

Mean: 1.3
Total: 23

95.6%
37.9%
0.4%

Steroid implants are a viable option for patients who do not respond to anti-VEGFA monotherapy:

1. Yes
2. No
3. Give me anything I am just an injecting machine!

Mean: 1.3
Total: 45

92.2%
15.1%
0.4%

3.2%
0.4%
New Drugs and Targets for Neovascular AMD

PRAVIN U. DUGEL, MD

SUMMARY
The widening gap between clinical trial results and real life data in nVAMD is alarming. The logistic and physiologic considerations for this gap will be discussed. Recent clinical trial results for anti-PDGF drugs have been disappointing. The latest data analysis of the Fovista trials will be presented. Finally, promising new drugs in the pipeline will be discussed.

NOTES
The widening gap between clinical trial results and real life data in wet AMD is growing and we are in need for new drugs that can be used alone or in combination with the current ones.

Brolizumab, also known as RTH, is a very small single stand antibody with a size of 26 kD. The first study testing its effectiveness was comparing it to ranibizumab. With a single injection, there was an equivalent decrease in the central subfoveal thickness when comparing the two drugs. As far as visual acuity was concerned, there may have been a slight advantage with the use of brolizumab. However, no firm conclusions could be made given the small sample size. What was actually quite impressive is that there may be a greater durability with this single injection. There were also no safety issues noted in the study.

Based on this, the phase-III program was launched.

Another next-generation anti-VEGF-A is Abicipar. Abicipar is a DARPin (designed ankyrin repeat protein) and is the first DARPin to have been used in the eye. DARPin is a natural product which can be customized based on how many repeat ankyrin proteins you have. The most important thing about the DARPin is that the way to select a drug is extraordinarily efficient. 64 naïve patients received three injections and then after eight weeks they did not receive any further injections. The comparison arm was ranibizumab which was given every four weeks or eight weeks and twelve weeks after the last Abicipar injection. There was a small trend towards better vision in the abicipar group and regarding safety there was more inflammation in the abicipar group compared to the ranibizumab group. Based on this, there are two phase-3 studies that are ongoing.

Combination therapy is also being investigated. Ophthea is a small Australian company with a product that suppresses VEGF-C and VEGF-D. VEGF-C is upregulated when VEGF-A is under blockade and it has been shown in the past that patients with wet AMD have elevated levels of VEGF-C. There is a study ongoing where it is used in combination with ranibizumab. The phase 1 study has not shown any safety issues.

Squalamine by Ohr pharmaceuticals is a very small molecule that can be placed into a drop. It has a very broad range of activity and inhibits a number of factors, including VEGF, PDGF, and Beta VEGF. Originally it was thought to increase the durability of our treatment strategy. The IMPACT study demonstrated that there were patients who did better when the drop was given, and based on that, a phase-3 trial was started, that was recently discontinued a couple of weeks ago.

Dr Dugel further discussed Ang-2 inhibitors. Ang-2 and VEGF-A are key drivers of angiogenesis. The Tie pathway, with angiopoietin, modulates cell stabilization. Ang-1 is always released at a basal level. Ang-1 is very important for binding to Tie-2 which will then signal drivers toward cell health and maintain the vasculature and maintain cell health. Now what happens when an angiogenic switch occurs? An angiogenic switch occurs when there's hypoxia, when there's certain chemokines, when there's decreased glucose. ANG-2, which is not secreted on a basal level is up-regulated. ANG-2 is a weak agonist of ANG-1. So effectively it's an antagonist but it's a weak agonist. ANG-2 will competitively occupy the space that ANG-1 will bind to.

What it does is that it doesn't allow for Tie to be phosphorylated, thus decreasing the stabilization of endothelial cells. But importantly, this part is really important, it attracts chemokines. It has a very important anti inflammatory factor to it. This is often coupled with an up-regulation of VEGF-A, and VEGF-A will promote uncontrolled and abnormal growth, will promote leakage, and cause photoreceptor disruption. RG7716 does, the Roche product, neutralizes both ANG-2 and VEGF-A. In so doing it maintains homeostasis and a healthy vasculature. It stabilizes the endothelium, reduces exudation and fluid leakages and reduces the influx of inflammatory cells. It's a bispecific product, meaning that there is one molecule that has two different targets.

In the Phase 1 study with a single injection, the patients that were enrolled here were patients who had very severe disease, and despite the fact that the duration of the disease was almost 3 years, the median change with a single dose was 7 letters of vision. With a multiple dose it was 7.5 letters of vision with a concomitant decrease in the central subfield thickness. Based on this there are three Phase 2 studies that have been launched; the AVENUE study looking at neovascular macular degeneration, the BOULEVARD study looking at patients with...
DME, and the STAIRWAY study looking at durability. Dr. Dugel stated that he felt that the Ang-2 inhibition pathway is the most promising and exciting one.

There's another important anti ANG-2; that is the Regeneron product, nesvacumab. The Phase 1 study is complete and it showed that there was increased durability. It didn’t just show that there is increased durability but it was also dose dependent. There were no safety issues and two more Phase 2 studies were launched, one for AMD and the other one for DME.

Dr. Dugel concluded his talk by briefly mentioning the failed trials with FOVISTA.

DISCUSSION

Q: Question | C: Comment | A: Answer

Q: Let's play alternative universe and say that Fovista actually worked, and you started your talk by saying we need to get some synthesis between studies and what happens to us in the weeds. Do you really think it was rational to take patients and bring them back and have them be re-injected given a) the injection burden that we all are dealing with, and b) the cost?

A: I've been involved with Genentech and with Regeneron with the anti-vegf-a therapy since they started, and I remember being in a meeting, a small meeting like this, standing up and saying exactly what you said. Talking to them and saying: Do you think that it's feasible that we're going to put a needle in the eye once every quarter, because that's what they had in mind, that our patients are going to tolerate a needle in the eye once every quarter for a year? If you think so, you guys are nuts. Let me tell you something, I have a relative who has a disciform scar in one eye and he's got 20/25 vision with the neovascular membrane in the other eye and he's been getting treated every four weeks for the last 12 yrs. And, at the end of the day, efficacy is king. We will do anything and everything to save us from going blind. The answer to your question is I don't know but I've been surprised. And we have an obligation to investigate.

C: Agreed, Pravin, but we also have an obligation to society in general and just the absolute cost that we are incurring.

A: That's a question that I'd love to get into a discussion with you about but at the end of the day there are lots of fantastic colleagues of ours that have done studies on cost, and recently Neil Bressler has published a study about the cost savings of even the branded drugs. The cost savings that we have, as expensive as the drugs are, and I'm the first one to tell you because I work in the weeds. I realize how difficult it is but I also do know that the cost savings that we have of preventing patients from going blind with what we have done is greater than probably any other therapeutic intervention that we have in medicine.

C: I was going to suggest we move out of the weeds and think big picture, and I actually think that additional anti-angiogenics don't have a great role in AMD. I think there are opportunities in DME and in RVO, but really in AMD that's not really what our problem is. Yes, it would be nice not to inject so frequently, I think the physicians actually are more bothered by that than the patients. But I think the big problem that we're facing, and I would say the unmet need is that you get to 5, 7, 10 years of treatment and in most cases patients lose vision. I think the reason for that is that we're uncovering, you know we've controlled the angiogenesis, the permeability, we're uncovering what is after all a neurodegenerative disease and we need to get to that. I know we talked a little bit about neuroprotection yesterday but I think the problem is the photoreceptors die. We need to deal with that.

A: We have patients in Cedar and Sequoia and I'm familiar with the phase II Darpin trial, there's always been this intraocular inflammation issue that's come up and my question to you, in your opinion and your experience do you think that is something that can impact approval or is that something that we're all going to have to mitigate in a commercial environment with a drug that may well last 12 weeks in a lot of patients. The Darpin that's used has gone through several formulations. What was used in the DME study that you've heard about was a Darpin that's a 3rd generation Darpin without the PG-20. What is used in the phase III trial is an entirely new formulation. It's a 3rd generation Darpin with the PG-20.

C: I want to just say something. I like the history of treatments, I like treatments that make big changes like PDT, laser, and anti-angiogenic therapy. Big changes are good and I think that's what we should look for.

For example, neuroprotection. But bevacizumab, in my opinion, is still “queen”. People are saying all the time, “no, this drug is a little bit better, no this is a little bit more better but no, do this because it's a little bit more better.” It's all the same.

A: I completely agree with you. You’re a wise man, I’ve learned a lot from you including this and surgery but what I would tell you is that we've been spoiled, right? We've been spoiled because anti-vegf-a monotherapy is so good and Genentech did so well and Regeneron did so well matching that decision map. It's very, very hard to beat that bar and I really think it's unrealistic to think that another drug would have an equal benefit. I think it would have an incremental benefit.
Due to the proprietary nature of this talk, the slides are not available for publication.
Polyoidal Choroidal Vasculopathy – A Variant of Type I CNV – Implications for Diagnosis and Management

GREGG T. KOKAME, MD, MMM

SUMMARY
Polyoidal choroidal vasculopathy (PCV) is a variant of subretinal neovascularization, which presents with signs and symptoms commonly seen in exudative age-related macular degeneration (AMD). PCV is much more common than has previously been recognized. Although more common in Asian populations, it also makes up a significant portion of what has been diagnosed as exudative AMD in Caucasian populations.

PCV is localized between the retinal pigment epithelium (RPE) and above Bruch's membrane. ICG angiography shows polyps with or without a branching vascular network (BVN), which correlate on optical coherence tomography (OCT) B scans to a inverted U-shaped elevation of the RPE as the polyp, and a low-lying elevation of the RPE (double line sign) as the BVN. The PCV lesion anatomically is thus not truly in the choroid, and is really a variant of type I subretinal neovascularization. Perhaps a better term for this lesion is Polypoidal Subretinal Neovascularization (PSN).

The most important diagnostic modality to evaluate for PCV is indocyanine green (ICG) angiography. ICG angiography is not always available in many clinics. Fluorescein angiography is not a reliable means of diagnosing PCV with the majority of cases showing occult leakage or hemorrhagic retinal pigment epithelial detachment. Alternative ways to diagnose PCV include en face OCT, which images PCV as a hyperechogenic vascular lesion with polypoidal dilations with slabs located at the level of the RPE. OCT angiography (OCTa) is a noninvasive technology to image vascular structures, and vascular flow through the PCV complex does show potential to produce imaging.

NOTES
PCV is a subtype of Type-1 subretinal neovascularization. It's between the retinal pigment epithelium and above Bruch’s membrane. It presents with macular leakage, bleeding, and pigment epithelial detachments similar to AMD. It's important because many of these cases are Anti-VEGF resistant. It's being increasingly recognized around the world including Europe and South America.

In Switzerland, 21.5 percent of Anti-VEGF resistant cases had PCV. In a recent Type-1 study that included a number of centers around the US, twenty one percent of the type-1 CNV were PCV.

This phenotypic subtype of subretinal neovascularization acts differently in different populations. In Asians, it's predominantly male, predominantly in the macula, and predominantly unilateral. In the Caucasian and Black population, it's predominantly female, peripapillary, and more often bilateral. Dr. Kokame presented some classic examples of PCV in Asians, Caucasians and African Americans.

ICG angiography is the gold standard for the diagnosis of PCV. At this point he commented that PCV represents an acute process in contrast to Dr Freund's theory that is a chronic disease and showed a case supporting his point.

Furthermore, he elaborated on the typical OCT findings in PCV. In 99% of the patients, OCT localization of PCV was above Bruch's membrane and below the RPE. The “double line” sign represents the branching vascular network and the “inverted U-shape” sign demonstrates the actual polyps.

Dr. Kokame continued his talk showing en face OCT data for PCV. The PCV complex was identified better with the ICG in 45% of cases, with the en face in 44% of cases, and equally well in 11% of cases. And the extent of the PCV was larger in about 65% of eyes with en face. In contrary, OCT angiography (OCTA) was not able to show the lesion as well as ICG in about 80% of cases. The OCTA did show some flow beneath the RPE and above Bruch’s Membrane, but in only a few cases was it actually better than ICG.

He concluded his talk with his treatment algorithm for PCV. If it’s subfoveal and the vision is good, he usually starts with anti-VEGF. If the vision is worse than 20/40, he often offers combination PDT and anti-VEGF as first line treatment. Dr. Kokame pointed out that PDT may be offered as a rescue treatment when anti-VEGF alone is not sufficient.

DISCUSSION
Q: Question | C: Comment | A: Answer

Q: I remember when I was a fellow, and I remember seeing a patient and going to Don Gass and saying “I’m seeing this” and Don said “You know what, I’ve seen something like this, and I wrote about this in the sixties. And the slides are under that foot stool over there.” And I think it was ’69, he published. Basically, an African-American nurse that he described as having bleeding eye disease, I think that’s what it was called. But what you’ve done is you’ve done pioneering work on Asians who
have this. So I guess my question to you is, do you get a sense, because it’s so racially driven, this disease. Do you get a sense that the prognosis is different, amongst different races?

A: Yes, I do. In the Asian population, as I mentioned, it’s more often in the macula. The prognosis, I think, tends to be not as good. But in the Black and the Caucasian population, if it’s peripapillary, they tend to do better long-term. So I do think there is a little difference, but actually a lot of my Caucasian population comes from the mainland and 20% of them have PCV. And we diagnose it all the time.

Q: Can you refresh us on the genetics of this? Does this sort the same way as all the other forms of neovascular AMD with regard to genetic association?

A: There are some common genetic markers, but there are others that are definitely different between the different ethnicities. So it doesn’t follow the same genetic markers as AMD in the Caucasian population. Actually, Carl Awh and I did some work and I looked at some of our cases with PCV, and unfortunately the majority of our PCV cases did not have high-risk characteristics, based on the commercially available gene testing.

C: And the other thing I would suggest, and I’m sure you have bright medical students in Honolulu, this is a beautiful series for machine learning. You’re presenting many, many images with varying features but you’ve identified some central themes, and you feed those. You’d be amazed, I bet you could develop a machine learning algorithm, that would be an incredible tool.

Q: Gregg, I’ve seen three African-American patients that have developed massive subretinal hemorrhages with PCV. And, do you have any sense of how often that occurs? I’ve become very afraid of this disease because of my own experience.

A: Yes, I think those are more likely early cases, that they mentioned from Dr. Gass. I have one patient, a black patient, with PCV. We don’t see that many elderly Black patients where I am. So I haven’t actually seen that much of this severe posterior bleeding. Dennis Marcus actually does PCV work in the Black population, so I work a lot with him. We share information all the time, he helped me with one of my patients on the studies.

C: Gary, I’ve operated on six patients like this in Miami. They presented with almost near-total hemorrhagic retinal detachment in one eye. And none of those eyes have done well. I mean we’ve stabilized the eye, we haven’t had to enucleate. But they’ve all had disease in the second eye that’s been fairly responsive to aggressive ongoing anti-VEGF. And I won’t stop treating because I’m terrified that they’re going to have a course more like the first eye. And I do think it’s different from what we’ve read about, what Gregg’s talked about, what the international literature is. I do think there’s a subset of very aggressive PCV that is associated with these hemorrhagic detachments. I don’t ever get to see them until the first eye’s had massive bleeding.

Q: Gregg, can you please comment on your PDT technique, regular or low fluence, and do you combine with steroids?

A: I don’t usually use steroid anymore. But I do believe in combination therapy with an anti-VEGF on the same day. Reduced fluence versus full fluence, it depends on where the lesion is. The way that we used to use PDT when we just did an FA and we drew a big circle and then you added 1,000 microns. Nobody in Asia does that. What we do now is we use the ICG and we look only at that region. Most of my colleagues, they only use exactly that, there’s no border but I use a 300 micron border. If it’s involving involving the fovea, and if there’s good vision, I’ll used reduce fluence. But if the vision is already poor I’ll use full fluence.

Q/C: As far as the full fluence versus half fluence, in patients with a generally thick choroid like PCV patients have, do you really think there is much danger of this severe visual loss with full fluence PDT? I don’t think there is. I think you can use full fluence in PCV patients.

A: Unfortunately, I think there is. After having gone around Asia, we are all still concerned of that choroidal ischemic event that can happen in people with good vision. I think it still happens.
Polypoidal Choroidal Vasculopathy – The Most Important Variant of Subretinal Neovascularization and Wet AMD to Recognize

Gregg T. Kokame, MD MMM
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Retina Consultants of Hawaii
Hawaii Macula & Retina Institute

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- Dr. Kokame is a speaker for Regeneron, Bayer, Second Sight, & Bausch and Lomb.

Last time at ARDS 2011
What happens when you ski with Ed and Jenny Ryan

Polypoidal Choroidal Vasculopathy (PCV)

- A subtype of type 1 subretinal neovascularization lying **beneath** the RPE and **above** Bruch’s membrane
- Presents with macular leakage, bleeding and RPED similar to wet AMD
- Important because more anti-VEGF resistance in PCV and other more effective potential therapies
- Increasing recognition around the world

PCV – Increasing Worldwide Recognition Based on ICG Angiography

PCV: Ethnic Differences in Clinical Presentation

- Asian PCV
  - Predominantly Male (63-83%)
  - Macular Location (68-83%)
  - Not as favorable prognosis
  - Unilateral involvement (83-93%)

- Caucasian/Black PCV
  - Predominantly Female (53-89%)
  - Postpapillary Location (56-70%)
  - Bilateral involvement (61-93%)

PCV: Epidemiology

<table>
<thead>
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<th>Characteristics</th>
<th>Asian</th>
<th>Caucasian</th>
<th>Black</th>
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<tr>
<td>Gender Predominance</td>
<td>Males</td>
<td>Females</td>
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<td>PCV Complex Location</td>
<td>Macular</td>
<td>Postpapillary</td>
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<td>Eyes affected</td>
<td>Unilateral</td>
<td>Bilateral</td>
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Asian PCV

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PCV Diagnosis and Management – Kokame

PCV: Marked Ethnic Variation

Asian PCV
- Predominantly Male (63-83%)
- Macular Location (85-93%)
- Not as favorable prognosis
- Bilateral Involvement (83-93%)

PCV In Black Patients
- Predominantly Female
- Penetrating Location
- Bilateral Involvement

Caucasian PCV

Polyoidal Choroidal Vasculopathy

An acute neovascular process with response to anti-VEGF drug

PCV: Marked Ethnic Variation

Caucasian PCV
- Predominantly Female (53-95%)
- Penetrating Location (39-75%)
- Bilateral Involvement (61-95%)

Polyoidal Choroidal Vasculopathy: Asian Female

In 1998, a 47-year-old patient noted visual stress for two weeks OD
BCVA: 20/20
PCV DIAGNOSIS AND MANAGEMENT – KOKAME

PCV ICG Angiography

- Early Phase ICG OD: Note Temporal SVN and Superior and Inferior Polyp
- Early Phase ICG OS: Note lack of PCV in peripapillary area

Polypoidal Choroidal Vasculopathy: Asian Female

- In 1998, at 47 years old, patient noted sudden onset of decreased vision for two weeks OD BCVA: 20/70
- 3 months s/p Macular Laser BCVA: 20/40
- 1 year Post ML BCVA 20/25
- 19 years Post ML BCVA 20/20

New Symptoms: Fellow Eye

- In 1998, fellow eye BCVA: 20/20
- 13 years later BCVA: 20/40 Noted Macular gray spot for the past two weeks

NEW SRNVM with Acute Symptoms and RPED

- Early ICG, 13 years prior
- OCT of New Onset PCV

ICG, new development of PCV in fellow eye

PCV Response to PEARL2 Trial

- ICG, s/p 6 months anti-VEGF therapy (2.0 mg ranibizumab)

PCV – A Type I SRNVM

- PCV - a variant of subretinal neovascularization - lies above Bruch’s membrane and below RPE
- Neovascular
  - develops with acute symptoms and without previous abnormality
  - responds well to anti-VEGF drug
- ICG – essential for diagnosis

Imaging Essential for PCV

- Will be missed with usual exam, FA and OCT map
- ICG angiography not always available and ICG interpretation & expertise for PCV not always available
- New alternative imaging modalities now available
- B scan Spectral OCT versus En Face OCT versus ICG angiography

Correlation of ICG findings to OCT in PCV

- 104 eyes of 86 patients
- ICG diagnosis of PCV
- OCT localization of PCV was above Bruch’s membrane and below RPE in 103/104 eyes (99%)
En face OCT

- Zeiss Cirrus HD-OCT
- Advanced Visualization of Slabs of Macular Cube 512x128
- Slab directed below the RPE
- Slab thickness: 25-33 micron thickness
- 100 eyes diagnosed with PCV by ICG

Two Assessments of ICG versus en face OCT

- Ability to diagnose PCV based on characteristic vascular lesion with branching vascular network and polypoidal dilations
- Ability to identify the size of the vascular lesion

PCV on ICG imaging

- 57 year old female Asian patient, no prior treatment, OD
- Branching vascular network with saccular polypoidal dilations on ICG

PCV on en face OCT

- Elevation of the RPE with polyps located beneath RPE and Bruch’s membrane – OCT line scan
- Dilated, irregular vascular structure with hyperechogenic borders and polypoidal vascular dilations - en face OCT

Anatomy of PCV Based ON OCT

- Polyps were imaged 99% of the time between RPE and Bruch’s membrane - a variant of type I CNV, NOT in choroid
- Branching Vascular Network (BVN) – diffuse low-lying elevation of RPE above Bruch’s membrane (double line sign)
- PCV often associated with RPED and polyps are located on undersurface of elevated RPE
67 year old male Caucasian patient, no prior treatment, OS

PCV diagnosis and extent visualized better on ICG angiography

PCV diagnosis and extent visualized better on en face OCT

PCV diagnosis and extent visualized better on en face OCT

PCV diagnosis and extent visualized better on en face OCT

PCV diagnosis and extent visualized better on en face OCT

PCV diagnosis and extent visualized better on ICG angiography

PCV diagnosis and extent visualized equally well on ICG and en face OCT

PCV diagnosis and extent visualized equally well on ICG and en face OCT

PCV diagnosis and extent visualized equally well on ICG and en face OCT

PCV diagnosis and extent visualized equally well on ICG and en face OCT

PCV diagnosis and extent visualized equally well on ICG and en face OCT

69 year old female Asian patient, no prior treatment.

ICG angiography

En face OCT

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA

OCTA
Results – possible factors increasing en face OCT use

- In 20 eyes with associated RPED, 17 eyes (85%) showed a larger extent of PCV on OCT.
- In 16 eyes with prior photodynamic therapy (PDT), 11 eyes (69%) showed a larger extent of PCV on OCT.

PCV and RPED

- 81 year old male Asian patient, previous Avastin treatment, OD

PCV diagnosis and extent visualized better on en face OCT

- PCV with RPED – larger extent of superonasal PCV visible on en face OCT

PCV and PDT

- 80 year old female Asian patient, previous Avastin, Lucentis, and PDT Lucentis/Dexamethasone treatment, OS

PCV diagnosis and extent visualized better on en face OCT

- ICG with less visualization of vascular anatomy and extent
- Line Scan OCT showing Type ICNV with Suspect RD

Results – Two Assessments of ICV versus en face OCT

- PCV Complex Identification – Better with:
  - ICG angiography in 45 eyes (45%)
  - en face OCT in 44 eyes (44%)
  - equally well in 11 eyes (11%)
- Extent of the PCV complex – Larger in:
  - en face OCT imaging 85 eyes (65%)
  - ICG angiography in 23 eyes (23%)
  - equally visualized in 12 eyes (12%)

Conclusions

- ICG angiography and en face OCT are complementary for the diagnosis of PCV.
- En face OCT defines a larger extent of PCV, especially with RPED and prior PDT
  - May include map of overlying RPE or non-perfused vessels
  - May be more definitive of actual anatomy
- En Face OCT images well PCV as a dilated, irregular vascular structure with hyperchogenic borders and polypoidal vascular dilations as visualized on ICG angiography


OCT Angiography versus ICG in the Imaging of PCV

- Ability to diagnose PCV based on characteristic vascular lesion with branching vascular network and polypoidal dilations on ICG compared with OCT angiography
- Ability to image flow in the PCV complex, including the polyps and the branching vascular network (BVN), and to what anatomic location
Correlation of ICG findings to OCTA in PCV

- PCV diagnosed in 45 eyes (40 patients) on ICG angiography
  - prospective study
- OCTA images with Zeiss Cirrus 5000 Angioplex™ OCT
  - 90,000 A-scans per second OCT scanning engine
  - Slab thickness below the RPE and above Bruch's membrane
  - Slab: Thickness: up to 35 microns
    - Vary to maximize image
    - Relieve the cuts

Results – ICG versus OCT A

- PCV Complex Identification: Better with:
  - ICG angiography in 36 eyes (80%)
  - equally well in 6 eyes (13%)
  - OCTA in 3 eyes (7%)

Results – Polyp and BVN Visualization on OCTA

- BVN on ICGA (noted in 98% of cases on ICG - 44/45 eyes)
  - Partially visualized (ICG better) 29 eyes (66%)
  - Comparable to ICG 8 eyes (18%)
  - Absent flow in 3 eyes (7%)
  - Better visualized in 4 eye (9%)
- Polyps noted in 18 of 45 eyes with PCV
  - 41 total polyps in study group identified on ICG
  - 13 of 41 polyps (32%) partially visualized on OCTA

PCV diagnosis and extent visualized better on ICG angiography

- 61-year-old female with previous Anti-VEGF treatment
- Large BVN not visualized well on OCTA

PCV diagnosis and extent visualized better on OCTA

- 87 Asian female with PCV OD and previous Anti-VEGF therapy
- Good visualization of BVN

PCV diagnosis and extent visualized better on OCTA

- 66-year-old male previously treated with Anti-VEGF
- OCTA showed hypofluorescent RPE in ICG
  - Dark region indicating the two corresponding to RPE leak in all eyes, and vascular flow noted in 2 eyes (14%)
OCT Angiography of PCV Summary

- OCTA visualizes flow through the PCV complex below the RPE and above Bruch’s membrane.
- Branching vascular network better imaged on OCTA than polyp because more flow through the BVN
- Majority of patients are previously treated which may be contributing to decreased imaging on OCTA
- RPED seen on ICG correlate well to OCTA imaging
- Thin En face Slabs (10 - 30 um) following RPE or choriocapillaris contour and segmented between RPE and Bruch’s membrane

Proposed Rx Algorithm for PCV

- Inactive PCV – observe
- PCV with active leakage or bleeding
  - Extrafoveal Polyp consider ML or PDT
  - Subfoveal PCV Complex
    - VA > 20/40 or better or dense SR HEME
    - Combination PDT/X-VEGF
    - VA worse than 20/40
      - Combination PDT/X-VEGF
        - Better anatomic and visual outcomes with less frequent treatment
        - X-VEGF alone – watch for relapse X-VEGF resistance and need to consider rescue PDT

Conclusions

- ICG angiography and en face OCT are complementary for the diagnosis of PCV.
- En face OCT defines a larger extent of PCV, especially with RPED and prior PDT
  - RPE and extravascular material draped over the type 1 subretinal neovascular complex
  - May be more definitive of actual anatomy, not flow
- OCT angiography and en face OCT confirm diagnosis of PCV between Bruch’s membrane and RPE
- OCT angiography able to detect flow but less able to image full extent of PCV complex in this exciting but early stage of development

PCV Conclusions

- The most clinically important subtype of SRNVM to identify because the diagnosis affects management and care
- PCV
  - Neovascular
  - Not in the choroid but underneath the RPE and above Bruch’s membrane
  - Dx requires more than clinical exam, FA and OCT map
- Diagnosis of PCV – requires ICG or en face OCT
- Treatment - More anti-VEGF resistance and better vision improvement in some cases with combined PDT and x-VEGF therapy than x-VEGF monotherapy
Peripheral Targeted Laser: WAVE and DAVE trials.

CHARLES C. WYKOFF, MD, PhD

PURPOSE: To investigate the effect of wide-field fluorescein-angiography (WF-FA) guided peripheral photo-coagulation on treatment burden in eyes with recalcitrant cystoid macular edema (CME) secondary to ischemic retinal vein occlusion (RVO).

METHODS AND RESULTS: Patients with center-involving CME secondary to RVO incompletely responsive to at least 2 previous monthly anti-vascular endothelial growth factor (VEGF) injections were enrolled in the WAVE phase IV clinical trial. Thirty eyes with ETDRS BCVA of 20/25-20/800 and retinal non-perfusion outside of the macular arcade vasculature amenable to photo-agulation were randomized 1:4 to monotherapy (n=6) with ranibizumab or combination therapy (n=24) with ranibizumab and targeted peripheral retinal photo-coagulation (TRP). All patients received 6 monthly ranibizumab injections followed by 6 months of pro re nata (PRN) re-treatment; patients in the combination therapy cohort received TRP to areas of peripheral retinal non-perfusion at week 1 and month 4.

At baseline, patients had received a mean of 10.1 prior anti-VEGF injections. Twenty-nine eyes (97%) completed month 12 (M12), at which point mean BCVA improved 10.7 and 14.9 ETDRS letters (P=0.46) and mean CRT improved 186 µm and 188 µm (P=0.99) in the monotherapy and combination therapy cohorts respectively. The mean number of injections administered through M12 was 9.5 (range 7-12) and 8.7 (range 5-12) in the monotherapy and combination therapy cohorts respectively, with 3.7 and 3.1 given during the 6-month PRN re-treatment period. Both cohorts demonstrated progressive decline in visual field through M12.

CONCLUSION: In this randomized trial of 30 eyes with CME secondary to ischemic RVO incompletely responsive to anti-VEGF injections, comparable visual and anatomic outcomes were demonstrated in both the monotherapy and combination therapy cohorts. TRP did not significantly impact treatment burden, with 0.6 fewer mean injections compared to monotherapy during 6 months of PRN re-treatment.

NOTES

Dr. Wycoff started his talk with a clinical case example of a patient with a retinal vein occlusion associated with macular edema, stating that patients and physicians want to know the number of injections that will be needed.

The most recent and maybe the most relevant place to look for this is the SHORE trial. This was a large, randomized trial that had over two-hundred patients with center involved macular edema from all types of RVO. All patients received six monthly doses or seven total doses of ranibizumab. When patients were stable, meaning their vision was stable and they had no fluid, they were randomized. Randomization was to either continue monthly injections or have PRN injections for a total trial duration of fifteen months. Importantly, PRN and monthly dosing were super-imposable. There was no difference in visual acuity outcomes.

Overall in the medical community we think that some of these patients have a finite duration to their disease, but the large majority need ongoing dosing. Dr. Wykoff continued by posing the following question: if you ablate the area of non-perfusion in the absence of neovascularization, can you impact treatment burden? This is how the WAVE trial was born. The WAVE trial was a randomized, open-label, phase four study. The goal was to simply assess the effect of wide-field, targeted laser on treatment burden in ischemic RVO eyes, but critically Dr. Wycoff wanted to try to isolate it to patients who had been responsive but incompletely responsive to previous anti-VEGF dosing. The inclusion criteria for the trial were: ischemic CRVO, BRVO or HRVO, vision between 20/25 and 20/800 and recurrent macular edema despite at least 2 monthly anti-VEGF injections. 30 patients were enrolled in the trial.

Both arms (combination laser and anti-VEGF; anti-VEGF monotherapy) received 6 monthly injections of ranibizumab. In the combination arm he applied targeted laser peripherally, both after the first dose and then again at month four if they needed it based on repeat angiography. Then, in the second half of the trial, the patients had monthly visits and PRN ranibizumab. The primary endpoint was the number of ranibizumab injections administered through one year, especially focusing on the PRN period, and then secondary endpoints were vision, OCT thickness data, visual fields, and perfusion based on the FA.

One-hundred percent of patients in the combination arm received laser after their first Ranibizumab dose and then fifty-eight percent received a second round of laser. On average these patients had received ten previous anti-VEGF injections in both arms, about a third of eyes were BRVO and the rest were mostly CRVO. Retention rate was good as one patient dropped out at month four, and four percent of scheduled visits were missed. There was no difference in the visual acuity at the end of the follow-up between the two arms. About 60 to 70% of both arms gained at least 10 letters, and about 30 to 40% of the patients gained 15 letters.
In terms of the treatment burden, the monotherapy arm received 3.7 injections in the PRN phase and the combination arm received 3.1. A difference of 0.6 injections which was not statistically significant.

There were no safety issues in the study. In the combination therapy arm, the patients experienced substantial loss in visual field, presumably due to the application of pretty heavy laser between baseline and month six. The visual fields were relatively stable between month 6 and month 12. In the monotherapy group there was stability in the first 6 months; however there was visual field loss between months 6 and 12, and at the end of the follow-up the patients had experienced the same amount of visual field loss compared to the combination arm.

Subsequently, Dr. Wykoff reported that there were no substantial differences between the populations in terms of retinal perfusion.

Dr. Wykoff continued his talk summarizing the results of other investigators paying particular attention to Dr. Campochiaro's study, the largest trial so far, that concluded that there were no long-term benefits of peripheral laser. He also mentioned briefly a similar trial his group conducted for patients with DME (DAVE trial) and the results were similar to the WAVE trial.

Plausible explanations for the failure of laser to show any benefit in this study were perhaps the need for heavier and more extensive laser treatments and short-term follow up in the study that may mask potential long-term effects of laser.

**DISCUSSION**

**Q:** Question | **C:** Comment | **A:** Answer

**Q:** So, Charlie, if you considered it targeted, but you left areas that were obviously ischemic, what's the definition of targeted?

**A:** I wanted to stay outside the macula and about a disc or two away from the nerve. I was trying not to do harm. Although I was trying to minimize the harm by staying away from the immediate posterior pole, we did see the change in visual field in the laser group.

**Q:** Great talk, Charlie. Two questions for you. One, in the context of protocol T, do you think another anti-VEGF therapy may have yielded different results? And the second question is, in your DME study, did you look for those?

**A:** Yeah. I don’t think we would have seen a difference with a different anti-VEGF agent. I don’t know; we haven’t done that, but I think it would have been very, very similar if not identical. And we have not completed the perfusion analysis. For all the angiograms I’ve looked at, and I’ve looked a lot of them, I haven’t seen any zones of clear areas of reperfusion.

**C:** It’s very interesting for me. I think part of the difference between trials might be the amount of ischemia that you start out with. Your eyes are really, really ischemic, and so the question is, how do we define ischemic RVO, for instance. And the results might have to do with that issue.

Another point, it was quite a few years ago at the Retina Society, we were talking about retinal reperfusion. We were using Macugen. I think we had ten cases that we followed with wide-angle angiography. And in half the cases we were able to find areas of reperfusion, but those cases were not as severe as the ones that you showed. Also, Jeff Heier looked at some of the recent data and saw maybe half of the patients had areas of reperfusion. But again I think it might be the amount of ischemia that you have. And one more thing I want to add, the Japanese, in a very interesting article a year or two ago, did wide-angle angiography on patients that were myopic and these patients were considered controls. And they found that ischemia also occurs in control patients. So, what we call ischemia might not be really ischemia.

**A:** Those are great points. The definitions that you bring up – I absolutely agree. It’s hard to know what the definition of ischemic RVO currently is. Certainly the CVOS and DVOS may be outdated, given the wide-field imaging that we have now. And we probably need to revisit that. Jeff Heier’s work with Chirag Shah is elegant. Those are amazing angiograms that he’s shown, and incredibly provocative conclusions. I simply haven’t seen that. And I’m extremely fascinated by that opportunity to have reperfusion of the retina with our treatments for our patients. I think that would be fantastic. But I’m not seeing it in the patients that I’m treating on a day-to-day basis, or in these trials.

**Q:** Charlie, I just want to ask a very practical question. It was a great talk. The assumption in all of these trials, and you’ve fairly quoted all of them, is that the areas that we define as “non-profusion” – and I put that in quotes because we really don’t know what that means – are the areas that are producing VEGF. We laser them; we destroy them; but we don’t know what they are. They may be dead, or there may be other areas that are so-called perfused, producing anti-VEGF. So given that, I’ve got a wide-field angiogram, say, and I do a fluorescein angiogram, listening to your talk. And I see areas of non-profusion there. What should I do?

**A:** Hard to know. I think those patients are at an elevated risk of neovascularization over time. So they probably need to be followed closer. I don’t think that, from the data that I’ve seen or have, that it should change your management options.
Q: I think the reperfusion thing is going to be really important. And I think your trial is incredibly well-designed and well-conducted. And I'd love to know – Thirty years ago, when the first presented example ever of reperfusion anywhere was presented, it was like you grew another eye. It was that rare. And now there are documented examples. But my question is, tell us about these patients. What are they like? The visual acuities are often so poor. What is your throwing-in-the-towel-point for these patients for monthly injections? Some RVO patients do great. But there are are group of people where you’re beating on, almost, dead eyes. What are your thoughts about when you throw the towel in?

A: I think that’s incredibly challenging. I absolutely agree. If the patient’s amenable to it, I will start patients on therapy up front, even if the macula totally black. I’ll try. Because sometimes you hit a home run and you give them 20/80 and they’re happy and it’s a win. Many times you don’t. And in those people, if I get them dry for three or four months, and I try to taper off and the fluid comes back, and it’s back, and they don’t notice any difference, and their other eye is normal, those are the patients who I’ll have a real discussion with. I’ll say to them, “Look, we can stop. You might continue to lose vision, but we can stop.” That’s not unreasonable. If I put what percent of patients that is for all my RVOs, where I stop, it’s probably one out of 20, so 5%.

Q: Charlie, what do you think about the risk of stopping – I don’t stop in those patients, not because of visual function but I think those are the patients that have the risk of neovascular glaucoma, potentially leading to enucleation.

A: Well, you can laser them. But, I mean, you’ve got to think of therapeutic strategies. One of the things we see in the radiation retinopathy patients is patients will stop treating. And then you get back to our old-school model, where 25% of the eyes are enucleated. If you inject them with an anti-VEGF, the enucleation rate might be zero. So I have a different discussion when it’s not vision. And I think you can inject those patients much less frequently and preserve the eye when vision is no longer that discussion point. But I still have that discussion with them. I think we probably all do.
PERIPHERAL TARGETED LASER: WAVE AND DAVE TRIALS – WYKOFF

SHORE: VA Outcomes

SHORE: Distribution of PRN Injection Frequency (n=86)

mean = 3.7

WAVE

- Randomized, open-label, phase IV trial
- Assess effect of wide-field FA-guided peripheral photocoagulation on Tx burden in ischemic RVO incompletely responsive to anti-VEGF dosing

WAVE Design

Endpoints

Primary
- Ranibizumab injections administered
- Mean change in BCVA & CFT
- Mean change in wide-field limited retinal area

Secondary
- Mean change in BCVA & CFT
- Mean change in wide-field limited retinal area

Management Options?

- Continue Ranibizumab
- Switch to Eylea
- Bevacizumab
- Alloveda
- Shire
- Exsight Xlense
- Translucence
-マンドリンコンソール
- Laser
- Surgery
- Peripheral

WAVE: Key PRN Re-Tx Criteria

Intraretinal or subretinal fluid on SD-OCT

Treated
Not Treated
PERIPHERAL TARGETED LASER: WAVE AND DAVE TRIALS – WYKOFF

**TRP Technique**
- RNP outside of the macula including penumbra
- 2 DD from ONH
- 1 spot diameter apart

Targeted Retinal Photocoagulation

<table>
<thead>
<tr>
<th>Combination Therapy Arm (n=24)</th>
<th>WRAP Technique</th>
<th>Patients Receiving TRP</th>
<th>Mean # Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 Week 2</td>
<td>TRP</td>
<td>24/24 (100%)</td>
<td>13.8 (range 10-20)</td>
</tr>
<tr>
<td>#2 Month 4</td>
<td></td>
<td>34/34 (100%)</td>
<td>4.25 (range 4-17.7)</td>
</tr>
</tbody>
</table>

**WAVE: Baseline Demographics**

<table>
<thead>
<tr>
<th>% Female (%)</th>
<th>Complete Population</th>
<th>Monotherapy (n=6)</th>
<th>Combination Therapy (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=56 (85%)</td>
<td>50% (28/56)</td>
<td>40% (2/5)</td>
<td>60% (16/27)</td>
</tr>
<tr>
<td>Age (range)</td>
<td>53.8 (15-87)</td>
<td>58.3 (61-77)</td>
<td>51.1 (39-80)</td>
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<tr>
<td>Sex (M/F)</td>
<td>32/24</td>
<td>12/4</td>
<td>20/20</td>
</tr>
<tr>
<td>NVD Subtype</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>SVD Subtype</td>
<td>24/52</td>
<td>12/3</td>
<td>12/21</td>
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<tr>
<td>Max Fix Anti-VEGF (range)</td>
<td>2.0 (1-4)</td>
<td>2.0 (1-4)</td>
<td>2.0 (1-4)</td>
</tr>
<tr>
<td>Mean CRT Fixation (µm)</td>
<td>228+/-128</td>
<td>228+/-128</td>
<td>228+/-128</td>
</tr>
</tbody>
</table>

**Mean CRT**

**Mean Visual Acuity**

**Visual Gains**

**WAVE: Patient Retention**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Enrolled</th>
<th>Completed 1 Year</th>
<th>Possible Visits</th>
<th>Missed Visits</th>
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</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td>6</td>
<td>6 (100%)</td>
<td>90</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>24</td>
<td>23 (96%)</td>
<td>358</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>29 (97%)</td>
<td>448</td>
<td>17 (4%)</td>
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</table>
Periipheral Targeted Laser: Wave and Dave Trials – Wykoff

Treatment Burden

<table>
<thead>
<tr>
<th>Duration</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
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<tbody>
<tr>
<td>0-1</td>
<td>62.5%</td>
<td>72.0%</td>
</tr>
<tr>
<td>1-2</td>
<td>3.7%</td>
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<td>2-3</td>
<td>3.7%</td>
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</tr>
<tr>
<td>3-4</td>
<td>22.6%</td>
<td>22.6%</td>
</tr>
<tr>
<td>4-5</td>
<td>22.6%</td>
<td>22.6%</td>
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</table>

Change in GVF Area Through M12

Safety

<table>
<thead>
<tr>
<th>Event &amp; Systemic AEs</th>
<th>Monotherapy (n=26)</th>
<th>Combination Therapy (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients Experiencing AEs</td>
<td>21/26 (80.8%)</td>
<td>26/33 (78.8%)</td>
</tr>
<tr>
<td>Systemic AEs</td>
<td>9/26 (34.6%)</td>
<td>10/33 (30.3%)</td>
</tr>
<tr>
<td>Retinal Hemorrhage</td>
<td>2/26 (7.7%)</td>
<td>4/33 (12.1%)</td>
</tr>
<tr>
<td>Systemic Medications</td>
<td>16/26 (61.5%)</td>
<td>17/33 (51.5%)</td>
</tr>
</tbody>
</table>

Wave

Goldmann Visual Field (GVF) Analysis

- Patients completing GVF at baseline, M6 & M12 with adequate fixation & cooperation (N=14)
- GVF sheets digitized and Adobe Photoshop CS6: manually delineate IIIe isopter
- Total area of the IIIe isopter quantified and change in GVF was plotted

Change in GVF Area Through M12

Longitudinal Retinal Perfusion

Baseline | Month 4 | Month 12

Notes:

- ASPEN Retinal Detachment Society Meeting Notes 2017
- WAVE Trail
- Progressive Retinal Nonperfusion in Ischemic Central Retinal Vein Occlusion
- 1 Year
PERIPHERAL TARGETED LASER: WAVE AND DAVE TRIALS – WYKOFF

Wide-Field Guided Photocoagulation for DME

Design

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>36</th>
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</thead>
<tbody>
<tr>
<td>Monotherapy N=20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Combination N=20</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Monthly ranibizumab |
| Monthly visits |
| PRN ranibizumab |
| TP as needed |

Baseline

Inclusion criteria
- 40 patients: center-involving DME
- 20/32-20/400 (Snellen equivalent)
- Extensive peripheral retinal non-perfusion

Month 6
PRN Treatment by Year

<table>
<thead>
<tr>
<th>Randomized ARM</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab</td>
<td>86%</td>
<td>73%</td>
<td>64%</td>
</tr>
<tr>
<td>Ranibizumab + VEGF</td>
<td>92%</td>
<td>80%</td>
<td>77%</td>
</tr>
</tbody>
</table>

Other reports? Why didn’t TRP work?

Reduction of severe macular edema in eyes with poor vision after panretinal photocoagulation for proliferative diabetic retinopathy

Improvement of Macular Edema after Panretinal Photocoagulation for Proliferative Diabetic Retinopathy

Scatter Photocoagulation Does Not Reduce Macular Edema or Treatment Burden in Patients with Retinal Vein Occlusion
Why didn’t TRP help?

- Peripheral retina not ablated enough
- Presumed retina not ablated enough
- Beneficial effects of laser counteracted by pro-inflammatory effects
- Benefits of laser only manifest with longer-term follow-up
- Areas of posterior retina not Tx by laser produce sufficient VEGF to cause recurrent CME

Targeted Retinal Photocoagulation

Summary

- Some trials have reported benefit in reducing Tx burden with TRP
- The current 2 randomized trials found no strong signal for a benefit of TRP, although rare cases suggested an impact
- Progressive ischemia is common in ischemic RVO and DME

ARDS2017

During the randomized SHORE trial investigating patients with CME secondary to RVO, the mean injection frequency during the 7-month PRN phase for patients randomized to PRN re-treatment was:

<table>
<thead>
<tr>
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ARDS2017

In the randomized, open-label WAVE trial, wide-field fluorescein angiography-guided peripheral photocoagulation to areas of retinal ischemia significantly decreased the need for ongoing anti-VEGF dosing in eyes with ischemic RVO:

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<th>2</th>
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<td>53.3%</td>
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</tr>
</tbody>
</table>

Thank you

WAVE Study Group

- Charles C. Wykoff, MD, PhD
- William C. Qua, MD
- syslog T. Lu, MA
- David W. Brown, MD, FABR
- Robert Court, MD
- Peter S. Stampley, PhD
- John M. Walsh, MD
- Richard H. Fish, MD
- Christopher K. Henry, MD
- Peter F. James, MD
- James C. Angiulo, Jr., MD
- Robert D. O'Malley, MD
- Amy C. Schuknecht, MD
- Anil K. Shah, MD
- Joan P. Wang, MD

Thank you
PANEL 2:
Advanced Pharmacotherapy and Surgical Management for Complex Retinal Disease

MODERATOR: TIMOTHY G. MURRAY, MD, MBA
Panelists:
Pravin U. Dugel, MD
Gregg T. Kokame, MD, MMM
Charles C. Wykoff, MD, PhD

SUMMARY
This panel will discuss complex pharmacotherapy targeted to improve outcomes for macular edema, vascular occlusion, severe diabetic retinopathy and tractional pathologies. The focus will include advanced diagnostic studies, incorporation of anti-VEGF and steroid deliveries. Finally, the impact of surgical management to improve visual functional and anatomic outcomes will be explored through surgical video and discussion. Decision making for combined treatments will be explored with active audience participation.

NOTES
It’s important that when we have a trial that fails, that we do whatever we can to show the results that are there. It’s a scientific data analysis and Tom Ciulla has been absolutely instrumental in pushing this forward with Ophthotech. The data presented was not complete data. They are still doing the analysis.

Although anti-VEGF monotherapy is superb, there are some unmet needs. The hope was that with anti-PDGF we would improve the efficacy in the near term and continue that improvement in the long term, and there was and is a very good scientific data in that regard.

There were numerous preclinical studies. For example, the corneal neovascularization model that showed maximal inhibition of neovascularization progression with combination therapy, and with that, the phase one study was done. It was a small study, and like any phase one study, they were very selective as to the patients that could enroll.

Despite their baseline severe vision loss, patients saw a median gain of 14 letters of vision and almost 60% gained three or greater lines. Again, this data comes from a phase one study, but it’s impressive data. Based on that, the phase IIB study was done. This was published and this was a fairly simple study design. Two doses of combination treatment versus monotherapy. It was a six-month study. It was a multicenter randomized double masked control study. The baseline variables were balanced.

The baseline variables underwent stratified randomization that was pre-specified. These baseline variables included visual acuity, lesion size, and OCT thickness. The P-value was adjusted to account for multiplicity.

With the higher dose combination there was a 62% improvement versus ranibizumab alone. It’s important to know that the pre-specified subgroup analyses were done, and regardless of how that was sliced, that clinical significance remained. The analyses looked at baseline lesion size, baseline fluid, and baseline vision, all of which showed a significant difference. Based on this, a number of trials followed. There was trial one, Ophthotech 1002, trial two, Ophthotech 1003, and trial three, which was Ophthotech 1004. Trial one and trial two were identical in the first year. In the second-year, trial one was going to be PRN and trial two was going to be every other month. So, the primary specified end-point was the mean change in visual acuity from baseline at month 12 and again in Ophthotech 1002 and 1003, when they looked at the baseline, and this hasn’t been presented before except in some very small settings, the baseline variables including visual acuity as well as the lesion size were indeed well balanced.

The primary efficacy end-point of Ophthotech 1002 and 1003 was the mean change in baseline visual acuity ETDRS letters from baseline at month 12. In the 1002 trial, the Fovista plus ranibizumab, the change was 10.74 letters. Sham plus ranibizumab had a change of 9.82 letters. A difference of 0.92 letters. In the 1003 trial, Fovista plus Lucentis showed a change of 9.91 letters of vision. Sham plus Lucentis had a mean change of 10.36 letters of vision. A difference of 0.45 letters of vision.

The pre-specified secondary end points were gaining greater than or equal to 20 ETDRS letters of vision or losing greater than or equal to 5 ETDRS letters of vision. Patients with greater than or equal to 20/25 visual acuity and patients with growth of CNVM from baseline did not show any significance. However, it should be noted that it may be irrelevant to look at secondary end points when the primary end point did not meet its specified goal.

There was no significant safety issue with the drug. There was a minor difference with the injection profile and that was probably because there were two injections that were required as opposed to one. There was no imbalance in the systemic side effects, but again, this was a short study. So, based on these results, the trial one and trial two were discontinued. Trial three is Fovista 1.5 milligrams plus bevacizumab or aflibercept versus bevacizumab or aflibercept alone. This trial is still ongoing. So, the idea is that this anti PDGF may be agnostic to whatever VEGF is used.
First, the primary end-point was not met. There was no benefit observed upon addition of Fovista 1.5 milligrams to a monthly ranibizumab 0.5 milligram regimen at one year. The secondary and supportive end-points are not relevant and not interpretable when the primary end-point was not met. There was no benefit observed in any subgroup analyzed including baseline visual acuity, lesion size, amount of classic component.

The third trial, the Ophthotech 1004 trial, which looks at bevacizumab and aflibercept is still ongoing. This analysis is in progress. What is being looked at right now are the imaging studies and the imaging analysis, and these will be presented in the near future.

**DISCUSSION**

Q: Question  | C: Comment  | A: Answer

C: First of all that phase IIIB study was literally for most of us, that would have been a Phase III study.

A: Yes

Q: It was huge and the data was so strongly significant. There were differences in the inclusion criteria and structure when they moved from Phase IIIB to Phase III. Could you comment on the decision making that went into that and how do you decide? Was that in hopes of potentially expanding the indication criteria for final approval or more rapid recruitment? Why would you have thought there would have been changes from one to the other with so much potentially at risk?

A: That’s an excellent question and maybe even more to that the question is why did you cherry pick classic lesions, right, that’s asked all the time. I’m glad you asked that question, because it’s important to look at all of this in context. Put yourself in a position where you may have a drug that may be able to show a regression of a lesion. So how would you measure that? You’d measure that by recruiting primarily classic lesions, right? Again, when you look back at the data if that by recruiting primarily classic lesions, because that’s important to look at all of this in context. Put yourself in a position where you may have a drug that may be able to show a regression of a lesion. So how would you measure that? You’d measure that by recruiting primarily classic lesions, because that’s the only way you could measure that, and that’s exactly what was done in Phase I and it showed that. Then you move that same inclusion criteria to Phase II, and indeed it showed that too, so what would you do in Phase III? Would you go back and start all over again in Phase I or would you just continue in Phase III?

Indeed, that was the reason why predominately classic was chosen to move on to Phase III and logically that would make sense, but then when that happened, the world changed, and we realized we weren’t going to be using FA’s much longer perhaps, and the company thought that OCT’s were going to come into play. They were convinced when they looked at the Phase IIIB data that reflected regression in every analysis that they did. That’s the reason they included subretinal hyper-reflective material (SHRM). You don’t necessarily have to use a fluorescein angiogram. So the question that Tim brings up is, did that make a difference in the study? My feeling is that I don’t think it did but we’ll still have to do the analysis.

Why I don’t think it made a difference is the following. SHRM we know is not necessarily SHRM. We know that HRM occurs under the retina, it occurs under the RPE, it occurs everywhere, in all kinds of lesions. We know that it doesn’t occur only in predominately classic lesions. We know it can occur in occult lesions, in RAP, and in PCV. Lesion characteristics didn’t seem to matter. The lesions characteristics simply didn’t matter. Yes, the HRM criteria may have let everybody in, but there was no differential benefit regarding lesion characteristics, does that answer your question?

Q: Sort of, so what are you attributing such a striking difference and outcome to?

A: The answer is, at the end of the day I think it’s statistics. When we say there’s a 95% confidence level, what we mean is that there’s a 5% chance that you’ll get a false positive, and I think what we saw in the Phase II was a false positive because right now we’ve got two fantastic companies Regeneron and Opthotech, and we ought to be grateful to them for doing terrific trials and giving us answers.

At the end of the day what we can expect, I think as scientific clinicians, is to work with industry and design really good trials to give us a definitive answer and then be able to stand up on a podium like this and others and say, “Look, this is what happened” and be as transparent as possible, and sometimes we don’t know. At this point the best answer I can give you, which may not be satisfactory but is honest, is that I think it was a false positive.

C: I look at that a little differently. I look at it from the perspective that there were changes within the study design from Phase II to Phase III that subsequently introduced the potential for a confounding variable and that introduced further uncertainty into the outcome. So you’re correct. I agree. Statistics are statistics and you could have done the exact same study, enhanced the recruitment numbers to meet a Phase III design criteria, extended the follow up, and it could have failed. But my feeling for that would be that every time that we try to extend, when we go from, particularly Phase II to Phase III, those are hugely committed choices, and I look at this and wonder in my heart, was this an example of a potential choice that was poorly made.

A: Well the only thing that was changed is the SHRM criteria, right? Again, when you look back at the data if indeed the SHRM had reflected mainly classic lesions, and you say, “Oh my goodness there was a differential response.” I’d agree with you, but there was no differential response. I don’t think it would have mattered at
all if it were primarily classic. If you could have a magic wand and say, “Look, I only recruited predominately classic lesions,” It still would have failed. I mean, every way we looked at it, every way we sliced it, there was absolutely no positivity whatsoever.

If you look at all clinical trials, and this is real data that I looked at and it will be published soon. If you look at all clinical trials and you look at Phase I study results and see how many patients – what percentage actually go to market? What do you think that is? Across the board in medicine?

C: 5%

An: 9.7%. And ophthalmology is actually at the upper end. Ophthalmology is about 11% if you look at Phase II positive results that go to Phase III, and that’s where the failure rate is the greatest. If you have fantastic Phase II results to go to Phase III, it’s less than 43%, so to see this kind of thing happen if you’re a hematologist, oncologist or rheumatologist. They’re used to this. We’re not.

C: In that Phase II study, the strength of that study and the breadth of the study design, you don’t see Phase II trials like that in oncology. A Phase II trial in oncology is like our Phase I trial. They make big decisions of study volumes of 25 to 50 people, not 450 people. To me, I agree, but understand there was a big commitment to a Phase II analysis and I think everyone in the room was surprised to see the results here, and I think you’re right, it does require a better understanding of clinical trial design.

Q: If you’re so convinced that there was no signal of any benefit then explain to us why the 1004 study should continue? Do you think it’s going to be a big difference?

A: It’s a great question Charlie, and right now it’s up to the investigator’s choice as to continue or not.

Q: So, do you think there’s any plausible mechanism as to why it might be a different result?

A: I don’t know. That’s the honest answer. It’s entirely up to the investigator whether they want to continue or not.

Q: What does that mean? It’s up to the investigator to continue?

A: The study started later, so the study is going on further. What Ophtotech has said is that it is up to the investigator to either continue that trial or just basically say, “Okay, I’ve seen their results. I’m going to stop it.”

ILM Peeling Issues
- Pre-operative indications for ILM Peeling
- Imaging for ILM peeling
- Technique for ILM peeling
  - Staining versus non-staining
    - Approaches to staining
  - Instrumentation for ILM peeling
    - Scrapper – Retinal Flexi-loop versus Tano brush
    - Forceps – ILM forceps

ILM Peeling Advantages
- Total removal of pre-retinal membrane
- Enhanced macular hole closure
- Improved resolution of macular edema
- Lowered incidence of epi-retinal reproliferation

ILM Peeling Disadvantages
- Thinning of retinal structural anatomy
- Microperimetry defects
- Increased non-foveal macular hole formation
- Increased risk of inadvertent retinal break
- Toxicity of staining and/or phototoxicity
Pre-operative Indications for ILM peeling

- Presence of ILM – Peel in all macular surgical cases
- Macular hole
  - All stages
  - Only stages 2/3
- Re-operations only
- Never
- Epiretinal Membrane
  - All cases
  - Same with severe central macular edema
- Diabetic Macular edema
- Tractional
- Diffuse non-tractional

Imaging for ILM Peeling

- Fundus imaging
  - Color
  - Red-free
  - Autofluorescence
- FA/ICG
- SS-OCT/swept source
- Intra-operative OCT

Technique for ILM Peeling

- First – Remove posterior Hyaloid
- Staining versus non-staining
  - Approaches to staining
- Instrumentation for ILM peeling
  - Scraper – Retinal Flexi-loop versus Tano brush
  - Forcep – ILM forcep
**Panel 2: Advanced Pharmacotherapy and Surgical Management for Complex Retinal Disease**

**ILM Peeling - Flex Loop**

**Impossible ERM Peel**

**ILM Peeling – Forcep/Flex Loop**

**Intra-operative Management**

**Impossible ERM/ILM peeling**
- Evaluate the membrane
  1. Pre-operative OCT
  2. Staining for ERM/ILM
  3. ICG pre-surgical staining of ILM
- Membrane Blue – Dual staining of both ILM/ERM
- Elevate the membrane
  1. Forceps technique – “pinch” and peel
  2. Suture technique – suture an edge and then switch to forceps
- Minimal peel to include FAZ
- Suppressive post-peeling inflammation/edema
  1. Intravitreal steroid/anti-VEGF

**“Inadvertent” Retinal Break/Detachment**
- MUST be recognized intra-operatively
- Typical causes of retinal break/detachment
- Principles of management

**“Impossible” ERM and/or ILM Peel**
- One of our most demanding surgical tasks
- Unable to elevate an edge
- Is peeling “complete” or “enough”?
- Complications of peeling

**Inadvertent Retinal Break**
Intra-operative Management
Inadvertent retinal break/detachment

- Recognize intra-operatively
  1. Excellent visualization
  2. Indirect wide-field illumination
  3. Macular break in “arc”
  4. Extend view beyond primary instrument
  5. Continuously assess for non-shedding instrument placement
  6. Focus on “innominate force” typically at lateral margins of traction

- Etiologies
  1. Instrument impact
  2. Direct tissue cutting
  3. Excessive tissue traction

Macular Surgery Panel
Clinical Pearls

- Excellent pre-operative assessment and planning
  - OCT critical
- Excellent visualization
  - Staining of ILM
- Macular contact lens
- Minimize surgical trauma
  - ILM Forceps
  - FlexLoop
- Adjunctive pharmacotherapy
  - Intravitreal Triamcinolone Acetonide

THANK YOU!
Timothy G. Murray, MD MBA
Panel
Pravin U. Dugel, MD, Gregg T. Kokame, MD MMM,
Charles C. Wykoff, MD PhD
ARDS 2017
Snowmass, CO USA
SUMMARY
The talk will cover the development of an epiretinal prosthesis to restore useful visual input to patients with end-stage loss of photoreceptors such as in Retinitis Pigmentosa. Clinical results leading to the approval of the retinal implant and post approval results will be discussed.

Argus 2 is the currently FDA approved prosthesis for end-stage retinitis pigmentosa. Argus in mythology was the God with many eyes, that served as a gatekeeper. Before Argus, there were other visual prostheses. The visual cortical implant was actually around in the 1970s where the camera took the information and would send it through an electrode array into the visual cortex.

Argus has a wearable component, in the camera and the glasses. The video processing unit that goes with the glasses is battery-powered, and it’s worn on your belt or can be put in a pocket. Both power and data are sent inductively into the implant. There is no battery in the implant. What does that mean? It’s wireless and only works within one inch. This inductive link needs to be within one inch. The pattern of stimulation then goes through the tiny electrodes, which stimulate the remaining nerve cells in the retina. And this information is sent to the brain.

Dr. Humayun started the project in 1987 and the very first thing he did was to see if there are any retinal cells alive in patients with RP. They did a morphometric analysis of post-mortem RP eyes and found that 30% of the ganglion cells were there. In a subsequent study with Dick Green, he showed that the inner retina was very much intact, although very reorganized.

That led to the 1992 short-term test where he put small electrodes into an awake patient, so he could ask questions. That led to the 2002 building of the Argus 1, which was similar to a cochlear implant that had 16 electrodes. It was behind the ear and the cable went into eye. This gave him a lot of information about how pattern electrical stimulation could be done. And then in 2007, his group built the Argus 2 which goes around the eye that in 2011 led to the C-Mark Approval, and now more than 200 implants have been implanted around the world.

Argus 1 has 16 electrodes and Argus 2 has 60. In terms of square localization there was no difference between the two devices. However, when detection of motion and grading visual acuity were tested, the patients with Argus 2 did better than patients with Argus 1. Thus, more electrodes translate to better visual function.

Dr. Humayun showed a video of a patient with the Argus 2 implant reading single letters. He continued by mentioning that the accuboost function of the device, that essentially zooms 16x, can enhance the visual acuity of a patient up to 20/200.

Packing more electrodes into the chip can be challenging as the electrodes may dissolve and the device may be short-lived.

He then touched upon experiments his group has done on the interaction of the Argus 2 device and the visual cortex. It has been shown in the past that visual deprivation leads to the visual cortex becoming active during non-visual tasks. His group found that extended use of the Argus 2 device will make the visual cortex less sensitive to tactile stimuli. In other words, the Argus 2 device can actually reverse-engineer the brain back to what it was used to be doing.

Lastly, he discussed color recognition with the Argus 2 device that can be modulated by changing the frequency that the electrodes fire. Dr. Humayun concluded his talk by showing an eye tracker his group built in the lab, which allows to help guide patients with macular degeneration so they’re able to track where they need to.

DISCUSSION
Q: So, Mark, is it another 30 years ‘til we get a 1000 electrode sensor?
A: Not another 30 years, but five.
Q: And what’s the resolution at 1000? It’s pretty remarkable, right?
A: 20/60. If everything works out.
Q: And what do you think about the e-contact lens and the impact of having other revenue sources that have deep pockets being excited about this kind of work?
A: The e-contact lens is a very interesting thing. You would walk around and look at what you want to buy. Blink and it would download and when you go to check-out everything would be there for you. So, they’re thinking about it very differently, it’s not to help
anybody who's got blindness or health problems, it’s really to help you be able to navigate the world in a very different way than maybe perhaps what we do, even with our PDAs today.

Q: But what about things like measuring IOP or blood sugar or things that might be more interesting to us?

A: To us. Yes. That’s what I like about it, but I think, as we develop this technology, we’ll be able to get those versions developed as well.

Q: Mark, thank you for such an amazing talk and given so warmly in a meeting that we all love. Could you comment on the sub-retinal approaches and the direct cortical approaches, because now there’s different options and technologies moving. How do you see those or what are your thoughts?

A: Thank you, and I didn’t have enough time to go through all those approaches. The sub-retinal approach, bigger surgery, you have to come through the outside, obviously. The idea is to stimulate the next cell in line, which is the bipolar cell and perhaps you can get more information encoding if you do that. So, that’s why it’s aimed to be what it is. But bigger surgery, and as I just mentioned, Robert Marks pointed out in his work that these bipolar cells are really not lined up with the ganglion cells. They do all sorts of rewiring. So, that thought process may not be all what it was made out to be. The sub-retinal approach has gotten some pretty good visual acuities, so well wait and see. The packaging has failed as far as I know, it doesn’t last more than a year. I think the surgery and the packaging they have to work on. But it’s good to have both approaches and to see where we end up. The cortical of course we need, because if we don’t have ganglion cells, we don’t have the optic nerve. We need to go there. But two points in the cortex don’t map out retinotopically in the same space so they could be next to each other but they could be very disparate in space. You have to do a lot of real-time software algorithms to take care of those sorts of activities.
THE ROAD TO DEVELOPING BIOELECTRONICS FOR OPHTHALMOLOGY – HUMAYUN

SSMP Argus II Retinal Prosthesis

- Dimensions: Equivalent to visual field of 20°
- Placed using standard vitreoretinal surgical techniques

Retinal task

Electrode Array

Argus II Clinical Trial Results

Data as of August 1, 2015

Worldwide

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<td>Cumulative Implant Time</td>
<td>160+ subject-years</td>
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* Range excludes one subject explanted at 14 months post-implant

Second Sight Argus II Study Group

- USC Eye Institute (Los Angeles, CA)
- Johns Hopkins Hospital (Baltimore, MD)
- Queen’s Eye (San Francisco, CA)
- University of California (San Francisco, CA)
- National Retinal Foundation (Boston, MA)
- Instituto Universitario de Oftalmologia (Caracas, Venezuela)
- Schepens Eye Institute of Harvard Medical School (Boston, MA)
- Women’s Eye Hospital (San Francisco, CA)
- Oxford University (New York, NY)
- Lighthouse International (New York, NY)
- Second Sight Medical Products, Inc.

Investigators

- Lisa Strick
- Mark Humayun
- Steven Engel
- Janet Dutton
- Mark Grainger
- James Mullen
- Andrew Stryker
- George Turner
- Mike Buse
- Melinda Bigelow
- Nancy Seader
- Jonathan Sarna
- Tracy C. Leung
- Michael A. Stone
- David Broida
- Eugene Price
- Rand Edelstein
- Ethan White
- Dawn Stiles
- Harry D. Kowalsky
- Thomas G. Wolf
- Charles W. Smith
- Julie Fendrich
- Susan M. Talley
- Robert Greenberg

Funding Support: National Institute of Health (UM1 EY02309) and Second Sight Medical Products, Inc.

Character Recognition

- Four sets of characters (all letters, in groups of increasing difficulty, with numbers 0 – 9)
- Characters were 9.6” high
- 4 trials of each letter, randomly presented
- Tested System ON and OFF

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<th>Characters in group</th>
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<tr>
<td>A, Z, O, V, W, N, O, C, D, M</td>
<td>78.9%</td>
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<tr>
<td>0, 1, 2, 3, 4, 5, 6, 7, 8, 9</td>
<td>87.5%</td>
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Orientation & Mobility – Door Task

Performance sustained to 5 years

Benefits of the Argus II System

- The Argus II System can improve patient’s orientation and mobility, activities of daily living, and well-being:
  - Locate doors and windows
  - Sort light and dark clothes
  - Stay within a crosswalk
  - Avoid obstacles
  - Feel more socially connected
  - Enjoy being “visual” again
  - Tracking players on a field
  - Watching fireworks
THE ROAD TO DEVELOPING BIOELECTRONICS FOR OPHTHALMOLOGY – HUMAYUN

Future Directions

- Improvements in image processing to Argus II
- Increase Resolution
- Increase Visual Field
- Provide Color Vision

Next Generation Device – could help 10's of millions of visually impaired
- Higher Resolution – potential 20/60
- Less Expensive
- Totally Intracocular implant

Post Approval Update
August 2015

- Argus II been implanted in more than 100 RP patients in 20 surgical centers
  - Italy, Germany, France, UK, Netherlands, Canada, and Saudi Arabia
- A post-market surveillance study has been initiated (22 months)

100+ Argus Implants Worldwide

- 30 USA
- 11 England
- 21 Italy
- 25 Germany
- 5 Saudi Arabia
- 7 France
- 3 Holland
- 2 Switzerland
- 2 Mexico
- 1 Canada

Concluding Remarks

- Argus II can reliably withstand long-term implant (> 5 years) in a significant number of subjects
- 100+ cumulative subject-years in RP
- Implant in GA in 2015 (P. Biaggio, Manchester, UK)
- Europe – CE Mark in 2011
- US – FDA approval in 2013
- CMS Reimbursement obtained
- First round of US clinical centers for implantation established
- First Commercial Implantation in US started in 2014
- Visit Second Sight Medical Products website for listing of centers

www.2-sight.com

Post Approval Study Adverse Events
Post Approval (2 SAE) vs. Clinical Trial (14 SAEs)
As of June 2014

<table>
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<tr>
<th>Serious Adverse Events</th>
<th># of Patients</th>
<th># of Events</th>
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<td>1</td>
<td>1.3</td>
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<tr>
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<td>1</td>
<td>0.8</td>
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<tr>
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<td>0.1</td>
</tr>
<tr>
<td>Total</td>
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Courtesy BBC TV
Common Infectious Posterior Uveitides

DEBRA A. GOLDSTEIN, MD

SUMMARY
One of the biggest mistakes in the treatment of uveitis is missing infectious causes of inflammation, and assuming that all uveitis is treated with corticosteroids. Another error is assuming that inflammation in the anterior chamber equates to a diagnosis of anterior uveitis. In fact, many forms of infectious retinitis present with significant anterior segment inflammation, therefore any patient with ocular inflammation needs a dilated fundus examination. The most common causes of infectious posterior uveitis are toxoplasmosis and necrotizing herpetic retinitis, although syphilis must be in the differential of any patient with uveitis. The focus of this talk will be on clinical clues to aid in the diagnosis of infectious causes of uveitis, through presentation of both classic and atypical cases of these conditions, as well as other infectious posterior uveitides such as DUSN, Bartonella and tuberculosis.

NOTES
Dr. Goldstein began by noting this was her first time at the ARDS meeting and she was grateful for the invitation. The focus of the talk was how to approach a patient with retinitis. Most people are in practices that don’t have a uveitis specialist, so the retina specialist may be the ones that manage the patients with retinitis.

Dr. Goldstein presented a series of cases for discussion:

A 68-year-old man initially presented in 2007 with floaters and decreased vision in the right eye. He was referred to the uveitis service with the diagnosis of primary intraocular lymphoma. VA 20/70 OD, 20/20 OS. Granulomatous KP, AC and vitreous cell were present OD. Additionally, the patient had CME and a few choroidal granulomas with no retinitis OD.

When Dr. Goldstein sees a patient with anterior chamber cells and vitreous cells, macular edema and choroidal granulomas, she said that she doesn’t think of lymphoma. Instead, the most likely diagnosis is sarcoid. She also thinks about TB and syphilis in every uveitis patient. For this patient she did the work up and his ACE was normal, it was actually low. He was on an ace inhibitor. His lysozyme was elevated. FTA-ABS for syphilis was negative, quantiferon gold for tuberculosis was negative. Chest x-ray showed a lung nodule. The nodule was biopsied, they found a non-caseating granuloma consistent with sarcoid. So he has a diagnosis of unilateral panuveitis secondary to sarcoid.

She treated him with a short course of topical steroids and a posterior sub-tenon’s kenalog. He did great, vision returned to 20/20. He was then lost to follow up due to travel distance. In 2013, he developed new floaters in his right eye and was seen by a retina surgeon in the community, in the suburbs where he lives. This doctor says, “Well you had sarcoid uveitis before, you have sarcoid uveitis again. You did well with a posterior sub-tenon kenalog so why don’t we do an Ozurdex today.” As the patient was lying down, ready, and prepped for his Ozurdex, the patient decides to not have the injection and return to Dr. Goldstein for an opinion.

Dr. Goldstein saw him again and his vision has decreased. Now he has confluent greasy KP, he’s got anterior chamber cell and flare, and a little bit of vitreous haze. So, what does he have now? Does that look like sarcoid? Everybody should be saying “no.” What does this look like? When you look at this you think: is this herpes zoster or herpes simplex? Is this CMV? Or is this toxoplasmosis? She did an AC tap and sent for VZV, HSV and CMV PCR analysis and also put the patient on Valtrex. The PCR came back positive for VZV. He did really well with just Valtrex and didn’t need further intra-vitreal injections. It was one small lesion that was not threatening vision. The points of this is to remember that even a patient with a known uveitic diagnosis can still get an infectious retinitis.

In medical school we all learn about Occam’s razor, but Dr. Goldstein commented that more important in her world is the opposite of Occam’s razor, it is Hickam’s dictum, which is that a patient can have as many diseases as they please.

In fact, this same patient came in recently with new floaters in his other eye. She thought, okay does he have sarcoid in his left eye now? Does he have ARN in his left eye? No, he had a hemorrhagic PVD with a retinal tear. There are a lot of reasons to have floaters and this patient now has three causes for floaters.

This is a a 71-year-old Caucasian male who complained of blurred vision and floaters OS for three weeks. He has end stage myelofibrosis and is on immunosuppression with ruxolitinib. The patient was first seen by an optometrist who diagnosed him with iritis and started him on homatropine and diltiaprednate. He then saw an ophthalmologist who diagnosed him with intermediate uveitis and started 20mg of PO prednisone daily one week prior to obtaining a uveitis consult. Dr. Goldstein went on to say “A 71-year-old guy with end stage systemic disease who’s being immunosuppressed, does not typically get a new non-infectious uveitis.”
The right eye was normal. The left eye had decreased vision with some AC cell, some vitreous cell, and very interestingly the patient also had posterior vitreous precipitates. Posterior vitreous precipitates are on the back of a PVD, sometimes you’ll see what look like first. In Dr. Goldstein’s practice, she feels this finding is most common in toxoplasmosis. So when she saw this patient she thought that when she looked in that she would see obvious toxoplasmic. Then in the periphery she saw atrophic retina with a brush fire border. This looked like necrotizing herpetic retinitis. The question is, is this toxoplasmic because of the of the posterior vitreous precipitates? Does this toxoplasmic look different because he’s immunosuppressed or is this ARN?

Dr. Goldstein did an AC tap again for PCR analysis for herpes viruses and this time added toxoplasmic. Because of the concern for ARN she gave intravitreal gancyclovir and foscarnet. The PCR came back negative for herpes viruses but positive for toxoplasmic, so she put the patient on Bactrim and continued his immunosuppressive therapy. It’s kind of questionable whether you do this or not, in this case this was palliative so the guy could breathe.

Remember infection! You don’t get your first episode of uveitis while you’re dying of systemic disease and you’re immunosuppressed. Posterior vitreous precipitate should make you think of toxoplasmic. They are character-istics but not pathognomonic. Assume that retinitis is infectious until proven otherwise. If you don’t know what it is, treat it as infectious. Not all uveitis is treated with steroids. Please don’t put an Ozurdex in until you’ve determined that something is not syphilis, sarcoid, TB, or ARN.

Toxoplasmic is the most common cause of posterior uveitis in people with normal immunity. It makes up a third of posterior uveitis. Everybody will see a case. Why is it important? Because it can present with pain, redness, photophobia, and granulomatous KP. Unfortunately, in the community, many physicians decide that something is anterior uveitis because they see cell and flare in the anterior chamber. That, however, is not anterior uveitis. Anterior uveitis means inflammation in the front of the eye without posterior involvement. It’s important to perform a dilated funduscopic examination before deter-mining whether or not the uveitis is anterior or posterior. Dr. Goldstein stated that she sees a lot of cases of toxoplasmic, ARN, syphilis, VKH, and sympathetic ophthalmitis that were diagnosed as anterior uveitis because nobody bothered to dilate the pupil.

Toxoplasmic is the most common cause of retinitis and most importantly this is not a diagnosis that we make with blood tests. If you go to Paris, it’s two-thirds of the population, and if you go to southern Brazil it’s almost everybody. So a positive toxoplasmic titer doesn’t make the uveitis you’re looking at toxoplasmic.

So how do we diagnose toxoplasmic? It’s a clinical diagnosis, and if you really need confirmation you take a sample of aqueous or vitreous for PCR. Remember the lifecycle of toxoplasmic, there are two forms of the organism. We can kill the rapidly multiplying tachyzoite, but we can’t kill the bradyzoite. Therefore, patients are at risk for recurrences forever.

How do we get toxoplasmic? Dr. Goldstein noted that even vegans can get toxoplasmic. About 10 years ago, there was an outbreak of toxoplasmic in contaminated bean sprouts. So, you can get toxoplasmic from anything – undercooked meat. We don’t generally see toxoplasmic in commercial beef cattle in the United States.

A patient was presented with congenital toxoplasmic with bilateral macular lesions, and subsequently images were shown when the patient had a recurrence. Recurrence typically occurs at the edge of an old scar. The old teaching is that most of ocular toxoplasmic is congenital. In fact, that is not true. Most of it is acquired postnatally and when you see a recurrence, it’s hard to tell if a recurrence is at the edge of an old scar that was acquired in utero, or afterwards. But bilateral macular lesions, that’s congenital.

The classic picture of reactivated toxoplasmic is that there is an old scar and then there is white retinitis adjacent to it. Things in the choroid are typically yellow and in the retina they are typically white. Often there’s surrounding retinal edema, we see vitreous cells overlying it, and you can get arteritis or phlebitis. It’s important to determine if the vasculitis is arteries or veins. In sarcoid there is always a vasculitis that’s along the veins, in Behcet’s it can be veins and arteries. When you see arteries, though, think of infection, e.g. toxoplasmic, ARN.

If you have a patient who comes in with floaters and decreased vision and on exam there’s a solitary white lesion in the retina, if you say toxoplasmic you are statistically right. Toxoplasmic is the most common cause of a single white lesion in the retina. All of these cases have a white lesion with surrounding retinal edema. You don’t get that with a lesion in the choroid. Remember, toxoplasmic is not in the choroid, it is in the retina. There can be underlying inflammatory choroiditis, but the infection is in the retina.

Remember in an immunocompromised host, toxoplasmic can look a lot like ARN. So, if you’re following a patient with necrotizing herpetic retinitis, and they are immunosuppressed and they are not getting better with treatment, think about toxoplasmic.
Another case was presented of a woman who, upon presentation, was initially diagnosed with intermediate uveitis. She presented with a string of pearls in the vitreous, and she wasn’t getting better on 60 mg of prednisone. Her retina doctor taking care of her was going to do an intravitreal triamcinolone injection, but then her husband said maybe they should get a second opinion. On exam there was a very large lesion superiorly with a brush-fire border. That was actually what we refer to as a massive toxoplasmosis granuloma. She did very well with therapy for toxoplasmosis and probably would have done much worse with an intravitreal triamcinolone.

Again, toxoplasmosis is a clinical diagnosis, we don’t use serum titers. If there’s a question, you can do PCR. There are a lot of therapies for toxoplasmosis, that tells you that we don’t have any ideal therapy. There’s no data that any one therapy is better than the other, but in Dr. Goldstein’s opinion, every antibiotic therapy is better than monotherapy with steroids. You can treat with azithromycin monotherapy or atovaquone monotherapy. These therapies are cysticidal. But they’re cysticidal in vitro, in vivo we still can’t prevent recurrences. Other treatment options include bactrim or clindamycin monotherapy. Intravitreal clindamycin is another option. We use this in patients who aren’t responding adequately or who don’t tolerate systemic therapy. If you inject intravitreal clindamycin with a steroid and if you want a steroid, please use dexamethasone. Please don’t put triamcinolone in there, because clindamycin lasts a couple of days and the triamcinolone will last three months.

The next patient presented, presented in March of 2015 and was diagnosed with toxoplasmosis. He was treated with azithromycin, he didn’t get any better, so he was injected intravitreal clindamycin and he got worse. So now what do we do? Well the first thing that you do when a patient’s not getting better is to reevaluate your diagnosis. We are all entitled to be wrong. So the patient had an aqueous PCR and it was positive for varicella. The treatment regimen was then changed based on this new diagnosis. But just remember if the disease is not responding as you’re expecting, reevaluate your diagnosis and then consider changing your treatment.

Let’s move on to ARN. ARN is usually unilateral at the beginning, but can become bilateral. If you look in the eye and there's something big and white and it's bigger than what we saw with toxoplasmosis and more peripheral, think about necrotizing herpetic retinitis. Whether it’s simplex or zoster, it depends on the age of the patient. Dr. Goldstein presented a patient with 360 degrees of retinitis. She stated that the patient’s condition was so advanced because someone diagnosed her with optic neuritis despite the fact that she presented with KP, a high IOP, and AC cells. The previous examiner didn’t look at her retina. They admitted her to the hospital and gave her IV Solu-Medrol. Subsequently, the patient lost all vision in one eye and saved some vision in the other eye.

Again, not everything with a swollen nerve, not everything with AC cell and flare, not everything with something in the retina is noninfectious uveitis. This is a clinical diagnosis, but it’s really easy to do an AC tap for confirmation and any lab can do PCR for simplex, zoster and CMV. For the treatment of ARN, when Dr. Goldstein trained, the induction therapy was IV Acyclovir. She doesn’t use IV Acyclovir anymore except for homeless patients or noncompliant patients who might benefit from being admitted to the hospital. We do induction with oral Valtrex 2 grams three times a day.

Dr. Goldstein also does intravitreal therapy for almost everybody as adjunctive therapy, but we need to treat them systemically. This is a bilateral disease in many cases. The text books all say that you treat from six weeks to three months but she’s never had anybody who was better in six weeks so we treat them as long as it takes to control the retinitis. Some of her patients are actually on Valtrex indefinitely. She has one patient with two ARN recurrences per eye so he’s now on Valtrex indefinitely. You can talk about whether you want to do prophylactic laser posterior to the retinitis. Dr. Goldstein prefers not to. She doesn’t think you decrease the chance of a detachment and you may use up valuable real estate that may be needed for a possible retinal detachment repair.

PORN is the same disease as ARN. It’s not a different disease, it’s the same bug in an immunosuppressed host, so there’s less vasculitis and less retinitis. Classically there are multifocal areas of necrosis, less vasculitis, and less vitreous haze.

Toxocara on the other-hand we expect to see in children. A classic presentation is with sub-retinal fibrosis, pre-retinal fibrosis, and pigmentary change around where the lesion was. Bendazole or thiabendazole can get into the vitreous at therapeutic concentrations, but by the time you see a patient with toxocara the organism is dead, so you treat with steroids.

There is very little DUSN in Chicago because the ground freezes so you don’t get infested with worms, but Janet Davis in Miami sees a fair amount of DUSN. This is a nematode and you get successive crops of white lesions in the retina, almost always unilateral and it is possible to find the little worm on exam. Don’t stop and take pictures, just laser the worm, shoot to kill and that’s how we treat it.
Bartonella. Everybody thinks about bartonella as being neuroretinitis. In fact, the more common presentation of bartonella is with a multifocal retinochoroiditis.

Dr. Goldstein stated that she wanted to end on syphilis because it is her single favorite disease. One nice thing about syphilis is that unlike many other causes of uveitis, you can cure syphilis. Fourteen days of IV penicillin and they're better and they're gone. Dr. Goldstein trained at McGill. She used to study in Sir William Osler's library, which was moved in its entirety to McGill medical school. And Sir William Osler said, "He who knows syphilis, knows medicine." Syphilis can present as anterior uveitis, scleritis, intermediate uveitis, retinal vasculitis, retinitis, choroiditis, or optic neuritis.

She presented a patient that was referred to her with a diagnosis of ARN. The patient had six weeks of floaters, but why is this not ARN? Aside from the fact that it was six weeks? Because there's no necrosis! This is an infiltrate. The most common cause of a ground glass appearing retinal infiltrate is syphilis. Sure enough we worked him up and he was FTA-Abs positive, RPR positive, and in fact HIV positive. He presented with bilateral intermediate uveitis and disc edema and with a gross rash. He had a rash everywhere, but not on his palms and soles and had been to 15 dermatologists and received 15 or 20 different treatments. There's nothing pathognomonic about vitritis and disc edema that says syphilis, but when you look at that skin rash, that's syphilis.

Dr. Goldstein tells her patients, "If you've ever had sex or ever been born you have risk factors for syphilis." A guy came in with his wife and two children and he had bilateral disc edema and bilateral vitritis. Again, nothing pathognomonic about this, but one of her former residents said, "Dr. Goldstein. I just diagnosed syphilis." Dr. Goldstein said, "How?" The resident goes, "I just shook his hand." There he is with these lesions on his hand. We made him take off his socks and his shoes and he has these characteristic lesions all over his feet and in fact, his wife says that he's having some balance issues and some memory issues. He also turned out to be FTA positive, RPR positive, lumbar puncture was positive for syphilis, and he was HIV positive as well. Thankfully, his wife only had syphilis from him, not HIV, and the kids were both negative for both diseases and Dr. Goldstein never saw him back after his 14 days of IV penicillin.

A patient with ground-glass infiltrate and little retinal precipitates was discussed. Only syphilis looks like this. The patient came with his wife and his sister and he has no risk factors, but when he was walked to photography he admitted that he may have had a couple of risk factors that he didn't want to admit in front of his wife. We worked him up, FTA-Abs positive, RPR positive, and HIV positive. Noting a trend here?

Another patient was referred to neurosurgery for a pituitary microadenoma. He had balance issues and decreased vision in his left eye. On exam there was a subtle infiltrate seen as a little yellow line. So maybe it's AZOOR. It could be AZOOR. On OCT you can see that he's got loss of the outer segments. The patient was worked up and he was FTA positive, RPR positive, HIV negative. Three months after IV penicillin his vision is back to 20/20 and you can see beautiful reconstitution of the outer retina. This was not an issue with a pituitary microadenoma.

Suspect syphilis in everybody. Retinitis, choroiditis, anything can be syphilis. Anybody that's referred to you with AZOOR, think about syphilis, but there's nothing pathognomonic about vitritis and disc edema.

Remember syphilis is not an AIDS-defining illness, but anybody with syphilis needs to be worked up for HIV. STDs travel in groups. A syphilis work-up should include both non-treponemal tests like VDRL and RPR, and specific treponemal tests because the non-treponemal tests can become negative in late stages like tertiary syphilis when they present with eye findings. So it's not okay that an RPR is negative, the patient can still have syphilis.

The first reported cure of syphilis with penicillin was reported in 1943. Dr. Goldstein went on to say “Everybody blames Christopher Columbus for bringing syphilis from North America, from the New World, back to the Old World, but this is where I think it gets interesting. I travel a lot and in every country I go to, I try to look up what they call syphilis. The Italians and Germans call it the French disease and the French blame it on the Italians and the Dutch blame it on the Spaniards and the Russians blame it on the Poles and the Turks blame it on the Christians and the Persians call it the Turkish disease. In India, it's the Portuguese disease and the Japanese call it the Chinese pox. So, if you know the history of syphilis, you know the history of all of Europe!"

The treatment for neurosyphilis is 14 days of IV penicillin. One of our oldest diseases is still sensitive to our very first antibiotic. So, remember when you see a patient with retinitis, assume it's infections, don't stick an ozurdex in before you've thought about syphilis and ARN and toxoplasmosis and TB, and remember not all uveitis is treated with steroids.
Approach to the patient with retinitis
Not all uveitis is treated with steroids

ARDS March 7, 2017
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Northwestern Memorial Feinberg school of Medicine

2007
- VA 20/70 OD, 20/20 OS
- Granulomatous KP OD
- AC and vitreous cell OD
- CME OD
- Few choroidal granulomas
- No retinitis

2007
- DDx: Sarcoid, TB, Syphilis. PIOD much less likely
- Work up:
  - ACE normal, lysozyme elevated
  - FTA Abs – NR
  - QuantIFERON – neg
  - CXR - lung nodule
    - Biopsy – non caseating granulomas c/w sarcoidosis
- Diagnosis:
  Panuveitis secondary to sarcoidosis OD

2007
- Short course topical steroids and posterior subtenon triamcinolone injection
- Complete resolution of inflammation
- VA returned to 20/20
- Followed for one year then lost to follow up for 5 years

2007
- 68 yo old WM with floaters and decreased vision right eye
- Referred to the uveitis service with diagnosis of primary intraocular lymphoma

A CASE OF FLOATERS

2013
- New floaters OD
- Seen by retina surgeon, dx with uveitis recurrence
- Dexamethasone intravitreal implant recommended
- As the patient lay draped and ready for injection, he began to have second thoughts...
  - Presented back to the uveitis service
2013
- BCVA 20/40 OD, 20/20 OS
- Slit Lamp Exam:
  - OD:
    - Almost confluent active greasy KP inferiorly
    - 2+ AC cell
    - 2+ AV cell, 1+ vitreous haze
  - OS:
    - Normal

Key Points
- Remember infectious causes of uveitis, even in patients with known non-infectious disease
- The opposite of Occam's razor is 'Hickam's dictum: "A patient can have as many disease as he or she pleasures"

INTERMEDIATE UVEITIS?

- 71 yo Caucasian male
- Blurred vision and floaters OS x 3 weeks
- Myelodysplasia dx'd 1994
  - End-stage disease
- Ruxolitinib 10 mg am/5 mg pm (JAK inhibitor)
- Seen by optometrist, diagnosed with iritis, started homatropine TID and diltiazem hydrochloride OID
- Seen by ophthalmologist, diagnosed with intermediate uveitis, started FO prednisone 20 mg daily one week prior to uveitis consult

- Unilateral "Intermediate uveitis" in immunosuppressed patient
- DDx?
Exam
- OD normal
- OS
  - BCVA 20/50
  - IOP 13
  - 1+ AC cell/2+ AV cell
  - Posterior vitreous precipitates
  - Vitreous haze

DDx
- Necrotizing herpetic retinitis
  - VZV
  - HSV
  - CMV
- Toxoplasmosis
  - Posterior vitreous precipitates
- AC tap
  - PCR for herpes viruses and toxoplasmosis
- Intravitreal injection
  - Foscarnet 2.4 mg/0.1 mL
  - Ganciclovir 4 mg/0.1 mL
- PCR results
  - VZV, HSV, CMV negative
  - Toxoplasmosis positive 415,000 copies
- Bactrim DS daily
- Continue ranolodin

Always consider infection, especially in immunosuppressed patients
- Posterior vitreous precipitates very characteristic of toxoplasmosis
- Toxoplasmosis can look like ARN in immunosuppressed patient
ASSUME THAT RETINITIS IS INFECTIOUS, UNTIL PROVEN OTHERWISE

IF YOU AREN’T SURE, TREAT AS INFECTIOUS

NOT ALL UVEITIS IS TREATED WITH STEROIDS

Which is infectious??

Which is infectious??

Which is infectious??

Infectious and non infectious posterior uveitis can’t always be differentiated based upon clinical examination
Infectious posterior uveitis

- Toxoplasmosis
- Herpes
- Toxocariasis
- Mycobacterial disease
- DUSN
- Bartonella
- Syphilis
- "Emerging infections"

Human infection

- Undercooked meat: pork > mutton > beef
- Vegetables may also be contaminated
- Hand contamination
  - Handling of cat feces
  - Water-filtration in US removes 99% of particles to 4μm
  - Allograft transplant
  - Heart, kidney, bone marrow
  - Transplantation
  - Inhalation

Toxoplasmic retinochoroiditis

- 25 – 30% of posterior uveitis in immunocompetent host
- May present with floaters, blurred vision, pain, redness, photophobia
- May have granulomatous iritis with high IOP

Congenital toxoplasmosis

Recurrence congenital toxoplasmosis

Toxoplasmosis

- Commonest cause of retinitis in people with normal immunity
  - 2.46 active cases/100,000 population/yr California
  - 0.6% have inactive retinal scars (Alabama)
  - 5.6% of all pediatric uveitis patients in one large series
    (Ophthalmology. 2009 Aug; 118(8): 1544–1551)

- 23% of US adults have IgG Ab
  - 67% France; 78% Nigeria, 98% southern Brazil

Toxoplasma gondii

- Tachyzoite
  - Obligate intracellular protozoan
  - Proliferative form
  - Crescent shaped, 7 μm x 3 μm
- Bradyzoite
  - Slow metabolizing organisms within cysts
  - Cysts to 100 μm in diameter
  - Outer cyst wall is from host
  - May lie dormant in retina for years
Common Infectious Posterior Uveitides – Goldstein

Recurrent toxoplasmosis
- Majority of toxoplasmosis is acquired
- Recurrent disease typically at edge of old scar
  - Congenital or acquired

Acquired toxoplasmosis

Recurrence of congenital toxoplasmosis

Toxoplasmic vasculitis
- Arteritis or phlebitis
  - May be close to or remote from site of retinitis

Toxoplasmosis in immunocompromised host
Monotherapy for Toxoplasmosis

- Azithromycin (Zithromax)
  - 500 mg loading dose then 250 mg/day
  - GI side effects
- Patients treated with azithromycin 2.5 times more likely to die from cardiovascular causes than those treated with amoxicillin
- Atovaquone (Mepron)
  - 750 mg PO TID or QID
  - Also used to treat Pneumocystis
- These two agents are cysticidal in vitro, but have not been demonstrated to prevent recurrences

Diagnosis of ocular toxoplasmosis

- Clinical diagnosis
- Positive serum antibody titer doesn’t make diagnosis
  - 23% of US adults have IgG Ab
  - 67% France, 78% Nigeria, 98% southern Brazil
- Negative doesn’t rule it out
  - If only focus is in eye, systemic titers may be low
- Aqueous & vitreous PCR for toxoplasmosis
  
  http://depts.washington.edu/molmicd/mytests/toxoplasma.shtml

Other Options

- Monotherapy with Bactrim
  - 1 DS PO BID
- Monotherapy with minocycline
  - 100 mg PO BID
  - May use long term for massive granuloma
- No good evidence that any one antibiotic is the best choice

Quadruple Therapy

- Pyrimethamine: 75 mg load, 25 mg PO QD or BID
  - Folinic acid 10 mg 2/week (bone marrow suppression)
- Sulfadiazine 2 gm load, 1 gm PO QID
  - Avoid sunlight
- Stevens-Johnson syndrome
- Clindamycin 300 mg PO QID
  - Pseudomembranous colitis
- Prednisone 60 QOD, or 20 – 40 QD, start two d after antibiotics
  - Rx at least 6 weeks (rarely that short)

Toxoplasmosis: intravitreal therapy

- Clindamycin 1-1.5 mg/0.1cc
- Dexamethasone 400 μg/0.1cc
- Q1-4 weeks
- 2-5 injections
- Do not use intravitreal triamcinolone!
  - Consider in
    - Difficult to treat disease
    - Patient intolerant of systemic therapy
    - Pregnancy
COMMON INFECTIOUS POSTERIOR UVEITIDES – GOLDSTEIN

- 3.10.2015
  - Clinical diagnosis toxoplasmosis
  - Started on azithromycin
  - Did not improve
  - Intravitreal clindamycin
- 3.31.2015
  - Now what?

- Aqueous PCR + Toxoplasmosis
- Atovaquone started, resolution of retinitis
- If disease not responding as expected
  - Reconsider diagnosis
  - Reevaluate therapy

Necrotizing Herpetic Retinitis

- Acute Retinal Necrosis (ARN)
- Progressive Outer Retinal Necrosis (PORN)
- Herpes zoster, Herpes simplex, CMV

ARN

- Sudden onset of decreased vision or floasters
- Pain and photophobia are common
- AC cells and flare
- KP
  - Small, stellate
  - Large, mutton fat
- Significant vitritis
- Scleritis
- Optic neuritis
- Importance of dilated fundus exam

ARN: Clinical Course

- Worse outcome correlated with
  - Increasing age
  - Increasing relative immunosuppression
  - Larger area of retinal involvement (Retina. 2010;30(5):795-800)
- Retinal detachment is frequent (up to 75%)
- RD usually occurs after the acute phase of ARN
- Infected necrotic retina thins
- Vitreous contraction = traction = large holes
COMMON INFECTIOUS POSTERIOR UVEITIDES – GOLDSTEIN

ARN
- Clinical diagnosis
- Goldmann-Witmer coefficient
- PCR on vitreous specimen
- PCR on aqueous specimen
  - Easier than vitreous

ARN: additional treatment
- Prophylactic laser photocoagulation immediately posterior to the necrotic retina (lose “real estate”)
- Systemic corticosteroids
  - e.g. prednisone 0.5 – 1.0 mg/kg/day
  - After anti-viral therapy
  - When unequivocal regression of retinal necrosis observed
  - No monotherapy with steroids

ARN: induction therapy
- IV
  - Acyclovir q8h for 10 – 14 days
    - 500 mg/m²
    - 5-10 mg/kg
    - Monitor renal function
- Oral
  - Valacyclovir (Valtrex) 2 gram PO TID
  - Famciclovir (Famvir) 500-1000 mg PO TID

ARN: local therapy
- Intravitreal ganciclovir (2000 mcg/0.05cc)
- Intravitreal foscarin (1200 mcg/0.05cc)
- Indications
  - Progression despite systemic therapy
  - Contralateral eye involvement developing on systemic therapy
  - Sight-threatening disease

Progressive Outer Retinal Necrosis (PORN)
- Immunosuppressed host
- Minimal or no AC reaction
- Little or no vasculitis
- Little vitritis
- Early posterior pole involvement
- Rapid progression to confluence
- Perivenular clearing of retinal opacification
- Poorer response to treatment

ARN: Treatment
- Duration of maintenance depends on immune status of patient
  - 6 weeks to 3 months if normal immunity
  - May be indefinite if immunocompromised or if recurrent disease
  - Decreases incidence of fellow eye involvement
  - Does not appear to decrease incidence of RD
**Toxocariasis**

- *Toxocara canis*
- Unilateral
- Endophthalmitis in young children
- Isolated granuloma in older child
- Usually no systemic eosinophilia

**Toxocariasis: therapy**

- Parasite assumed to be dead when the patient presents with either cicatricial or acute inflammatory changes
- Treatment with albendazole or thiabendazole
  - Probably achieves intraocular levels
  - Provides no benefit in cicatrical disease
  - Rarely given
- Corticosteroid therapy can reduce secondary damage from intraocular inflammation

**Toxocariasis: surgical therapy**

![Images of eye with Toxocariasis](Courtesy of Bob Moomy)

**DUSN**

- Diffuse unilateral subacute neuroretinitis
- Nematode
- Early stage
  - Successive crops of evanescent lesions
  - Grey-white or yellow-white
  - Deep layers of retina
  - Lesions fade > RPE changes
  - Mild disc edema
  - Mild to moderate vitritis
  - Mobile worm may be seen next to active lesions

Find the worm: Shoot to kill
**Bartonella**

- Multifocal retinochoroiditis more common than neuroretinitis

**Syphilis**

- "Great imitator"
  - Anterior uveitis
  - Intermediate uveitis
  - Retinal vasculitis
  - Retinitis
  - Choroiditis
  - Optic neuritis
  - Scleritis

"He who knows syphilis knows medicine."
— William Osler
Syphilis
- Suspect in patients with
  - Retinitis
  - Chorioiditis
  - Retinal vasculitis
  - Optic neuritis
  - Vitritis
  - Any form of inflammation

Syphilis
- Caused by spirochete Treponema pallidum.
- The acquired form is transmitted by sexual contact.
- Stages
  - Primary: painless chancre at site of penetration of organism
  - Secondary: systemic symptoms and skin lesions, typically 2–12 weeks after initial contact
  - Latent: asymptomatic, can last for months or a lifetime, most relapses occur within the first year
  - Tertiary: cardiovascular and neurologic sequelae
  - Ocular manifestations can occur at any stage

Syphilis
- Not an AIDS defining disease
- May be first presentation of HIV
- Most common in MSM
Common Infectious Posterior Uveitides – Goldstein

Syphilis testing

- Non treponemal tests
  - RPR
  - VDRL
- Treponemal tests
  - FTA-ABS (fluorescent treponemal antibody-absorption)
  - MHA-TP (microhemagglutination assay T. pallidum)
  - TPHA (T. pallidum hemagglutination)
  - TPAT (T. pallidum particle agglutination)
  - Treponemal enzyme immunoassay (EIA) for IgG and IgM

Syphilis history

- First reported in Europe around the 15th century
- Rapid spread in Europe began shortly after Christopher Columbus returned from the new world
- First reported cure with Penicillin 1943

Syphilis testing (world history?)

- Italians & Germans - “French disease”
- French - “Italian disease”
- Dutch - “Spanish disease”
- Russians - “Polish disease”
- Turks - “Christian disease”
- Persians - “Turkish disease”
- In India - “Portuguese disease”
- Japanese - “Chinese pox”

Syphilis treatment

- Treat syphilitic uveitis as neurosyphilis
- Gold standard is 14 days of IV penicillin
- Interesting that one of our oldest diseases remains sensitive to our first antibiotic

Syphilis testing: PCR

- Newest test for the direct detection of T. pallidum
- Several PCR methods have been reported, each using a different target gene
- May be performed on vitreous and aqueous
  - Br J Ophthalmol. 2006 May; 90(5): 647–648
- Rarely clinically required, as serologic testing almost always positive in cases of syphilitic uveitis

Approach to the patient with retinitis

- Work-up of all uveitis patients should include syphilis testing
  - Non-treponemal test
  - Specific treponemal test
  - If serologic testing is positive
    - LP: VDRL, protein, WBC (negative LP doesn’t rule out dx)
    - HIV testing
  - Start with presumption that disease is infectious
  - Not all uveitis is treated with steroids
Toward More Precise Subretinal Therapeutic Delivery: New Techniques and Instrumentation

ALLEN C. HO, MD

SUMMARY

Cell therapies for atrophic AMD and other new potential retinal therapies such as gene therapy for neovascular AMD require safe, controlled and reproducible subretinal delivery techniques and potentially new instrumentation. We will review the current status of the cell therapy trials for atrophic AMD and report on the phase 1/2a Janssen cell therapy program and status of the phase 2 trial.

Although transvitreal approaches in subretinal delivery are most familiar, a retinotomy to access the subretinal space may permit egress of therapeutics into the vitreous cavity reducing precision in therapeutic delivery. A potential solution is therapeutic subretinal delivery without retinotomy. We have developed new microcatheters and other instrumentation that permit a suprachoroidal and then transchoroidal approach to the subretinal space without retinotomy in the macula. In preclinical and clinical testing in the Janssen CNTO 2476 phase 2 trial, we have refined and tested these instruments and techniques and will present the surgical technique and instrumentation via surgical video.

NOTES

There are a lot of new interventions looking at ways to treat atrophic AMD. The question here is, can cell therapies support or replace cells or tissue in AMD? These cell therapies are categorized by DONOR (autologous, allogenic), SOURCE (blood, bone, marrow, embryo), POTENCY (multipotent, pluripotent), and defined by MECHANISM OF ACTION.

The Janssen cell line was derived from one woman’s umbilical cords stem cells. These cells are trophic in nature — not intended to replace photoreceptors or RPE cells, compared to regenerative stem cells — intended to replace injured tissue. The cells were expanded and tested extensively. These specific cells were picked because after multiple rounds of testing they were shown to increase phagocytosis in RPE cultures and also induced ganglion cell synapse formation. This cell line was first used in an RP patient, who subsequently had a tractional retinal detachment (TRD). Knowling this, a surgical approach limiting egress of cells into the pre-retinal space, for example through a retinotomy, was desired.

The current surgical method was born out of a phase 1/2a study (CNTO 2476 phase 2) that failed. The cells were well tolerated but the problem was the approach. The approach was with a subretinal catheter. This approach demonstrated a high incidence of tears and detachments (5/30 patients). The subretinal approach created a bleb in the periphery and then a cannula was passed in the subretinal space. Once in the posterior pole another bleb was created. The purpose of this was to have attached retina between site of entry and where the cells were delivered to limit egress of cells into the preretinal space. In the middle of the trial an endoscope was used to try to reduce risk of tears and detachments once this was observed.

Despite surgical failure, there were indicators for a good efficacy and potential for the cell line to improve vision. The cells were also well tolerated without signs of inflammation or tumor development.

There was a control (fellow eye), patients weren’t masked to the intervention, so there was intervention bias, people taking VA were potentially biased because they knew which eye had the surgery. Treated eyes maintained or had slight improvement (1 or 2 letters). Untreated eyes declined, but they also had small areas of atrophy.

What was very intriguing to the sponsor was the 2-3 line gainers (20-30% of treated eyes at 6 and 12 months), but again not masked. Something less subject to bias was area of GA. There was no difference in baseline in GA area in the treated or untreated eyes.

In summary, the cells were tolerated, but the initial surgery was not safe. There was a potentially positive stimulus which gave hope for development and through these complications a new surgical technique was developed. A method that would cannulate the suprachoroidal space and only enter the subretinal space in the posterior pole through the RPE. With this approach there is no chance for egress of cells in the preretinal space.

Current (New) Procedure:

The chandelier and infusion cannula are placed in standard fashion. Peritomy is performed. A special marking pen that assists with placement of mattress sutures marks the sclera. The mattress sutures help stabilize the flexible microcatheter. The markings ensure that the microcatherer is parallel to the incision. Any scleral fibers overlying the sclerotomy incisions are...
removed. A flexible 1.5 mm microedge catheter is passed in to the suprachoroidal space. This passes easily in 80% AMD patients. Through a chandelier and wide angle viewing system you directly visualize the tip of the cannula as it is passed in the suprachoroidal space. Then a micro-catheter enters into subretinal place. A bleb with saline is created, followed by a small air bubble to confirm you are in the subretinal space, then the desired therapy is injected. The device comes out and incisions are closed. This is a way to deliver interventions into the posterior pole without creating a retinotomy.

An important note in GA studies is that VA testing in patients with GA is very challenging. Be careful when reports give this and you see data on this, particularly in these types of trials with no real control group.

**DISCUSSION**

**Q:** If you were doing a different trial with less risk of the treatment egressing would you still use this modality?

**A:** I think the transvitreal approach is technically most transferable. If you have something that is going to work then, transvitreal with retinotomy is the way to go. However, let’s say you are doing a trial for gene therapy for AMD. You have a lot of variables: intervention, surgeons, dosage etc. To me there are still many confounding factors that could undermine efficacy. For example, surface area of bleb, especially in gene therapy where dosage needs therapy to touch the cell. So, I think this technique is still relevant. It might also be diagnostic or therapeutic. Why can’t we suck out blood from subretinal space with this technique? Surgical trials are plagued with confounders and limiting those is helpful. If leakage from the retinotomy is a confounder – then this is the way to go.

**Q:** If you had a child would you recommend this way?

**A:** I might, vitrectomies in kids are not easy.

**Q:** So now we are starting to look at GA better, how do we look at trial endpoints that are going to be valid for us and valid for our patients?

**A:** GA, little bias can be had with this. But patients don’t care about GA, they care about vision. So it’s very challenging. Vision is a horrible endpoint for these patients. Microperimetry is another possibility, but there’s still subjectivity.

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**Disclosure**

| Aerie (C) | Johnson (C, O) |
| Azlon (C, O) | NEI/NIH (O) |
| Allergan (C, O) | ONL (O) |
| Apilis (O) | Optikon (C, O) |
| Bausch & Lomb (O) | Optikomed (O) |
| Covidien (O) | PanOptix (C, O) |
| DiSight (C, O) | PRN (C, O) |
| Genentech (C, O) | Regeneron (C, O, C) |
| Iridex (C, O) | Second Sight (C, O) |

Palpacuer and the new device and procedure presented here are being developed by Johnson & Johnson Vision. The video case presented is from a patient enrolled in a Phase 2a study of palpacuer that was funded by Johnson.
Cell therapy has figured prominently in medicine since 1818

1818
Blood transplantation was used successfully

1969
Bone marrow transplantation is a widely accepted form

Cell delivery strategies

Transvitreous

Suprachoroidal

Cells with therapeutic application can be
categorized based on the donor, and the source...

...as well as the potency and the mechanism of action

Phenotypic
- Can produce all cell types in the body
- Endo- and mesenchymal cells

Multipotent
- Can generate multiple, but fixed, cell types
- Endo- and mesenchymal cells, endo- and mesenchymal cells

Reparative
- Cells by matrix-integrated tissue
- Cells expanded and differentiated

Trophic
- Cells to support matrix-integrated tissue
- Cells expanded, but not differentiated

Janssen CNTO 2476: Human Umbilical Tissue Derived Cells

Produced in accordance with cGMP and cGTP Guidelines

Defined Cell Expansion

Cryo preserved cell suspension

CTO 2476
TOWARD MORE PRECISE SUBRETINAL THERAPEUTIC DELIVERY – HO

**Janssen CNTO 2476 Human umbilical tissue cells (hUTC) and hUTC-Conditioned Media Promote Phagocytosis in Vitro**

![Graph showing phagocytosis data](image)

**CNTO 2476 Phase 1/2a Study in GA Patients**

- Single ascending dose, open-label safety study evaluating four concentrations of CNTO2476 cells delivered to the subretinal space via the IRBAC microinjector.
- **Patients with History**:
  - Ph 1: 12 patients (6 male, 6 female) with GA
  - Ph 2a: 3 patients (1 male, 2 female) with GA
- **Dose concentrations**:
  - Low: 1,000, 2,000, 3,000, 5,000 cells
  - High: 10,000, 20,000, 30,000, 50,000 cells
- **Objectives**:
  - Evaluate safety of intravitreal injections and cells
  - Observe potential off-target effects

**Janssen Safety Summary Ph 1b/2a**

- **Ocular AE Summary**
  - 2 subjects treated for retinal detachment post procedure and administration of the cells
  - 1 subject who did not undergo the procedure and was not administered any cells was treated for retinal detachment.
- **No reported cases of endophthalmitis, vitreitis, or ocular tumors**
- **No reported immune response noted to date**

**Safety Conclusions**

- The surgical procedure to deliver the cells to the subretinal space requires modification prior to further development.
- In general, the cells were well-tolerated at one year following resolution of surgical sequelae.

**CNTO2476 Ph 1 Trial in Advanced RP Patients**

- Single dose, open-label safety study evaluating CNTO2476 cells delivered to the subretinal space via a transtrabecular route.
- **Subjects**: 8 patients with RP
  - 4 male, 4 female
  - 6 patients (20/200 to 20/300) with minimal macular edema.
  - 2 patients (20/100 to 20/300) with minimal macular edema.
- **Dose**: 1.0 × 10^6 cells
- **Outcomes**:
  - Evaluate safety of delivering procedure and cells in the subretinal space
  - Observe potential off-target effects

**Cell Therapy in Atrophic AMD**

- Cell therapies compete in a landscape of strategies for atrophic AMD and are characterized by donor, cell source, cellular potency and mechanism of action.

- **Janssen Phase 1/2a Human umbilical cord tissue-derived cell therapy (CNTO 2476, palucellular)**: well tolerated for atrophic AMD (n=38) when delivered without retinal break, but Phase 1/2a subretinal procedure demonstrates a high incidence of retinal detachment and retinal scar.

- **CNTO 2476 (Palucellular)**: may yield favorable clinical response in some subjects with atrophic AMD – need controls.

- **Retinal targeted delivery for Phase 2a Efficacy feasibility study** to the subretinal space with a new subretinal microinjector delivery system.

---

**Janssen CNTO 2476**

**Data from Subjects 1092-459**

- [Graph showing data](image)

**Janssen CNTO 2476**

**Data from Subjects 1092-459**

- [Graph showing data](image)

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105 ASPEN RETINAL DETACHMENT SOCIETY MEETING NOTES 2017
Cell Therapy in Atrophic AMD

- Cell therapy is a promising approach for atrophic AMD and is characterized by donor, cell source, cellular potency and mechanism of action.

- Janssen Phase 1/2a human umbilical cord blood-derived cell therapy (CNTO 2476, palv Objective) was tested for atrophic AMD (n=38) when delivered without retinal break, but Phase 1/2b subretinal procedure demonstrated a high incidence of retinal detachment and retinal tear.

- CNTO 2476 (Palvocore) may result in favorable clinical response in some subjects with atrophic AMD – need controls.

- Retinal targeted delivery for Phase 3 RCTs is approached at procedure to the subretinal space with a new subretinal microinjection delivery system (Phase 2B/3 RCT in 2018).

Mean change from baseline in GA area (mm²)

Mean change from baseline in BCVA at 12 months

Mean change from baseline in BCVA at 24 months

Percent of ≥10 and ≥15 letter gains from baseline
### Janssen Phase 1b/2a Conclusions

<table>
<thead>
<tr>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNTX 2476 was well-tolerated as a single dose therapy</td>
</tr>
<tr>
<td>When subretinal administration was achieved without a retinal break, administration of these cells was well-tolerated and not associated with substantial ophthalmic adverse events</td>
</tr>
<tr>
<td>Further refinements of the surgical procedure and delivery system are needed to reduce the ocular complications associated with cell delivery observed in the current study</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Efficacy</th>
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<tbody>
<tr>
<td>Subretinal administration of CNTX 2476 may result in a vision benefit in some patients with geographic atrophy</td>
</tr>
<tr>
<td>Further evaluation of efficacy in a randomized, controlled, masked trial is required</td>
</tr>
</tbody>
</table>

### Cell Therapy in Atrophic AMD

| All cell therapies compete in a landscape of strategies for atrophic AMD and are characterized by donor, cell source, cellular potency and mechanism of action |
| Janssen Phase 1/2a human umbilical cord tissue-derived cell therapy (CNTX 2476; palucorron) is well-tolerated for atrophic AMD (n=35) when delivered without retinal breaks, but Phase 1/2a subretinal procedure demonstrates a high incidence of retinal detachment and retinal tear |
| CNTX 2476 (Palucorron) may result in favorable clinical response in some patients with atrophic AMD — need controls |
| Refined surgical delivery for Phase 2b RGCT suprachoroidal procedure to the subretinal space with a new subretinal microcatheter delivery system: Phase 2b RGCT (n approx 160) pending |

### Suprachoroidal without retinotomy approach may minimize egress of cells or gene therapy

**Suprachoroidal**

### Subretinal Delivery System
Management of Radiation Retinopathy

IVANA KIM, MD

SUMMARY
Radiotherapy provides excellent local control for choroidal melanoma. However, significant visual loss occurs due to radiation retinopathy. Various treatment approaches for radiation retinopathy have been attempted, including laser and intravitreal pharmacotherapy with steroids and anti-VEGF agents. Results have been variable, but generally, earlier treatment may be more efficacious. Some cases that have been recalcitrant to anti-VEGF therapy may respond to intravitreal steroid.

More recently, prophylactic approaches have been investigated utilizing steroids, anti-VEGF agents, and even vitrectomy with silicone oil. A prospective investigator-sponsored clinical trial was performed at our center evaluating the use of ranibizumab given every 2 months for 2 years after proton irradiation for small/medium choroidal melanomas close to the fovea and/or optic disc.

At two years, 88% of patients treated with ranibizumab had visual acuity of 20/40 or better compared to 47% of historical controls (p<.001). Further details of this study will be discussed.

NOTES
Dr. Kim started by thanking Tim and Don for the invitation. This was her first time at the ARDS meeting.

She provided an update on our current thinking about how to treat radiation retinopathy. Although it's probably not the most common condition you will see in your practices, the strategy that we're using requires more intensive pharmacotherapy these days, and you may be asked to co-manage these patients more and more often with an ocular oncologist. It is something to keep in the back of your mind because it can mimic other maculopathies.

We know that radiation retinopathy is an occlusive microangiopathy which occurs months to years after ocular exposure to ionizing radiation. Similar to diabetes, the vascular endothelium is the primary focus of damage. The peak incidence occurs at about two years following radiation therapy. Radiation retinopathy affects approximately 40% to 64% of patients after irradiation for choroidal melanomas that involve or are near to the macula. This currently is probably the most common condition which we see in patients post radiation for melanoma, so this is what the focus is for today's talk.

Basically, everything that has been tried for any other cause of macular edema, especially diabetic macular edema, has been tried for radiation maculopathy. The first attempts were a macular grid or focal laser photocoagulation. Hykin et al (Ophthalmology 1998) used grid laser for radiation maculopathy after plaque radiotherapy for choroidal melanoma. This was a retrospective review of 42 patients, 19 treated and 23 untreated. Initially the laser group at 6 months had improved vision and reduction of macular edema but this was not sustained at 24 months.

Kinyoun (Trans Am Ophthalmol Soc 2008) published a retrospective study with 42 eyes with macular edema and non-proliferative radiation retinopathy. Nineteen eyes were treated and 23 eyes were untreated with a mean follow up of 51.5 months. Most cases received external beam radiotherapy for non-ocular tumors. The multivariate regression analysis revealed some benefit of macular photocoagulation.

Since we've evolved in our practice to treat macular edema with pharmacotherapy. Previously, anti-VEGF agents were not available, and so corticosteroids were tried in this condition due to the suggestion of therapeutic effect in other cases of macular edema and with the knowledge that corticosteroids suppress vasogenic edema and CNS radiation injury due to the suppression of multiple factors that contribute including VEGF, TNF, and ICAM-1.

One of the early studies involving intravitreal triamcinolone came from the Wills group by Shields et al. (Ophthalmology 2005). This was a prospective, non-randomized study with 31 patients who had just a single intravitreal injection of 4 mg of triamcinolone at the time of diagnosis of radiation maculopathy. There was a positive effect on visual acuity. A higher proportion of triamcinolone treated patients had improvement or stabilization of vision, and the baseline OCT appeared to decrease within the first month, but then there was a gradual increase in retinal thickness and a return of macular edema by six months.

After seeing a short term positive effect of steroids, people turned to the dexamethasone implant. Several case series were done most of which used the Ozurdex implant. Again, these are very small case series, not the level of evidence that we have for diabetic macular edema. But these series (Russo et al. 2012; Bailiff et al. 2014; Bui et al. 2014; Caminal et al. 2015) found a general trend towards some anatomic and visual effect, mostly minimal improvements, but some improvements in anatomic stabilization. It's important to note that a lot of these patients had failed other prior therapies, so this is somewhat promising.
Now with the advent of anti-VEGF therapy, we have a few large case studies in the literature with their use. Shah et al. (2012) has published the largest series of patients (n=159). An important distinction in this series is that these patients were OCT diagnosed cases of macular edema. You can see that with a follow-up of three years, they have visual results that compared very favorably to those reported in COMS at three years. So, there is benefit from anti-VEGF therapy, but it’s a prolonged treatment and multiple treatments without the same visual impact as we see in other cases of macular edema.

To show how differently radiation retinopathy can respond, Dr. Kim presented a few cases to demonstrate the extremes. A patient with choroidal melanoma in very close proximity to the fovea. Two years after proton irradiation, the visual acuity dropped to 20/125. Intra-vitreal bevacizumab x2 was given and vision dropped to 20/160, without any real anatomic improvement either. A bolus of triamcinolone was given, again, with minimal visual or anatomic benefit. This is the kind of patient that sometimes does respond to the Ozurdex implant.

On the other extreme, another patient presented 19 months after proton irradiation for choroidal melanoma, the vision dropped to 20/320 from radiation maculopathy. Then over the course of 4 years, the vision improved to 20/50 without treatment. So, there are some patients that may spontaneously improve, we do not have a way to predict who will or even know the chance of spontaneous improvement but maybe 20% to 30% may have some spontaneous improvement.

These are the two extremes of the types of patients we see with radiation maculopathy. We have to keep these patients with spontaneous regression in mind because uncontrolled studies do not take into account the natural history that we are seeing here.

A new approach that is under investigation is a prophylactic approach. The thought is if we catch it early enough and begin treating with pharmacologic agents when it is first detectable by OCT, possibly prior to visual decline, maybe the results will be better. So the next step was can we achieve better benefit with prophylactic treatment. A prophylactic surgical approach has even been advocated by Tara McCannel that involves doing vitrectomy and silicone oil tamponade at the time of plaque placement to potentially shield the retina from the scatter of the radiation from the plaque. This surgical approach is still a bit controversial.

One of the early studies involved periocular triamcinolone. The Shield’s group (Horgan N. Shields CL, Mashayekhi A, et al. Ophthalmology 2009) performed a randomized control trial in which they gave 40 mg of triamcinolone sub-tenons at the time of plaque application, with repeat injections at four and eight months afterwards. Follow-up was 18 months, which is a relatively short follow-up for radiation maculopathy, but at 18 months they did see a statistically significant reduction in macular edema in the patients treated.

Another approach is with anti-VEGF therapy. Prior to the investigation of prophylactic approaches, we have seen increasing use of anti-VEGF therapy for the treatment of established radiation maculopathy and papillopathy. Retinal vasculopathy is thought to be analogous to blood-brain barrier disruption in CNS radiation therapy. Tsao et al. (J Neuropathol Exp Neurol 1999) showed that VEGF is upregulated following radiation therapy in a rat model with spinal cord injury. In that same model, Nordal et al. (Clin Cancer Res 2004) showed that there may be some neuroprotective effects to suppressing VEGF in the context of radiation injury.

There is also the potential theoretical benefit of anti-VEGF therapy and maybe synergism with radiation. In a glioma model by Winkler et al. (Cancer cell 2004 Dec) anti-VEGF therapy was shown to have the effect of what we call tumor vessel normalization. With tumor vessel normalization, you actually improve oxygen delivery to the tumor and radiation is dependent on the creation of oxygen free radicals, so there’s potential that if you give radiation and anti-VEGF at exactly the right time, perhaps there could also be some synergy with radiation.

One of the early studies looking at bevacizumab prophylaxis for radiation retinopathy came from the Shields group (Shah SU, Shields CL, Bianciotto CG et al. Ophthalmology 2014). Their plan was to give bevacizumab every four months for two years from the time of plaque removal through two years. They enrolled 292 patients. This was elective, so 292 patients decided themselves to receive bevacizumab and 126 patients decided that they didn’t want to receive bevacizumab. The follow-up in this study was inconsistent. Only 9% of all the patients actually received all planned seven injections, and the mean injections given over the study period was just four. Despite that, there was some benefit of bevacizumab treatment in terms of OCT-detectable macular edema and the incidence of moderate vision loss.

Dr. Kim performed a much smaller study that was prospective and with ranibizumab. They enrolled two cohorts. The FDA actually asked them to enroll large tumors first, just to prove that it was safe, so in cohort one, they enrolled 15 patients with large tumors and 5 patients with small tumors close to the disc or macula. In a second cohort, they enrolled 20 more patients with small tumors.
The schedule was to give the first dose of ranibizumab at the time of tumor localization, which happened to be about 10 days before the first dose of proton irradiation. These patients were given ranibizumab every two months for two years.

The inclusion criteria were large tumors, greater than 15mm in diameter or greater than 5mm in height. Then the high-risk small and the medium tumors, less than 15mm diameter, less than 5mm in height, and the location needed to be within 2 disk diameters of the fovea or optic nerve.

Dr. Kim noted that they were primarily interested in safety but certainly the secondary outcomes they were interested in were vision and OCT-detectable macular edema, radiation maculopathy, papillopathy, and also neovascular complications in the patients with large tumors.

Of the 40 patients that enrolled, 32 completed two years of the study. Eight patients discontinued the study, only one of which came from the small tumor group, which is the focus of the discussion.

In terms of safety, there was no serious ocular or systemic adverse event that they could relate to ranibizumab treatment in this cohort of patients. In terms of tumor control, they did see three cases of metastasis in patients with very large tumors. Two of these patients did pass away from metastasis during the study. One patient in the small tumor group at his very last follow-up for the study, did present with a small, local tumor recurrence. He was successfully retreated with additional proton radiotherapy and is doing quite well.

Since they did not have a randomized control group, they selected a group of historical controls that were treated with proton radiation alone. They were matched for tumor size and location, and had at least the same length of follow up as the patients treated with ranibizumab.

Looking at visual acuity results, a low bar of visual acuity, 20/200 or better, at two years after radiation, the ranibizumab-treated patients did have a significantly higher percentage 85.7% vs 34.3% (p=0.01) of patients with visual acuity of 20/200 or better. In the small to medium tumors, it was 100% of the patients treated with ranibizumab versus about 70% in the historical controls (p=0.001).

For the higher bar of visual acuity, better than 20/40 at two years after radiation, remember these are tumors that are very close to the fovea or disc, the small to medium tumor group treated with ranibizumab, 87.5% of them had 20/40 or better compared to about 46.8% of the historical controls, and that was highly statistically significant (p<0.001).

Looking at moderate vision loss at month 24, there was also fewer patients treated with ranibizumab who had moderate vision loss compared to historical controls. In the large tumor group 42.9% in the treated group vs. 71.3% in the historical control group (p=0.12) and in the small tumor group 20.8% of the treated group lost vision compared to 45.2% in the untreated group (p=0.03).

Looking at actual radiation vasculopathy, definitely fewer patients treated with ranibizumab had evidence of maculopathy or papillopathy, and that was significant. Of those that did develop signs of the maculopathy or papillopathy, a higher proportion of ranibizumab-treated patients actually retained vision.

In terms of other outcomes, in the large-tumor group, there are no cases of neovascular glaucoma in the treatment group compared to about 26.1% in the historical controls at 24 months. There appeared to be some resolution of exudative retinal detachments, with 55% (6/11) resolution but there was no good historical control data for that. There was only one enucleation, which was by patient request and not because of complications.

In conclusion, ranibizumab appears safe when administered in conjunction with proton radiation for melanoma. When administered every two months, it appears to have a potential beneficial effect on visual acuity in comparison to historical controls.

Clinical signs of radiation retinopathy and papillopathy were observed in fewer ranibizumab-treated patients compared to the historical controls. When it does occur, it seems to have less visual impact with ranibizumab treatment, but certainly longer-term follow up of larger numbers of patients is required.

To summarize overall, Dr. Kim thinks that pharmacotherapy for radiation maculopathy is efficacious, although we do not have very high-level evidence at this point. She believes that sustained anti-VEGF treatment is required for a visual benefit, and corticosteroids, both Triamcinolone or Ozurdex may provide benefit in cases refractory to anti-VEGF therapy.

Dr. Kim finished by saying “I think we’re going to do the best when we do prophylactic or even early image-guided treatment, as Tim has shown us. I think Jose Pulido had a very nice paper recently that showed that OCT-A can probably detect signs of radiation vasculopathy even earlier than structural OCT. Possibly by monitoring our patients with OCT-A early in the post-radiation course, we can defer treatment until changes are seen but still early enough to be able to catch the full benefit of this prophylactic treatment.”
DISCUSSION
Q: Question | C: Comment | A: Answer

C: When you look at OCTA in these tumor patients, there are alterations in the foveal avascular zone that occurs incredibly early. In fact, what’s interesting is you can see alterations in the foveal avascular zone in eyes with tumors before they’ve been treated when the tumor is distant. We’ve always talked about tumor associated factors that alter vasculature and we’ve never really understood that role, but it seems like that does play a part here.

Q: Do you have any inkling that this might also apply to optic neuropathy following radiation?

A: I don’t think we’ve been able to separate it out, at least in our cohort. We did a subgroup analysis, and my clinical impression and the inkling that we get from this is that it’s more effective in maculopathy.

C/Q: I think it’s interesting because I think if you treat early, it seems like the incidence of papillopathy is delayed. So, I don’t see radiation papillopathy as early as I used to, and I don’t think it is as aggressive as it has been, but when it occurs, it’s too me more devastating and less responsive to treatment. Those are eyes I’ll treat with a heavy anti-VEGF and a concomitant heavy steroid delivery. So, one of the things I thought was interesting is what made you choose eight weeks, just out of curiosity?

A: It was more of a practical consideration. A lot of these patients come from great distances, as you know, and it was just a matter of trying to keep the frequency high enough so that there would be close to some levels in the interval between injections and yet not put too much of a burden on patients so that we would have a high dropout rate.

C: I think there’s the potential to even improve upon these results by using a more frequent interval. I think that the controversy in the ocular oncology field initially was that people would give one injection and see the patients back in six months and say, “oh, it didn’t work.” I think that most of us would feel that if you gave one injection for neovascular AMD and saw the patient back in six weeks, it wouldn’t work either.

Q: I had a patient who had a tumor much too large to plaque, and he used gamma knife. That was two years ago and I just saw her. She has no radiation retinopathy at all. This massive tumor has disappeared. It almost looks like there was nothing there. What is your experience with gamma knife?

C: So the European gamma knife experience is a little bit broader, and leksell gamma knife was actually a treatment of choice and I was involved in the data and safety monitoring committee. I will tell you that the retinopathy incidence was significantly higher and the enucleation rate was significantly higher. So, tumor control is achievable, but with gamma knife the retinopathy was significantly higher, and the incidence of neovascular glaucoma was significantly higher, and the enucleation rate was significantly higher.

Q: The best way to deal with radiation retinopathy is not to get it in the first place. Is there a way to lower the dose of radiation used to prevent the development of retinopathy, at least for smaller tumors?

A: We’ve argued and strategized about dose reduction for a long time. The problem is that this is such an orphan disease for us, which is the hardest part.

Q: So, I know you probably have experience with this, but aflibercept? Do you think that your results would be different or have you tried aflibercept for this?

C: We’ve done a clinical trial with Regeneron using aflibercept, and I want to thank the companies because I can tell you that I spent decades talking about and trying to get an interest in doing this. I will tell you from experience for us that the best response seems to be with aflibercept. What was interesting is that I was hoping the best response would translate into a prolonged response, and it’s looking that the anatomic improvement in the visual recoveries are better, but we’re not really able to push the interval of treatment. Not everybody responds. In our first 40 patients, we have two patients of the 40 now approaching a year that have not been able to be held there. We are still looking for best response characteristics for these patients.

Q: When you say they respond better to early treatment, are they clinically established cases or OCT diagnosed or the OCT-A diagnosed ones that you see?

C: So, for me, remember the data in the Houston paper. You could be 20/25, but you couldn’t be 20/20. Every patient had to have declining vision, and you had to have radiation maculopathy using that modified Shields grading criteria that we used. So, I think you don’t need to treat prophylactically, though I’m not opposed to that as long as you see the patients often enough that there’s not a delay. You don’t want to have a three-month window from there and see progression from no maculopathy to massive maculopathy.

You are going to start to see more and more of these patients in your offices, because they just can’t travel to get injected every four to six to eight weeks. If you look and there is any evidence of leakage on the OCT, please, please inject them because it’s amazing how rapidly the macular edema progresses with no injection. I don’t care what you inject them with. Use your anti-VEGF treatment of choice. If there are large cystic alterations in the retina, those eyes may better respond to a steroid.

Q: Do you still wait for a vision drop?

C: I don’t think you should wait for a vision drop if there’s macular changes on OCT. I’m uncertain what OCTA is going to show us, but I’m kind of fascinated by that.
**Management of Radiation Retinopathy**

Ivana K. Kim, MD  
Retina Service  
Massachusetts Eye and Ear Infirmary  
Harvard Medical School

**Disclosures**

- Genentech: consultant, research support  
- Iconic Therapeutics: consultant  
- Allergan: consultant  
- Off-label use of dexamethasone implant (Ozurdex), bevacizumab, ranibizumab is discussed

**Radiation Retinopathy**

- Oclusive microangiopathy which occurs months to years after ocular exposure to ionizing radiation  
  - Vascular endothelial cell primary focus of damage  
- Peak incidence at about 2 years after radiation  
- Affects approximately 40-64% of patients after irradiation for choroidal melanomas involving/inviting macula

**Photoacoagulation**

- Grid laser for radiation maculopathy after plaque radiotherapy for choroidal melanoma  
- Retrospective review  
  - 19 treated  
  - 23 untreated  
- VA improvement and reduction in macular edema at 6 months, but not sustained

**Corticosteroids**

- Suggestion of therapeutic effect in other causes of macular edema  
- Suppression of vasogenic edema in central nervous system radiation injury  
  - VEGF  
  - ICAM-1  
  - MMP2  
  - TNFα

**Intravitreal Triamcinolone**

- 31 patients  
- Prospective, non-randomized  
- Single intravitreal injection of 4 mg triamcinolone at time of diagnosis of radiation maculopathy

**Dexamethasone Implant**

- Dexamethasone implant
  - Tolerability  
  - Estimate  
  - Retreatment

Adapted from: Retina. Curr Opin Ophthalmol 2015; 26:157–166
**Anti-VEGF**

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Drug</th>
<th>Treatment Period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phanik et al. 2015</td>
<td>86</td>
<td>Bevacizumab</td>
<td>38 mos</td>
<td>89% patients off-of-therapy (mean Vz &lt; 30) over 3 years, 69% at 5 years</td>
</tr>
<tr>
<td>Markoy et al. 2014</td>
<td>30</td>
<td>Bevacizumab</td>
<td>6-14 mos</td>
<td>50% with decreased CMT (&gt;15% decrease vs. baseline) 42% with improved Vz (&gt;1 mm) 44% with stable VA</td>
</tr>
<tr>
<td>Shah et al. 2013</td>
<td>133</td>
<td>Bevacizumab</td>
<td>36 mos</td>
<td>46% with Vz &lt; 20/20 51% with VA &lt; 20/20</td>
</tr>
</tbody>
</table>

**Prophylactic Treatment**

- Pharmacologic
  - Triamcinolone
  - Anti-VEGF

- Surgical
  - Vitrectomy/Silicone Oil (McCannel)

**Periocular Triamcinolone**

  - Randomized, controlled trial
  - 108 pts triamcinolone, 96 pts control
  - Periocular triamcinolone 40 mg in 1 ml
    - Sub-Tenon
    - 4 months
    - 8 months
  - 18 month follow-up
  - Multivariate Cox proportional hazard analysis
    - Hazard estimate < 0.45 for risk of macular edema with triamcinolone treatment (P < 0.05)
    - No statistically significant difference in IOP elevation or cataract progression between groups

**Rationale for Anti-VEGF Therapy**

- Increasing use of anti-VEGF therapy for radiation maculopathy and papillopathy
- Retinal vasculopathy analogous to blood-brain barrier disruption in CNS radiation injury
  - VEGF expression upregulated in astrocytes 16 weeks after radiation in rat model of spinal cord injury (Stein et al. *J Neurosci* 2001;21:8267-83)
  - Decreased VEGF expression precedes angiogenesis (Miyata et al. *Cancer Res* 2004;64:3192-9)

**Potential Synergism with Radiation**

- VEGFR2 blockade in orthotopic glioma model
- Tumor vessel normalization
- Increased tumor oxygenation
Bevacizumab
- Bevacizumab 4-6 mo x 2 years
- N=292 (17 mo tu)
  - 126 controls (not randomized, 21 mo tu)
  - 19% received all 7 injections
    - Mean=4 injections

Two-Year Results
- 40 patients enrolled
  - 18 large tumor patients
  - 22 small tumor patients
- 32 pts completed month 24 visit
- 8 patients discontinued study
  - 1 pt required enucleation (large tumor group)
  - 5 pts withdrew or did not follow-up (1 small, 4 large)
  - 2 developed metastasis (large tumor group)

Trial Design
- Cohort 1
  - Large Tumors N=18
    - 0.5 mg
  - Small Tumors N=19
    - 0.5 mg
- Cohort 2
  - Small Tumors N=20
    - 0.5 mg
  - Large Tumors N=6
    - 1.0 mg

0 0.5 1 2 4 6 8 22 24 Months

Inclusion Criteria
- LARGE TUMORS
  - >15 mm diameter and/or
  - >5 mm is height

- HIGH RISK SMALL/MEDIUM TUMORS
  - >15 mm diameter AND
  - >5 mm h/k
  - <2000 from fovea or optic nerve

Safety
- No serious ocular or systemic adverse events related to ranibizumab
- Tumor control
  - 3 cases of enucleation in patients with very large tumors
  - 2 of these patients died from metastasis 3 years later
  - 1 case of local recurrence in small medium group; detected at mo 24

Outcome Measures
- Safety
- Secondary Outcomes
  - Proportion of pts with VA ≥ 20/200

Baseline Characteristics

```
<table>
<thead>
<tr>
<th></th>
<th>Small/Medium</th>
<th>Large</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.9 (46.9-57.9)</td>
<td>60.7 (55.0-66.7)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>76.0 (75.0-77.0)</td>
<td>72.6 (69.0-76.0)</td>
</tr>
<tr>
<td>BSCVA (LogMAR)</td>
<td>0.5 (1.0-0.0)</td>
<td>0.1 (0.0-0.0)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.9 (7.5-10.5)</td>
<td>8.9 (7.3-10.5)</td>
</tr>
<tr>
<td>Height (mm)</td>
<td>12.1 (1.4-14.4)</td>
<td>25.0 (20.0-30.0)</td>
</tr>
<tr>
<td>EOM (mm)</td>
<td>1.7 (1.0-2.0)</td>
<td>2.7 (1.5-4.0)</td>
</tr>
<tr>
<td>DVM (mm)</td>
<td>1.1 (0.8-1.4)</td>
<td>1.6 (0.8-2.4)</td>
</tr>
</tbody>
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```
### Management of Radiation Retinopathy – Kim

#### Visual Acuity ≥ 20/200

<table>
<thead>
<tr>
<th></th>
<th>RBZ+ PBI</th>
<th>PBI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>96.4% (30/31)</td>
<td>44.3% (30/205)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large</td>
<td>85.7% (7/7)</td>
<td>34.3% (7/213)</td>
<td>0.01</td>
</tr>
<tr>
<td>Small/Medium</td>
<td>100% (24/24)</td>
<td>69.3% (24/35)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

#### Moderate Vision Loss (≥3 lines)

<table>
<thead>
<tr>
<th></th>
<th>RBZ+ PBI</th>
<th>PBI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>26.8% (6/23)</td>
<td>63.4% (13/205)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large</td>
<td>42.9% (3/7)</td>
<td>71.4% (10/213)</td>
<td>0.12</td>
</tr>
<tr>
<td>Small/Medium</td>
<td>20.8% (5/24)</td>
<td>46.2% (20/262)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

#### Visual Acuity ≥ 20/40

<table>
<thead>
<tr>
<th></th>
<th>RBZ+ PBI</th>
<th>PBI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>77.4% (24/31)</td>
<td>22.4% (48/205)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large</td>
<td>42.9% (3/7)</td>
<td>11.9% (3/213)</td>
<td>0.05</td>
</tr>
<tr>
<td>Small/Medium</td>
<td>87.5% (21/24)</td>
<td>46.8% (21/82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

#### Radiation Vasculopathy

<table>
<thead>
<tr>
<th></th>
<th>RBZ+ PBI</th>
<th>PBI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopathy</td>
<td>33.3% (3/9)</td>
<td>47.7% (14/29)</td>
<td>0.04</td>
</tr>
<tr>
<td>with VA 20/140</td>
<td>87.5% (8/9)</td>
<td>87.5% (8/9)</td>
<td>0.48</td>
</tr>
<tr>
<td>with VA 20/200</td>
<td>100% (10/10)</td>
<td>100% (10/10)</td>
<td>0.3</td>
</tr>
<tr>
<td>Papillopathy</td>
<td>83.3% (3/3)</td>
<td>83.3% (3/3)</td>
<td>0.2</td>
</tr>
<tr>
<td>with VA 20/140</td>
<td>50.0% (1/2)</td>
<td>50.0% (1/2)</td>
<td>1.1</td>
</tr>
<tr>
<td>with VA 20/200</td>
<td>100% (1/1)</td>
<td>100% (1/1)</td>
<td>29</td>
</tr>
</tbody>
</table>

#### Overall Group

**VA Retention ≥ 20/200**

Log-rank p < 0.001

#### Large Tumor Group

- No cases of neovascular glaucoma
- 26.1% at 24 mo in historical controls
- Exudative retinal detachment resolved in 55% (6/11)
- 1 enucleation
  - Patient request
  - Occurred in first year of study

#### Small-Medium Tumors

**VA Retention ≥ 20/40**

Log-rank p = 0.11

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115 Aspen Retinal Detachment Society Meeting Notes 2017
Conclusions

- Ranibizumab appears safe when administered in conjunction with proton beam irradiation for choroidal melanoma
- Ranibizumab administered every 2 months appears to have a beneficial effect on visual acuity in comparison to historical controls

Conclusions

- Clinical signs of radiation retinopathy/papillopathy were observed in fewer ranibizumab-treated patients compared to historical controls
  - Radiation vasculopathy may have less visual impact with ranibizumab treatment
- Longer-term follow-up of larger numbers of patients is required

Summary

- Pharmacotherapy for radiation maculopathy is efficacious
  - Sustained anti-VEGF treatment is required for visual benefit
  - Corticosteroids may provide benefit in cases refractory to anti-VEGF therapy
    - Transconjunctival
    - Oquistel
  - Prophylactic or early image-guided treatment may prove most beneficial

Acknowledgements

- Evangelos S. Gragoudas, MD
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- Purva Jain
- Ashley Fisette
Update on Aflibercept and Combination Therapy for AMD and Polypoidal Choroidal Vasculopathy

GREGG T. KOKAME, MD, MMM

SUMMARY
Antiangiogenic therapy has revolutionized the treatment of exudative age-related macular degeneration (AMD) over the past 15 years. Staging of exudative AMD introduced by Gass is based on location, including type I subretinal neovascularization (sub RPE), type II subretinal neovascularization (above the RPE) and type III neovascularization (neovascularization within the retina with subretinal neovascularization).

However, another variant of subretinal neovascularization is polypoidal choroidal vasculopathy (PCV). This variant is a type I subretinal neovascularization lying beneath the RPE and above Bruch’s membrane, and is NOT in the choroid. The importance of this variant is that the diagnosis of PCV may affect therapy and even change decisions in regards to therapy.

Treatment with antiangiogenic injections are important at decreasing exudation and bleeding in PCV. However, there is a higher incidence of resistance to antiangiogenic injections with PCV. The Everest II study is a multi-centered trial done in Asia (Singapore, Japan, South Korea, Taiwan, Hong Kong, Malaysia). This study compared monthly ranibizumab to combination photodynamic therapy (PDT) and ranibizumab with 2 subsequent loading doses of ranibizumab in a multi-centered randomized clinical trial involving 322 patients. After the first 3 months treatment was PRN for both groups. Combining PDT with 3 ranibizumab loading doses resulted in better vision, less residual fluid, and more polyp regression than ranibizumab monotherapy alone.

This trial emphasizes that PDT is still important, and that combination PDT should be considered even as primary therapy, and not only as rescue therapy. This is especially considered when vision is significantly decreased (worse than 20/40) and when ICG angiography is able to localize the lesion to a non-foveal area and when frequent doctor visits are not possible.

NOTES
PCV is becoming much better recognized around the world. There are ~20% in the US, but we are still not recognizing it to that degree. Dr. Gass’ classification of CNV classification is:

- Type I: Under the RPE
- Type II: Above the RPE and under the retina
- Type III: NV within the retina or RAP

Case examples of different types of CNV:
- Type 1 CNVM: 72 yo female with decreased vision for 2 weeks. Visual acuity is 20/50. Type 1 CNVM below showing flow very nicely on OCTA. How would people treat this? … Anti-VEGF
- Type 2 CNV (not AMD): 35 yo with decreased vision for 1-2 weeks; Visual acuity is 20/200. FA showing diffuse leakage late on FA. OCTA shows type 2 CNVM. How would people treat? … Anti-VEGF
- Type 3 CNV case: 80 yo female with 1-2 years of metamorphopsia; Visual acuity is 20/400. OCTA shows neovascularization within the FAZ. How are you going to treat? Anti-VEGF … Especially in this case, it is very sensitive to antiVEGF

In all the cases it doesn’t change what we are going to do. We would treat all of these cases with Anti-VEGF.

PCV case: Patient with 20/400 vision and acute loss of vision. ICG shows polyps. There might be good reason not to treat with anti-VEGF initially in this patient, unlike the above 3 cases. It’s important to make the correct diagnosis of PCV because treatment may be different. This patient improved to 20/50 with resolved fluid. PDT works, but is it better?

Proposed treatment algorithm for PCV:
1. 50% PCV is asymptomatic – don’t do anything
2. PCV with active leakage
   - Extra-foveal – treat with thermal laser or PDT
   - Subfoveal complex:
     - VA 20/40 or better or dense heme: anti-VEGF
     - VA worse than 20/40 consider using primarily combination treatment: Anti-VEGF and PDT. (Some people would consider anti-VEGF alone but in those cases you have higher resistance. So you should potentially be thinking of something else as well.)

Anti-VEGF is effective in decreasing leaking and bleeding, but less effective in anatomical closure of polyps. This was shown in the EVEREST I trial. The general consensus in Asia is that aflibercept is better for PCV. Also, PDT is an important part of treatment of PCV in Asia, but much less so in the United States.

PLANET Study:
The PLANET study has never been presented in the US before. It is a global study and is a randomized clinical sham controlled study phase 3b/4 at 62 sites throughout...
Asia, Hungry, and Germany. It was designed to look at safety and efficacy of aflibercept monotherapy vs combination therapy of aflibercept with PDT. In this trial only 7% of patients received PDT. It is not an effective way to look at the PDT question, but it does provide good data on monotherapy response to aflibercept.

The results showed similar response of both groups with a 10 letter increase. 97% in both groups didn’t lose 3 lines of vision. The results showed aflibercept was effective and safe for the treatment of PCV at 52 wks. The study used 2 mg aflibercept monthly for 3 months followed by q8 weeks treatment for the first year. The next portion of the trial is not complete and it looks at this interval vs a treat and extend arm, providing information on how long these patients can be extended out.

Of interest is that the PLANET (aflibercept) study when compared to EVEREST II (ranibizumab) showed that aflibercept may be better as a monotherapy; 10.7 letters with aflibercept vs 5 letters gained for ranibizumab. The possible explanation of this could potentially be shown by a study done in Germany in animals. This study showed that ranibizumab penetrates through intercellular spaces and goes around RPE cells whereas aflibercept, because of the Fc segment, goes through the RPE cells by being actively transported. Because PCV is a type 1 CNVM, this characteristic of aflibercept may be relevant.

**EVEREST Trials**

EVEREST was the first clinical trial to look at ranibizumab vs combination therapy of ranibizumab and PDT, but duration of the study was only 6 months. It didn’t show statistically a significant difference in vision. However, the results were still important by showing more polyp regression with PDT. The problem with the study was its length.

EVEREST II looked at ranibizumab + vPDT combination therapy vs ranibizumab monotherapy. 12 month results are out but 24 month results are not yet available. Patients had to be symptomatic and have macular PCV confirmed on ICGA in 1:1 randomization. There was a central reading center in Singapore, that is excellent. There had to be a hyperfluorescent polyp surrounded by a hypofluorescent ring.

Study design: Initially everyone in the PDT group got treated with PDT on presentation and then ranibizumab monthly x 3 months. The ranibizumab group only got injections, no PDT. They were treated for three months then PRN. Results were noted at 12 months. As needed PDT was applied if a patient had confirmed leaking or bleeding polyps. All patients were Asian. The vision was slightly lower to start in patients enrolled in PLANET (58) compared to EVEREST II (61). The key finding was that VA was better in the ranibizumab + PDT combined group compared to the ranibizumab monotherapy group (8 vs 5 letter gain). A majority of patients in the combined treatment group achieved polyp regression. We knew this from before but these results were even better than the EVEREST I trial. Central thickness decreased significantly more in the PDT group. Most people only required one PDT and 90% had two or fewer treatments. The combination therapy group required on average 4 ranibizumab injections compared to 7 in the monotherapy group.

Primary objectives in EVEREST II were met. Ranibizumab + PDT was superior to ranibizumab monotherapy by:

- Improving vision at 12 months
- Achieving complete polyp regression at 12 months
- Fewer number of treatments 4 vs 7 injections

**Case presentation of a patient who refused monthly anti-VEGF therapy**

The patient was treated with PDT, anti-VEGF and steroid. After the first treatment, OCT showed that the PED was less and the fluid improved but was present. The patient had 2 more injections and 4 years later it was not active. The patient’s vision was 20/30. There was a tremendous decrease in treatment burden.

This PCV subgroup is the most important subgroup to identify because: 1. Neovascularization is NOT in the choroid but under the RPE and above bruchs membrane, and there is IMPROVED treatment with combination therapy. Clinical exam and FA is not enough to make this diagnosis.

One thing that should be noted is what Dr. Gass described – close clinical observation and making the correct diagnosis is very important. If we are missing PCV and not making the correct or best diagnosis, we are not going to give the best possible treatments for these patients.

**DISCUSSION**

**Q:** Question | **C:** Comment | **A:** Answer

**C:** I find the best time frame to see the polyps are between 2-5 min. I have found that either too early or too late it is not as beneficial.

**C:** I think PDT is inflammatory and I’m for using steroids at the same time. I use PDT, avastin, and steroid.

**Q:** What is the reason for the vascular biology sensitivity to combination treatment with anti-VEGF and PDT in PCV?
C: I think it’s flow, because there’s less flow through polyps it’s hard for anti-VEGF to shut them down. I don’t have a good study to prove that, but it just makes sense.

Q: that makes sense to PDT but what about anti-VEGF? Why is it less susceptible?

C: Bigger chunky vessel. I think the difference is size. I use full fluence for NV and ½ fluence for CSR. When people labeled fluence, it was not done by a scientist, and the time was decreased by half not the dose. I also treat larger than the lesion. I would still to use anti-VEGF if the vision is better than 20/40

Q: Do you think the Asian variant is applicable to the Caucasian population?

A: I do

Q: Who does combined FA/ICG vs FA only?

Of the audience who responded, 50% stated they did FA/ICG and 50% stated they did FA only.

Q: Why did they do ranibizumab and not aflibercept in EVERST II?

A: The sponsor of the study was Novartis, which runs ranibizumab and PDT. I feel aflibercept may do better than ranibizumab alone. So, in that setting, if aflibercept was used, the vision in the monotherapy group may have been better and more challenging to beat with the combination therapy. When I go to Japan they have a heavy preference for aflibercept.
AFLIBERCEPT AND COMBINATION THERAPY FOR AMD AND PCV – KOKAME

Type 1 CNV
72 yo female complains of decreased vision for 1-2 weeks, left eye.
Med Hist: none
Ocular Hist: none
VA: 20/300- IOP: 15

PCV Images (Pre-PDT)
64 yo female complains of worsening, severe, blurred vision with distortion, right eye
Med Hist: DA, HTN, MCL
Ocular Hist: None
VA: 20/60, IOP: 15

Type 2 CNV
35 yo female complains of decreased vision for 1-2 weeks, left eye.
Med Hist: none
Ocular Hist: none
VA: 20/200, IOP: 12

PCV Images (Post PDT)
VA: 20/80
Resolved Polyp and IPED

Type 3 - RAP
88 yo female complains of blurred vision ODD: 20/400, 1.2 years with worsening
Med Hist: HTN
Ocular Hist: none
VA: 20/400 IOP: 12

Proposed Rx Algorithm for PCV
- Inactive PCV – observe
- PCV with active leakage or bleeding
  - Extrafoveal Polyp consider ML or PDT
  - Subfoveal PCV Complex
    - VA 20/40 or better or dense SR HEME
    - X-VEGF
    - VA worse than 20/40
      - Combination vPDT/anti-VEGF
    - Better anatomic and visual outcomes
      - X-VEGF alone - watch for relapse X-VEGF resistance and need to consider vPDT rescue therapy

Anti-VEGF Therapy
- Effective at decreasing leaking and bleeding in PCV
- Less effective at anatomic polyp closure than vPDT
- General consensus of many in Asia that aflibercept may be more effective than ranibizumab or bevacizumab for PCV
Conclusions

- Afiblercept monotherapy was effective and safe in treatment of PCV over 52 weeks, with an improvement in BCVA of 10.7 ETDRS letters.
- 2mg afiblercept monthly for 3 months followed by q 8 weeks for rest of the first year; second year will be treat and extend.
- Only 7% of patients received active vPDT – not adequate study for role of vPDT – must look at EVEREST II.
- 10.7 letter increase at one year with afiblercept versus 5.1 letters with monthly ranibizumab in EVEREST II – different studies but similar entry criteria.

EPIC Study
Afiblercept (Eylea) for Polypoidal Choroidal Vasculopathy

6 Month Prospective Study Results

Gregg T. Kokame MD MMM1, 4 James C. Lai MD1, 4 Raymond Wue MD2, 4 Ryan Yanagihara BS2, 4
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EPIC STUDY

- The EPIC trial (Intravitreal Afiblercept Injections (Eylea®) for Polypoidal Choroidal Vasculopathy with Hemorrhage or Exudation)
- Investigator Sponsored Prospective Clinical Trial of Afiblercept treatment for PCV
- Entrance Criteria with ICG diagnosis of PCV and active leakage or bleeding
- 3 monthly injections followed by mandatory q 8 weeks injections but PRN in between q 8 week injections
- 21 Patients Enrolled


EPIC Study Design
A prospective, open-label trial

PROPHET Trial
Polypoidal Choroidal Vasculopathy

- Safety assessments
- ETDRS
- OCT
- FA & ICG Angiography

Case Report: 1003
84 yo Asian Man, Unilateral PCV, Prior Treatment (PEARL2)

Results: Anatomical Changes of Fundus From Baseline (Month 6)

- Macular edema: Improved in 13/17 (76%) eyes
- Subretinal/Intra-RPE Hemorrhage: Resolved in 6/8 (75%) eyes
- Subretinal Fluid: Resolved or decreased in 16/18 (89%) eyes
- Retinal Pigment Epithelial Detachment (RPED): Resolved or decreased in 13/18 (72%)
- Polypoidal complexes: Polyps decreased in 14/21 (67%) eyes
  - CNV remained stable in size in all patients

Results: Bimonthly versus Monthly Treatments at 6 Months

- Monthly injections: 6/21 (29%) eyes
- Every 8 week Injections: 15/21 (71%) eyes

Case Report: 1016
87 yo Asian Male, Unilateral PCV, Prior Treatment (PEARL2 – 24 months High Dose Ranibizumab)

Case Report: 1016
87 yo Asian Male, Unilateral PCV
Resolved Polyps on Bi-Monthly Aflibercept After 24 High Dose Ranibizumab Injections
Treatment QVW since M3

Aflibercept

- Generally recommended in Asia for PCV
- Higher vision gain in PLANET study (10.7 letters) than ranibizumab in the EVEREST II Study (5.1 letters)
- Marked response to aflibercept in patients with persistent disease after 24-months of high dose ranibizumab
- Ranibizumab penetrates through intercellular spaces, whereas aflibercept with an Fc fragment is actively transported through the RPE (Julien S et al, BJO 2014; 98: 813-825.Tuebingen, Germany)
**Role of verteporfin PDT (vPDT)**

- Photodynamic therapy (vPDT) an important part of therapy in Asia for PCV
- Much less frequent use in the anti-VEGF era
- Evidence for continued role supported by recognition of PCV and new study results

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**Everest II**

Ranibizumab and vPDT combination therapy versus ranibizumab monotherapy for macular PCV: 12-month results from the EVEREST II study

Adrian Koh1, Timothy Y. Lo2, Kenji Takeuchi3, Lien Y. Wong1 Lee-Jen Chen4, Puan Kamvivutbd5, Colin S. Tan6,8, Chrysele Feller6, Philippe Margaron1, Tock H. Lim4, and Won Ki Lee13

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**Background**

- The EVEREST I study was the first randomized, active-controlled trial in patients with macular PCV to assess treatment outcome with vPDT either alone or in combination with ranibizumab and ranibizumab monotherapy.
- In that 6-month study of 61 patients, vPDT combined with ranibizumab or vPDT monotherapy was statistically superior to ranibizumab monotherapy in achieving complete polyp regression.
- No significant difference in best-corrected visual acuity (BCVA) gain between groups was reported, but the study was not powered to detect differences in BCVA change from baseline.

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**EVEREST II**

EVEREST II is an ongoing, 24-month, phase IV, randomized, double-masked, multicenter study designed to compare the effects of combination therapy versus ranibizumab monotherapy with respect to change in BCVA from baseline and complete polyp regression at Month 12.

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**Key inclusion criteria**

- Patient age ≥18 years.
- Symptomatic macular PCV confirmed by Central Reading Center as defined by presence of active macular polypoidal lesions on ICGA and by presence of serosanguineous maculopathy on fundus photography and FA.
- BCVA letter score of 78 to 24 using ETDRS chart at a starting distance of 4 m (approximately 20/32 to 20/320 Snellen equivalent).
- Greatest linear dimension of total lesion area (BVN + polyps) <3400 μm (approximately 5 MPP disc areas) as delineated by ICGA.

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**EVEREST II recruitment map**

**EVEREST II - study design**

- 122 patients.
- BC500043732.
- Primary endpoint at 12 months.
- Final follow-up at 24 months.

**Treatment schedule**

**Key inclusion criteria**

- Patient age ≥18 years.
- Symptomatic macular PCV confirmed by Central Reading Center as defined by presence of active macular polypoidal lesions on ICGA and by presence of serosanguineous maculopathy on fundus photography and FA.
- BCVA letter score of 78 to 24 using ETDRS chart at a starting distance of 4 m (approximately 20/32 to 20/320 Snellen equivalent).
- Greatest linear dimension of total lesion area (BVN + polyps) <3400 μm (approximately 5 MPP disc areas) as delineated by ICGA.
**CRC definition of characteristic polyoidal lesion**

- Early subretinal focal ICGA hyperfluorescence (appearing within the first 6 min of ICGA)
- AND
- One of the following angiographic criteria:
  - Association with a branching vascular network
  - Presence of polyps
  - Nuclear appearance when viewed stereoscopically
  - Presence of hyperfluorescent halo (in first 5 mins)
  - Orange subretinal nodules in stereoscopic color fundus photograph
  - Associated with massive submacular hemorrhage

**12 Month Results**

- 91.5% of patients in both groups completed the first 12 months of the study
- Main reasons for study discontinuation were AEs and withdrawal of consent

<table>
<thead>
<tr>
<th>Disposition reasons, n (%)</th>
<th>Ranibizumab 0.5 mg + vPDT (n=164)</th>
<th>Ranibizumab 0.5 mg (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>168 (100)</td>
<td>151 (100)</td>
</tr>
<tr>
<td>Completed 12-month study</td>
<td>156 (94.9)</td>
<td>136 (88.3)</td>
</tr>
<tr>
<td>Discontinued study prior</td>
<td>11 (6.7)</td>
<td>13 (8.5)</td>
</tr>
<tr>
<td>Month 12</td>
<td>13 (8.0)</td>
<td>17 (11.1)</td>
</tr>
<tr>
<td>AEs</td>
<td>4 (2.4)</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Subject withdraw consent</td>
<td>1 (0.6)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Late follow-up</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Aseptic cause death</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

**Patient demographics**

- Overall, patient demographics and baseline characteristics were well-balanced between the two treatment groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ranibizumab 0.5 mg + vPDT (n=164)</th>
<th>Ranibizumab 0.5 mg (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>68.0 (12.5)</td>
<td>68.2 (12.9)</td>
</tr>
<tr>
<td>Age category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–65</td>
<td>61 (37.2)</td>
<td>53 (34.4)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>109 (66.4)</td>
<td>114 (74.2)</td>
</tr>
<tr>
<td>Female</td>
<td>55 (33.6)</td>
<td>40 (25.8)</td>
</tr>
<tr>
<td>Predominant race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>168 (100)</td>
<td>154 (100)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>64 (38.1)</td>
<td>59 (38.3)</td>
</tr>
<tr>
<td>Indian</td>
<td>3 (1.8)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Japanese</td>
<td>46 (27.4)</td>
<td>38 (24.7)</td>
</tr>
<tr>
<td>Other</td>
<td>55 (33.6)</td>
<td>55 (35.7)</td>
</tr>
</tbody>
</table>

**Baseline ocular characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ranibizumab 0.5 mg + vPDT (n=164)</th>
<th>Ranibizumab 0.5 mg (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA, mean (SD), letters</td>
<td>61.1 (12.2)</td>
<td>61.2 (13.9)</td>
</tr>
<tr>
<td>CSFT, mean (SD), µm</td>
<td>415.5 (143.7)</td>
<td>416.4 (139.7)</td>
</tr>
<tr>
<td>CCL, mean (SD), µm</td>
<td>238.5 (106.8)</td>
<td>276.9 (89.6)</td>
</tr>
<tr>
<td>Presence of massive subretinal hemorrhage, n (%)</td>
<td>19 (11.7)</td>
<td>14 (9.7)</td>
</tr>
<tr>
<td>Presence of serosanguineous hemorrhage, n (%)</td>
<td>94 (56.0)</td>
<td>88 (57.1)</td>
</tr>
<tr>
<td>Presence of polyps, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2 (1.2)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>166 (98.8)</td>
<td>151 (98.7)</td>
</tr>
<tr>
<td>Polyp size, mm², mean (SD)</td>
<td>0.410 (0.63)</td>
<td>0.370 (0.58)</td>
</tr>
</tbody>
</table>

**Mean change in BCVA from baseline up to Month 12**

- Ranibizumab 0.5 mg + vPDT (n=164)
- Ranibizumab 0.5 mg (n=154)

**Proportion of patients with BCVA ≥69 letters at baseline and Month 12**

- Ranibizumab 0.5 mg + vPDT
- Ranibizumab 0.5 mg

**Majority of patients treated with ranibizumab + vPDT achieved complete polyp regression over 12 months**

- Ranibizumab 0.5 mg + vPDT (n=164)
- Ranibizumab 0.5 mg (n=154)
Deaths, ocular and non-ocular SAEs up to Month 12

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab 0.5 mg + vPDT (n=172)</th>
<th>Ranibizumab 0.5 mg (n=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths</strong> <strong>†</strong></td>
<td>1 (0.6)</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Ocular SAEs in study eye (%)</td>
<td>1 (0.6)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>1 (0.6)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Non-ocular SAEs, total</td>
<td>18 (7.6)</td>
<td>21 (14.4)</td>
</tr>
<tr>
<td>Intracranal hernia</td>
<td>2 (1.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0.0)</td>
<td>2 (1.3)</td>
</tr>
</tbody>
</table>

**Notes:**
- SAE = Serious Adverse Event
- *P<0.05 as compared to the treatment arm without vPDT

Summary

- The primary objectives of the EVEREST II study were met.
- In patients with symptomatic macular PCV, ranibizumab + vPDT was superior to ranibizumab monotherapy in:
  - Improving VA at 12 months
  - Achieving complete polyp regression at 12 months
  - Fewer number of treatments - 4 versus 7 injections (median)
- Overall, ranibizumab achieved high visual outcome in PCV patients
- Combining vPDT with ranibizumab resulted in additional vision improvement, more complete polyp resolution and better control of disease activity
- There were no new safety signals in comparison to the established safety profiles of ranibizumab and vPDT and no cases of sudden vision loss after vPDT

Long Term Stabilization of Vision and Anatomy with Primary PDT for PCV

25th Anniversary of The Retina Center at Pali Momi

- Pre-ARVO - first in Hawaii
- Halekulani Hotel on Waikiki Beach, Honolulu
- Friday April 27 – Sunday April 29, 2018
- National and International Speakers
- Imaging Conf
- Free Papers

Wet AMD & PCV Conclusions

- **PCV** - The most clinically important subtype of wet AMD to identify because the diagnosis affects management and care
  - Neovascular and **Not in the choroid** but underneath the RPE and above Bruch’s membrane
  - Dx requires more than clinical exam, FA and OCT map
- **Treatment**
  - Anti-VEGF effective – Possibly more with aflibercept
  - More anti-VEGF resistance in PCV
  - Better vision improvement with less frequent treatment with combined vPDT and x-VEGF therapy than x-VEGF monotherapy alone
  - Useful at decreasing treatment burden with better vision
In the multi-centered multinational EVEREST II trial polypoidal choroidal vasculopathy after photodynamic therapy combined with ranibizumab had better vision and less injections than ranibizumab mono therapy.

1. True
2. False

Pre 88.6%
11.4%
Post 0.8%

Table 1.1 Total 44

Table 1.2 Total 64

The diagnosis of polypoidal choroidal vasculopathy requires more than a clinical exam, OCT and fundus/angiography. Other ways to image polypoidal choroidal vasculopathy include:

1. ICG angiography
2. en face OCT
3. OCT angiography
4. all of the above

Table 3.1 Total 30

Table 3.2 Total 16
Optogenetic Vision Restoration

GARY W. ABRAMS, MD

SUMMARY
Inherited retinal degenerations (IRGs) are a significant cause of blindness. In most IRGs, the connections to the visual cortex remain intact and a common characteristic of many IRGs is retention of functioning inner retinal neurons, including ganglion cells and bipolar cells, in spite of loss of photoreceptors. There are a number of exciting new strategies under investigation to restore vision in patients blind from IRGs including bioelectric stimulation, gene therapy, retinal stem cell transplantation and optopharmacology (administration of light responsive drugs).

Optogenetics is the introduction of a gene for a light-sensitive protein into the cell membrane of a light insensitive cell such as a ganglion cell or a bipolar cell to make the neuron respond to light. Optogenetics was made possible by the discovery of Channelrhodopsin 2 (CHR2) by Nagel in 2003. Pan first showed the possibility of optogenetic vision restoration in 2006 when he delivered a precursor gene for CHR2 with a viral vector into the vitreous of blind retinal degenerate mice and demonstrated a light response in the ganglion cells and a visually evoked response in the primary visual cortex. CHR2 is activated by bright blue light and recent work has produced newer channelrhodopsins that have greater light sensitivity and that respond to light in a more natural red spectrum. Initial clinical studies in humans using CHR2 have recently commenced.

NOTES
Dr. Abrams began by thanking Don and Tim for the invitation. Dr. Abrams has been to the ARDS meeting multiple times in the 80s. He mentioned that the last time he was here was probably in 1990. This is a phenomenal meeting and it’s even better now than it was then.

Victor Curtin was one of Dr. Abrams’ main mentors. He had a tremendous impact on him. Dr. Abrams showed a picture of Dr. Curtin in his pathology laboratory. When Dr. Abrams was doing a year of research with Dr. Machemer, on Monday mornings, Dr. Curtin would have his gross pathology readout session. Dr. Machemer would be there, Don Gass would be there, Ed Norton would be there, and many of the other faculty members would show up for the gross readout. The discussions were unbelievable, and some major discoveries came out of those sessions. So many wonderful memories there.

Dr. Abrams then proceeded to talk about optogenetic vision restoration. We’re talking about vision restoration, and we’re talking about restoring vision in a blind person. Blindness has many different definitions. Here we’re going to define blindness as diffuse loss of useful vision. There are many different causes of blindness. Some of them are correctable. Some are not correctable. Of these, we’re going to talk about diffuse inherited retinal degenerations, because those are the kind that will be potentially managed by a retina specific treatment. The prototypical diffuse retinal degeneration is retinitis pigmentosa. It’s really a group of diseases with a lot of common characteristics.

With the inherited retinal degenerations, common to them, they have loss of the photoreceptors. Many have thought that with the retention of the inner retina, that there can be a retention of the bipolar cells. Many of these patients, in fact most of them, will have retention of the ganglion cells, the third order neurons. The connections to the visual cortex remains intact and functional in these eyes. This is the basis on which we may be able to restore vision.

In these inherited retinal degenerations, in the late stage, you may see retinal disorganization. Even late in these late stages, with severe degeneration, the ganglion cells may yet survive, even in these eyes with marked disorganization of the retina. The transmission structure to the upper centers of the brain also remain intact, in spite of these very severe degenerations.

There have been a number of vision restoration strategies that have been worked on and continue to be worked on. These are in eyes with loss of the photoreceptors but have intact inner-retina nerve fiber layer, optic nerve and connections to the visual cortex. The one that’s been most popular is the electrical stimulation of the retina or the retinal implant. These have been quite successful to restore low vision in patients with very severe vision loss.

Gene therapy has been effective in some conditions, such as Leber’s congenital amaurosis. It is probably going to be less effective in eyes that have complete loss of the photoreceptors. Retinal stem cell transplants are being studied, as well as optopharmacology. Optopharmacology is using chemical photo switches to stimulate the inner retina, and they have shown some promise for vision restoration.

Dr. Abrams felt that the method that shows the most promise is optogenetics, which is the subject of his talk. What is optogenetics? Optogenetics is the introduction
of a gene for a light-sensitive protein into the cell membrane of a light-insensitive cell, such as a retinal bipolar, or a ganglion cell, to effectively turn that neuron into a photoreceptor. The technique was first described by Boyden and colleagues from the Deisseroth Laboratory at Stanford University in 2005.

This has become an incredibly powerful neuroscience research tool. It was designated the: “method of the year” by the journal, Nature Methods, in 2010. The first use for restoration of vision was by Bi, et al from the Pan Laboratory at Wayne State University in 2006. They were able to transduce a gene for a light sensitive protein into the inner retinal neurons of a retinal degenerate mouse and restore evidence of visual, or at least light perceptive, activity.

Many people now regard Dr. Pan as the inventor of optogenetics. In fact, he submitted his paper for vision restoration of optogenetics well over a year before the Boyden paper was published, but it was rejected. It was submitted again, and rejected again. One of the most interesting summaries of the rejection letter was, “We don’t believe that this technology will be of interest to the neuroscience community.”

The Ligon Research Center of Vision is a research center that was dedicated to vision restoration in the blind. This was founded in 2000 at the Kresge Eye Institute of Wayne State University. The initial studies were on electrical and chemical stimulation of the retina. The first discussions of optogenetic stimulation of the retina occurred in 2001. Dr. Pan was at a seminar talking about electrical and chemical stimulation of the retina and he approached Dr. Abrams after the lecture and said, “You know, there may be another way that we could stimulate the retina. We might be able to implant a protein into the inner retina and restore some vision function.” Dr. Abrams felt that was an interesting idea. But in 2001, they didn’t even have the tools to do this. But he kept thinking about this idea.

Optogenetics was born in Germany, in the Peter Hagemann Laboratory in Germany. The first photoactive proteins were discovered in 1973 and 1982: bacterial bacteriorhodopsin, and halorhodopsin. But they never really caught on, because their mechanism of action did not make them very useful for putting them into a neuron or into the retina. They had low light sensitivity which also hindered their usefulness.

What made optogenetics possible was the discovery of channelrhodopsin 2, a microbial rhodopsin. It was discovered by Nagel in 2003. Nagel was in Peter Hegemann’s laboratory also in Germany. Channel rhodopsin 2 is isolated from green algae. In green algae, it is light sensitive, and it’s responsible for phototaxis.

In a scum pond you’ve got green algae, and the channelrhodopsin 2 directs the organism to light to best accomplish photosynthesis.

Channel rhodopsin 2, when it’s attached to a viral vector, can be incorporated into the cell membrane of a light insensitive neuron, such as a ganglion cell. It produces a change in the cell membrane that opens a light sensitive ion channel. The neuron is triggered by blue light to fire an action potential, which effectively turns that neuron into a photoreceptor. The ganglion cell can then send a signal toward the brain that is interpreted as a vision signal.

A cartoon was shown describing how optogenetic vision restoration works. We have an algae here and you have the channelrhodopsin here in the cell membrane, and the channelrhodopsin is actually an ion channel that’s in the cell membrane. We can then take the gene for this protein and put it in an AAV2 vector and then inject it into the eye. It’s then incorporated into the inner retinal neurons. Now, a retinal neuron communicates with other cells by firing. It’s an electrical signal that is created by opening of the ion channel, and so then we can take a blue light, we can stimulate the retina with a blue light, and we can fire an action potential that is then propagated to the brain, and interpreted as a visual signal.

The first experiments on optogenetic vision restoration were in mice. Dr. Pan used Rd1/Rd1 mice that have a retinal degeneration similar to humans. They did an intravitreal injection of an adeno-associated virus (AAV), with the gene for the precursor protein for the channelrhodopsin 2, that’s called channelopsin or Chop2. Green fluorescent protein was attached to the Chop2 gene to confirm by fluorescent microscopy that the gene was successfully inserted into the neuron.

Channelrhodopsin-2 is formed when the chromophore all-trans-retinal, which is already present in all the neurons, attaches to the Chop2, affording light sensitivity. A chromophore is the portion of a molecule that gives color to the cell and affords light sensitivity.

This is the adeno- associated virus (AAV2) vector cassette that’s used for insertion of the Chop2 gene. Enhancers and promoters help to get the proteins into the cell membrane, and also to stabilize them in the cell membrane.

These are fluorescent micrographs after injection of the Chop2 green fluorescent protein into a normal mouse. You can see in the low power, the green coloration of the inner retina, and this shows that you’ve had transduction into the inner retina. On the right, you see a high power view of a ganglion cell, and you can see the labeling of that ganglion cell really quite well with the green
Using a patch clamp technique, we were able to show the light of occurrence that occurred in these retinal neurons. This is done by dissecting free one of the inner retinal neurons, and you can see here that it’s labeled with the green fluorescent protein. Then blue light, or the light at various frequencies, is flashed at it after it’s cannulated with a little glass pipette, and you can record an action potential with this patch clamp technique. You can see here that the maximum response is at 460 nanometers, which just happens to be the peak spectral sensitivity of channelrhodopsin-2. You see over at 580 nanometers there is no response. We’ve gone into the red wavelength at 580 nanometers, and there’s no response. You can tell from this that the response is due to the channelrhodopsin-2.

Even more exciting, Dr. Pan was able to record visually evoked potentials, that were recorded from the primary visual cortex. At the top, we see a normal wild-type mouse, and you can see a very robust response to both 460 nanometer light as well as 580 nanometer light. In the middle we see the Rd1/Rd1 blind mouse, and after injection with the channelrhodopsin, you see a robust response at 460 nanometers while at 580 nanometers there is no response, so this says that the response is due to the channelrhodopsin. Below is an Rd1/Rd1 mouse control that was not injected, and you see no response at 460 nanometers. So, we can see that the response of this blind mouse with VEP was due to the insertion of the channelrhodopsin.

This is a more recent experiment that we did, and the testing mechanism is to put a mouse in a little cage and then have a virtual OKN drum in blue light that surrounds its cage. Then you can rotate this and you can then see the optokinetic response of the mouse to see if they have any visual function. When this is done in a normal mouse when the drum is rotated, the head of the mouse will go in the direction of the rotation of the drum.

So let’s look at one of our experimental mice. You turn the drum and initially he’s a little excited but watch his head, he follows it. Then spin it in reverse and you see the head movement that goes in the direction of the rotation of the drum. Now, these are transgenic blind mice, and these are absolutely completely blind transgenic mice. Sometimes it’s difficult to make a mouse completely blind, interestingly. But these are completely blind, and here is the untreated. He just sits there a little bit. There’s a little random activity, but you don’t see any movement of this in the direction of the optokinetic drum. Now this is the treated mouse, and his head movement going in the same direction as the drum. When we reverse it, the same thing happens. Here we showed restoration of visual activity in a mouse. It’s been shown to persist more than a year in mice and at least three months, which was as long as we followed them, in primates. These results have been duplicated by others.

The restoration’s optimum motor responses have been confirmed by Tomita and colleagues and other light induced behavioral responses by others. Now, Dr. Pan and Dr. Ivanova have shown gene transduction, a light response demonstrated in primates. They used a marmoset monkey, which is a New World Monkey. They found that, in marmosets, the degree of gene transduction into the retinal neurons was reduced compared to that found in mice. The concentration of this CHOP to green fluorescent protein was greatest in the foveal area in the far peripheral retina. The pattern of labeling correlates with thin areas of the internal limiting membrane. There is greater labeling in young animals than old marmosets because the ILM seems to be thinner in the younger animals.

An article by Yen and colleagues from Rochester, and they delivered green fluorescent protein with an AAV2 virus into the macaque monkey retina. They didn’t use channelrhodopsin, it was just green fluorescent protein. They saw bright fluorescence in the perifoveal area. Note that there is no labeling, no florescence elsewhere. With adaptive optics they showed that the uptake was in the ganglion cells, but they did not see uptake elsewhere. This is very similar to what we found with the marmoset monkey.

We think this is very, very promising work. There are barriers to success. The kinetics with channelrhodopsin 2 are slow. It can be driven to a maximum firing frequency of about 42 hertz, which is much slower than the normal ganglion cell firing rate. Newly engineered varieties of channelrhodopsin have faster kinetics. Chronos, which is a recently discovered channelrhodopsin, can be driven to a frequency of 200 hertz, which is similar to the normal ganglion cell firing rate. So, we think these kinetics will not be a major problem.

Light sensitivity is a barrier. The light threshold for activating wild-type channelrhodopsin 2 is that the intensity of indirect sunlight, which is 4 to 5 log units
higher than the threshold for cones. Several engineered varieties, however, have significantly improved light sensitivity. We’ve produced two variants with a light threshold that are 2 log units lower than the wild-type channelrhodopsin 2. So, we think that the light sensitivity will not be a big issue.

The spectral sensitivity is a potential problem. Channelrhodopsin 2 has a spectral sensitivity as we showed, at 460 nanometers, which is in the blue light range. Blue light at high intensities may be damaging to the retina. Newly engineered and recently discovered natural channelrhodopsin have spectral sensitivities that are shifted toward the red range. So, they’re more consistent with regular daylight, and they’re safer at high light intensities.

Another barrier is the penetration of the virus into the human retina. The primate ILM is thicker than the ILM of mice, and in monkeys transduction was limited to the perifoveal area as has been shown in both macaques and marmosets.

Other methods may be needed to enhance transduction in the human retina. New viral promoters and enhancers may be effective. Pharmacologic treatment of the ILM may be helpful in some cases. Surgical peeling of the internal limiting membrane may be necessary and actually, Leo Kim at Mass Eye and Ear, has shown that this actually does improve transduction.

The other is retinal remodeling. This may be the major threat to successful restoration of vision. Some of those with very severe rod and cone degenerations may progress to very severe remodeling and disorganization of all neurons with a marked reduction in ganglion cells. One ray of hope in this is that with electrical stimulation, they’ve shown that even some of these eyes with severe degenerations have recovered some vision.

The first human clinical trial of channelrhodopsin 2 for vision restoration has been started by a company, RetroSense Therapeutics out of Ann Arbor, Michigan, which was just recently purchased by Allergan. They have a current phase I/IIa open-label dose-escalating study of the safety and tolerability of intravitreal RST-001, which is channelrhodopsin in patients blind from retinitis pigmentosa. This clinical trial is being carried out at the Retina Foundation of the Southwest in Dallas, Texas. We don’t have any preliminary results yet on these first patients that have been injected at the lowest doses.

GenSight Biologics, which is based in Paris, France, they are also working on optogenetics and they’re working with a red shifted channelrhodopsin and they are planning on a clinical trial which should be starting sometime in the next year or so.

In summary, optogenetics is an exciting advance that has the possibility of restoring vision in blind patients with inherited retinal degenerations. Channelrhodopsin, especially the newer varieties, have kinetics similar to human rhodopsin. Studies in retinal degenerative mice have demonstrated a robust light response in the retina, good cortical responses on VEP, and light directed behavioral responses. Genes have been introduced into the non-human primate retinas with evidence of light response. Various success includes low light response, slow kinetics, blue light spectral sensitivity, and reduced incorporation into the primate retina. All of these are likely manageable barriers. Retinal remodeling may limit success in some patients with advanced inherited retinal degenerations. A human trial of optogenetic vision restoration in retinitis pigmentosa has begun.

Dr. Abrams then acknowledged the Ligon Research Center of Vision team, which includes Dr. Pan and the other researchers that have done this remarkable work.
Optogenetic Vision Restoration

Dr. Abrams was a member of Medical Advisory Board and owned stock options in Retrosense Therapeutics, LLC prior to its purchase by Allergan, Plc.

Retrosense Therapeutics provided research funds to Ligon Research Center of Vision prior to its purchase by Allergan, Plc.

Vision Restoration

To restore vision in a blind person

Blindness

Many different definitions

- Here defined as diffuse loss of useful vision

Many different causes:

- Cataract and media opacities
- Macular degeneration
- Glaucoma
- Trauma
- Optic nerve diseases
- Cortical blindness
- Diffuse inherited retinal degenerations

Retinitis Pigmentosa

Retinal detachment after intraocular lens implantation

The Stamm macular series and conservative management

The use of gas in retinal detachment
Inherited Retinal Degenerations

- Loss of photoreceptors, first order neurons
- Possible retention of inner retina
  - bipolar cells, second order neurons
  - ganglion cells, third order neurons
- Connections to visual cortex remain intact and functional

Inherited Retinal Degenerations

- Late stage with severe degenerations may see retinal disorganization
- Even late, with severe degeneration, the ganglion cells may survive and the transmission structure to the upper centers of the brain remain intact

Vision Restoration Strategies

- Loss of photoreceptors, but intact inner retina, nerve fiber layer, optic nerve and connections to visual cortex
  - Electrical stimulation of the retina: Retina Implants
  - Gene Therapy
  - Retinal Stem Cell transplants
  - Optopharmacology
  - Optogenetics

Optogenetics

- Introduction of gene for light-sensitive protein into cell membrane of light-insensitive cells such as retinal bipolar or ganglion cells to effectively turn the neuron into a photoreceptor
- Technique first described by Boyden and Colleagues from Deisseroth laboratory at Stanford in 2005
- Powerful Neuroscience research tool: “Method of the Year”, Nature Methods, 2010
- First use for restoration of vision by Bj, et al from Pan laboratory at Wayne State University in 2006
  - Gene transduction of light sensitive protein into inner retinal neurons of retinal degenerate mouse

Ligon Research Center of Vision

- Research Center dedicated to vision restoration in the blind
- Founded in 2000 at Kresge Eye Institute of Wayne State University
- Initial studies on electrical and chemical stimulation of the retina
- First discussions of optogenetic stimulation of the retina in 2001

Birth of Optogenetics

- First photoactive proteins discovered
  - Bacteriorhodopsin (1973)
  - Halorhodopsin (1982)
- Mechanism of action and low light sensitivity hindered usefulness

Channelrhodopsin 2

- A microbial rhodopsin discovered by Nagel in 2003
- Isolated from green algae
- In green algae, it is light sensitive and responsible for phototaxis: directing the organism to light so best to accomplish photosynthesis
Channelrhodopsin 2

- When attached to a viral vector, incorporates into cell membrane of light-insensitive neuron such as a ganglion cell.
- Produces change in cell membrane that opens light-sensitive ion channel.
- The neuron is triggered by blue light to fire an action potential, effectively turning the neuron into a photoreceptor.
- The ganglion cell can then send a signal toward the brain that is interpreted as a visual signal.

Optogenetic Vision Restoration in Mice

- Rd1/Rd1 mice with retinal degeneration similar to humans.
- Intravitreal injection of adeno-associated virus (AAV) with the gene for the precursor protein for channelrhodopsin 2, channelrhodopsin (Chop2).
- Green fluorescent protein (GFP) was attached to the Chop2 gene to confirm by fluorescence microscopy that the gene was successfully inserted into the neuron.
- Channelrhodopsin 2 (ChR2) is formed when the chromophore, all-trans retinal (already present in all neurons) attaches to the Chop2, affording light sensitivity.
- A chromophore is the portion of a molecule that gives color to the cell and affords light sensitivity.

Adeno-associated virus (AAV-2) vector cassette with channelrhodopsin-green fluorescent protein (Chop2)-GFP

CAG: A hybrid CMV enhancer/chicken β-actin promoter.
WPRE: Woodchuck post-transcriptional regulatory element.
BGH: A bovine growth hormone polyadenylation sequence.
Optogenetic Vision Restoration

ChR2 Restoration Light Sensitivity
- Effect following a single injection has been shown to persist more than 1 year in mice and at least 3 months in primates
- Results duplicated by others
- Restoration of optomotor responses (directed eye movements in response to light) in retinal degenerate mice reported by Tomita, et al and light-induced behavioral responses by others

ChR2 in Primates
- Gene transduction and light response demonstrated in primates by Ivanova, Pan and Troilo (marmosets)
- In marmoset monkeys, the degree of gene transduction into retinal neurons reduced compared to mice
- Concentration of Chop2-GFP labeling greatest in foveal area and far-peripheral retina
- The pattern of labeling correlates with thin areas of the ILM: no labeling where ILM is thick
- Greater labeling in young than old marmosets (ILM is thinner in younger animals)

Optomotor response testing
Normal mice

Optomotor response testing
Blind mice
Untreated
Treated

Barriers to Success: Slow Kinetics
- ChR2 can be driven to a maximum firing frequency of about 42 Hz, much slower than normal ganglion cell firing rate
- Engineered newer varieties of ChR have faster kinetics
- Chronos, a recently discovered ChR can be driven to a frequency of 200 Hz, similar to the normal ganglion cell firing rate
Barriers to success: Light Sensitivity
- Light Threshold for activating wild-type ChR2 is at the intensity of indirect sunlight which is 4-5 log units higher than the threshold for cones
- Several engineered variants have significantly improved light sensitivity
- Our laboratory has produced 2 variants with light threshold 2 log units lower than wild-type ChR2

Barriers to Success: Spectral Sensitivity
- ChR2 has a spectral sensitivity of 460 nm, in the blue light range
- Blue light at high intensities may be damaging to the retina
- New engineered and recently discovered natural channelrhodopsins have spectral sensitivities shifted toward the red range:
  - more consistent with daylight
  - safer at high light intensities

Barriers to Success: Penetration of Virus into Human Retina
- Primate ILM is thicker than ILM of mice.
- In monkeys, transduction limited to foveal area in macaques and fovea and far-peripheral retina in marmosets
- Other methods may be needed to enhance transduction in the human retina:
  - New viral promoters and enhancers
  - Pharmacologic treatment of ILM
  - Surgical peeling of ILM

Barriers to Success: Retinal Remodeling
- Retinal remodeling may be the greatest threat to successful restoration of vision in patients with inherited retinal degenerations
- Some retinal degenerations have very good preservation of much of the inner retina including ganglion cells and bipolar cells
- Those with severe rod and cone degenerations may progress to remodeling and disorganization of all the neurons, including most of the ganglion cells

Human Clinical Trial
- Retrosense Therapeutics, LLC based in Ann Arbor, MI (purchased by Allergan, Plc in October, 2016)
  - Current Phase II/III open-label, dose-escalating study of the safety and tolerability of unilocular intravitreal RST-001 in patients blind from retinitis pigmentosa
  - RST-001 is Channelrhodopsin in AAV-2 vector cassette
  - Retina Foundation of the Southwest in Dallas, TX
- GenSight Biologics based in Paris, France

Summary
- Optogenetics is an exciting advance that has the possibility of restoring vision in blind patients with inherited retinal degenerations
- Channelrhodopsins (especially newer varieties) have kinetics similar to human rhodopsin
- Studies in retinal degenerate mice have demonstrated robust light responses in the retina, good cortical responses on VEP and light-directed behavioral responses

Summary
- Genes have been introduced into non-human primate retinas with evidence of light response
- Barriers to success include low light response, slow kinetics, blue light spectral sensitivity and reduced incorporation into the primate retina: all likely manageable barriers
- Retinal remodeling may limit success in some patients with advanced inherited retinal degenerations
- A human trial of optogenetic vision restoration in retinitis pigmentosa has begun.

Ligon Research Center of Vision
Zhou Hua Pan
Shengjie Cui
Anding Bi
Qiu
Tushar Gaikwad
Gary W. Abrams
Which one of the following statements about optogenetics is true?

1. It may involve the introduction of a gene for a light-sensitive protein into the cell.
2. It involves a light-sensitive protein fused to a transmembrane light sensor.
3. Optogenetic vision restoration attempts to restore the function of the rod photoreceptors.

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Mean: 1.0  Total: 13
Retinopathy of Prematurity and Associated Diseases

HUGO QUIROZ-MERCADO, MD

SUMMARY
About 400 to 600 infants each year in the US become legally blind from ROP. In September 2005 we performed anti-Angiogenic therapy in a very low weight premature baby having bilateral VH and bilateral persistent fetal vasculature which prevent laser treatment. Based on a bilateral remarkable improvement 48 hours after treatment we started exploring and collecting data on this therapy.

Anti-VEGF treatment is considered in some centers as an effective alternative to laser surgery however laser is still considered a standard of care for some researchers. We will present our personal experience, we will discuss risks and complications and other issues like neuro-development. Advantages of this treatment mainly in hospitals where laser machine is not available is an important indication to prevent blindness in ROP.

Interesting cases associated to ROP and differential diagnosis will be presented.

NOTES
Goals of Lecture:
• To review the literature about Type I, Type II ROP
• To recognize the needs for anti-VEGF treatment in ROP
• Review Dr. Quiroz-Mercado’s recommended algorithm
• Review importance of FA for the treatment of ROP
• Importance of anti-VEGF treatment in ROP

Classification
It is very important to recognize that once we see tortuosity in any retina, this equals hypoxia. Even if you can’t see in the periphery with your imaging modalities, like an iPhone and 20D lens or expensive cameras, if you see tortuosity in the posterior pole then you know these patients need to be monitored closely or treated. Plus disease is arteriolar tortuosity and venous engorgement in the posterior pole. Also be aware of iris vascularization engorgement, pupil rigidity and vitreous haze.

Pre-plus disease is vascular abnormalities of the posterior pole that are insufficient to diagnose plus disease, but demonstrate more arteriolar tortuosity and venular dilation than normal. It is important for these changes to be diagnosed, because in early ROP these can evolve plus disease.

Dr. Quiroz-Mercado discussed the importance of ETROP, which was to determine whether early treatment using ablation of the vascular retina in high-risk pre-threshold ROP results in improvement either in visual acuity and anatomical function. The results showed treatment in high-risk pre-threshold significantly reduced unfavorable outcomes.

The study also classified Type I and Type II ROP. The most important to diagnosis is Type I, because it requires treatment in 48 hours or less. Type II is less severe but it is recommended to have frequent follow-up with fundus exams.

Treatment
We don’t have any question or doubt that the best treatment for ROP so far is laser. Retreatment with laser is probably between 11-20% versus 4% for some cases with anti-VEGF. With laser, the visual field is reduced, and myopia, nyctalopia can all occur. With treatment, it’s important that the surgeon has experience in doing laser. If it takes more than two hours, we need to keep in mind that the patient can end up with another comorbidity secondary from the laser treatment and anesthesia as general anesthesia is frequently used for laser treatment.

Dr. Quiroz-Mercado did anti-VEGF for the first time in a patient with vitreous hemorrhage where they couldn’t see. The patient had persistent vessels over the iris and there was no view. They did one eye, the patient improved and then they did the second eye a few days later. Unlike the VEGF drive in diabetic retinopathy, in ROP there is a peak of VEGF that occurs and then it decreases. Dr. Quiroz-Mercado feels that a few injections can potentially cure the disease. Benefits include not needing as many re-treatments compared to laser treatment.

Dr. Quiroz-Mercado presented an algorithm of treatment for ROP. In patients treated with anti-VEGF, either bevacizumab or ranibizumab, they are observed at one week. After one week, if the ROP regresses, then the patient is treated as if it were Type 2 ROP and they are followed up closely. If they recur, then they are treated with another injection or laser. Anti-VEGF therapy may be very important for patients with posterior ROP requiring treatment. Intravitreal anti-VEGF injections can allow for further vascular development and if laser is needed then the ROP might not be so posterior when applied.
For type 2 ROP, these patients can be followed by serial examination. It is very important that if they reach type 1 ROP, we treat. Fluorescein angiography can be helpful to distinguish between type 1 and type 2 ROP. FA also shows changes in the macular vessels in the setting of ROP and in prematurity.

Prevention is also a key part of ROP. In many places around the world larger, older babies are noted to have ROP. Oxygen use plays a big part of this. Using blenders and other devices to prevent unregulated oxygen delivery can play a big role in prevention of ROP.

With regards to vitrectomy, obviously, the best scenario is if it is not required. Patients with severe disease, like retrolental membranes, have very atrophic retinas and the retina is not healthy to start with, making surgery very hard.

**Possible Complications**

So, do we have ocular adverse events in ROP after treatment? We have some, like crunch. There have been traumatic cataract, retinal detachment, and vasculitis. Vascular abnormalities that people have described to be from anti-VEGF are the same changes we have noted in the macula in patients with ROP and who had never been treated.

Dr. Quiroz-Mercado discussed the concern for risk of hemorrhages within the brain that may be caused by anti-VEGF therapy. Studies have shown no brain toxicity on intrathecal injections of bevacizumab. He suggested that the neurodevelopmental problems associated with ROP is likely from the prematurity itself rather than treatment. Dr. Quiroz-Mercado recommends possibly doing more CNS anti-VEGF to help stabilize fragile vessels that may actually help prevent bleeding.

**DISCUSSION**

**Q: Question | C: Comment | A: Answer**

**C:** Paul’s traveled internationally to teach laser techniques and I think when you go there, you know, he’s got some stories with lasers that took half a day. And you look at that and you realize that the morbidity is not the ROP any longer, the morbidity was how long it took to keep that baby under anesthesia and what it’s going to mean to recover that baby off a ventilator again.

**C:** Bevacizumab, internationally has been a game changer. At these hospitals where the ophthalmologist can’t laser, and you don’t have cryo, anti-VEGF may all you have.

**Q:** You’re saying that it may be a smarter strategy considering all the limitations to deliver this treatment in the developing world?

**C:** I think smarter isn’t necessarily the word I’d use. I think it’s a matter of necessity. The reality is that now you can actually treat these children without knowing how to do laser. You may not have to do indirect ophthalmoscopy when you can potentially make the diagnosis through imaging. They can treat these kids easily and very quickly and without anesthesia, but the problem is the follow-up. And these kids need good pre and post treatment management. What’s interesting, is that people internationally are sometimes treating earlier. Maybe because giving anti-VEGF is theoretically not that difficult to do compared to laser. So, even though we know that there are potential issues with the technique or injection or punching the lens or hitting the retina, they’re not following criteria because they think “okay I’m going to treat this prophylactically that kid’s going to be fine”. But then they run the risk of sending these children out and then they come back with a detachment because they reactivate. Big issues here. And I don’t think that we can say that anti-VEGF treatment is recommended for the primary treatment for all cases of ROP that need treatment. I still laser children and use anti-VEGF selectively.

**Q:** Is there anybody on the front lines in the community here?

**C:** For the really sick babies or zone I, I start with anti-VEGF and then follow them. I do lasers when it gets to anterior zone II. I’ve been doing the ROP in Greenville for 30 years, had 2 detachments in that time, the last one was over 25 years ago.
ROP and Associated diseases

Hugo Quiroz-Mercado, MD

Director of Research, APEC Mexico City
Professor University of Colorado Denver

Financial Interest

• None

OBJECTIVES

• 1- Historical background
• 2- To recognize ROP that needs treatment with anti-VEGF
• 3- Treatment algorithm at APEC (México)
• 4- Use of FA and OCT in ROP
  – Its implications after anti VEGF therapy usage
• 5- Neurodevelopment and anti VEGF

Plus disease

• Arteriolar tortuosity and venous engorgement of the posterior pole
• Iris vascular engorgement
• Pupillary rigidity
• Vitreous haze

Pre-plus disease

• Vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arteriolar tortuosity and more venular dilatation than normal
• Pre-plus disease early in the course of ROP is strongly associated with development of severe ROP that required laser treatment

Retinal Circulation

The high oxygen demands of the retina are thought to contribute to the particular vulnerability of the retina to vascular disease.

Vascular Tortuosity = Hypoxia

Aggressive Posterior ROP (AP-ROP)

• An uncommon, rapidly progressing, severe form of ROP is designated AP-ROP was later added to the classification.
• 8 Characteristic features of this type of ROP are a posterior location, plus disease, and the ill-defined nature of the retinopathy, which usually progresses to stage 5 if untreated. This rapidly progressing has also been referred to as "Rush disease".
ROP AND ASSOCIATED DISEASES – QUIROZ-MERCADO

**Posterior ROP**

![Image of posterior ROP](image)

**ETROP**

- **OBJECTIVE**

  To determine whether earlier treatment using ablation of the avascular retina in high-risk prethreshold retinopathy of prematurity (ROP) results in improved grating visual acuity and retinal structural outcomes compared with conventional treatment.


- **ETROP**

  Early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcomes to a clinically important degree.


**TREATMENT**

- **Laser therapy**

  - Diode laser
  - Argon laser
  - Experience (anesthesia)

**Prolactin 16 Kd**

- **16 Kd Prolactin RNA has expression in fibrovascular membranes**


**Mild ROP**

- Stage 1 or 2 in zone 2 WITHOUT plus disease
- Any stage in zone 3 WITHOUT plus disease

**Type 2 ROP (requires close observation without immediate treatment)**

- Stage 1 or 2 in zone 1 WITHOUT plus disease
- Stage 3 in zone 2 WITHOUT plus disease

**ROP type 1 (requires treatment in less than 48 hours)**

- Stage 2 or 3 in zone 2 WITH plus disease
- Stage 2 in zone 1 WITHOUT plus disease
- Any stage in zone 1 WITH plus disease

**VEGF Secretion**

- ROP
- Other vasoproliferative disorders

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**ASPEN RETINAL DETACHMENT SOCIETY MEETING NOTES 2017**
Why anti-VEGF treatment

- Regression of the tunica vasculosa lentis and vascularization
- Apoptosis of the fetal vasculature

Our first case 2005


Outcomes Anti-VEGF vs Laser for ROP

- Both IVB and laser are effective
- BETA-ROP study higher recurrence after PRP vs IVB (22% vs 4%) overall. 35% vs 3.2% for zone 1
- Hwang recurred 14% of IVB and in 3% of PRP. One RD in laser group. Less myopia in IVB


PERFORM FLUORESCEIN ANGIOGRAPHY
WHEN:
Doubt between stage 2 or 3
Worsening ROP
Differential Diagnosis

Retinal fluorescein angiographic changes following intravitreal anti-VEGF therapy

Aitor Izuzquiza Berro, MD; Garin-Gutierrez A, MD; Hugo Quiroz-Mercado, MD; and Ana Ana Martínez Castellanos, MD.

JAPOS 2014;18:120-122
Retinal fluorescein angiographic changes following intravitreal anti-VEGF therapy

Andrew Henao-Berna, MD, Gerardo-Gerónimo Arias, MD, Elvio Quiróz-Mercado, MD, and María Ana Martínez-Cambreros, MD

J AAPOS 2014;18:120-123

Stage 2 to 1 without treatment
Macular vascular maturation

Demarcation line
No leaking

Stage 2 to stage 1 without treatment in 8 days

Stage 3 with new vessels
ROP AND ASSOCIATED DISEASES – QUIROZ-MERCADO

Ocular Adverse Events

Persistent avascular peripheral retina

Retinal Detachment “crunch”

Normal oxygen

Hyperoxya
Vitreous hemorrhage

Ocular Adverse Events

Sub-conjunctival hemorrhage after injection.

Subretinal hemorrhage

Iatrogenic traumatic cataract

Regmatogenous retinal detachment

VASCULITIS

VASCULITIS
Retinopathy of Prematurity

Vitrectomy
- Pars plicata
  - Lens - sparing vitrectomy (Maguire, Tresel)
  - Lensectomy - vitrectomy (Machemer, DeJuan)
- Open sky vitrectomy (Schepens, Hiroshi)

Is anti-VEGF safe treatment in ROP?
- Our first cases in 2005 (10 years follow-up)
- Normal neurologic evaluation
- Normal retina, macula, ON evaluation

Is anti-VEGF safe treatment in ROP?
- Serum Levels of Vascular Endothelial Growth Factor and Related Factors After Intravitreous Bevacizumab Injection for Retinopathy of Prematurity
  - VEGF, VEGF receptor 1 (VEGFR1), VEGFR2, Tie2, erythropoietin, transforming growth factor β1, insulin-like growth factor type 1, angiopoietin 1, angiopoietin 2, angiopoietinlike 3, and angiopoietin 4

Is anti-VEGF safe treatment in ROP?
- Bevacizumab levels elevated first day up to 8 weeks
- Serum VEGF levels were suppressed for the same period
- No changes were identified in the serum levels of any of the other factors
Is anti-VEGF safe treatment in ROP?

- Serum VEGF levels were suppressed for 2 months after IVB owing to the leakage of bevacizumab into the systemic circulation.


- Significant vascular and macular abnormalities of eyes in the bevacizumab group. Long-lasting implications of these abnormalities for visual function of the child need to be studied.

- A stage 3, zone I ROP with plus disease treated with conventional laser progressed to a complete retinal detachment 4 weeks after treatment. A second eye also with stage 3 zone I ROP with plus disease and treated with conventional laser progressed to stage 4a and underwent lens-sparing vitrectomy with a favorable structural outcome.

- Main outcome on type 1 ROP treatment is to prevent retinal detachment.

Neurodevelopment

- 11 patients who did not meet current recommendations for ROP laser treatment were included in that group
- Authors pointed out that more severe ROP were treated with bevacizumab
- Infants laser vs IVB (SNAP-II) score had statistical difference.

Disruptive Technology

Clio Armitage Harper, III, MD  
Austin Retina Associates  
Austin, TX
ROP in Developing Countries

- Occurring in later term and larger infants compared to developed countries
- Oxygen is given more liberally with the object of preventing cyanosis rather than treating it.
- Per one study, when contacted one of the treating pediatricians felt that high oxygen reduced the stay of the child in the hospital.

Call for Primary Prevention

The recent Global Burden of Disease estimated that 257,000 years lived with disability worldwide in 2010 were associated with visual impairment secondary to ROP.

Oxygen Blenders

- An oxygen blender proportions air and oxygen according to a predetermined ratio
- Oxygen blenders current commercial cost is around $860
- Need for low-cost oxygen-blending device
- Oxygen sensor into each prototype to ensure accuracy and measure the effectiveness of the device

What is the goal SpO2? Recent Trials

- SpO2 target ranges: 85–89% versus 91–95%; infants of <28 weeks of gestation
  - U.S. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network (SUPPORT)
  - Benefits of Oxygen Saturation Targeting (BOOST II)
  - Canadian Oxygen Trial (COT)
- Median SpO2 readings at, or beyond, the upper limit of this range, only separated by 3-4%
- SUPPORT and BOOST II showed modest increase in mortality in the lower SpO2 group (COT did not)
- All studies showed dramatic increase in severe ROP in higher SpO2
- Still unclear what target SpO2 should be

Acknowledgments

- Mariana Martinez, MD
- Linda Cernichiaro, MD
- Armie Harper, III, MD
- R.V. Paul Chang, MD,
Role of Vitreoretinal Surgery in Patients with Choroidal Melanoma

IVANA KIM, MD

SUMMARY
Vitreoretinal surgical techniques are playing a growing role in the management of patients with choroidal melanoma. At the time of primary treatment, transvitreal biopsy is often performed for prognostic and sometimes diagnostic purposes. More controversial surgical interventions for primary treatment include vitrectomy with silicone oil and primary endoresection.

Following radiotherapy, the most common indications for vitrectomy include vitreous hemorrhage and exudative retinal detachment. Considerations regarding the surgical approach in these patients will be discussed and results of a small series of patients who underwent vitrectomy for these indications will be reviewed. Patients with vitreous hemorrhage after radiation for choroidal melanoma may have significant visual acuity improvements after vitrectomy. However, recurrent hemorrhages are common. Vision improvement is seen in a minority of patients after vitrectomy for exudative retinal detachment. Earlier intervention may improve outcomes.

NOTES
The indication for surgical intervention in melanoma patients falls into two broad categories: in the setting of primary treatment for melanoma (molecular prognostication, endoresection, oil shielding) and complications after radiation (vitreous hemorrhage and exudative RDs).

With regards to biopsy there are two main approaches to fine needle aspiration biopsy; transscleral and transvitreal. Transscleral is typically done for tumors anterior to the equator. Transvitreal tends to be the most common. There are two approaches for transvitreal, either using indirect ophthalmoscopy and a 20 diopter lens or vitrectomy style approach. With regards to the vitrectomy, some will do a thorough vitrectomy while others are minimalists and do a two-port procedure with light pipe and needle, and don’t do vitrectomy. Both have pros and cons.

Endoresection has waxed and waned in favor over numerous decades. It still remains controversial. There is controversy if it should be done with adjuvant radiation therapy or not. There are significant reported complications including retinal detachment, tumor recurrence, and death. Death is not from metastasis but there have been several cases of reported death from air embolism during surgery, thought to be from exposed choroid.

The more recent literature on endoresection is quite good. A group from Spain looked at endoresection compared to brachytherapy. They showed that there was no significant difference in visual outcomes. Interestingly there was also no significant difference in local recurrence, although the rate of local recurrence for endoresection was higher and they do comment that after this series they’ve started adjuvant radiotherapy in all their endoresection cases.

Dr. Kim’s opinion is that there is not a visual benefit to doing this strategy but it may be a viable alternative in areas or in cases where radiotherapy is not available.

Dr. Kim mentioned silicone oil tamponade in the setting of plaque radiotherapy and this has been presented by Tara McCannel and it’s still investigational. Dr. McCannel’s initial series in medium tumors did not show a visual benefit but a more recent series in patient with large tumors did show a trend towards improved visual outcomes with a mean follow up of about 28 months. In the original series she also noted less macular edema and fewer abnormal macular findings. The idea behind this is that silicone oil attenuates radiation and so it might limit the scatter of radiation to other parts of the eye.

Dr. Kim thinks that in theory it makes sense for potentially equatorial or anterior tumors. It’s not clear for posterior pole tumors where the radiotherapy has to go through the macula in order to treat the tumor.

The safety of operating in these eyes that have been irradiated for melanoma has been demonstrated by many series. The source of hemorrhage may be necrotic tumor vessels, traction, or proliferative radiation retinopathy. Persistent exudative retinal detachment from the so-called toxic tumor syndrome may exacerbate exudative retinal detachment.

Dr. Kim presented an exploratory series of patients treated and who received surgery in the past decade at MEEI. The group had treated more than 800 patients with PBI, and only a handful of patients elected to or had indications to have surgery. It’s less than 2%, which shows the success of radiotherapy for melanoma. The series included mainly large tumors and the mean time to surgery after radiation was almost three years.

Patients with vitreous hemorrhage had vitrectomy and the tumor and ischemic retina was lasered.
The cases with pure exudative detachments had vitrectomy, internal drainage, retinotomy, and occasionally retinectomy with Silicone Oil. One patient had a scleral buckle.

Visual acuity improvement was about 40%. 4/13 had more than three lines gained. Three of these were the patients with vitreous hemorrhage. The patients with vitreous hemorrhage, as you would expect, do better with intervention than the patients with exudative retinal detachment. Patients with vitreous hemorrhage, a significant proportion of them had excellent visual outcomes. The patients with prolonged exudative retinal detachment did not have such good visual outcomes. Patients that had the better visual outcomes in general were the ones who started with better vision. There were 8 exudative retinal detachment cases in this series. Two patients had visual improvement, six of them had attached retina at the last follow-up, and one required an enucleation.

In the vitreous hemorrhage cases three patients had visual improvement. Three required additional procedures. These are not your standard “let’s clear the blood and we’re done” cases. We think that there is a higher rate of reoperation due to vitreous hemorrhage. They may be slightly more prone to rhegmatogenous retinal detachment. They can go on to develop other complications of radiation retinopathy. They need to be followed carefully, even after they have their good initial visual improvement.

**Case Presentation: Vitreous hemorrhage**

Vitreous hemorrhage, medium sized tumor, pre-radiation visual acuity was 20/20. A year after radiotherapy visual acuity decreased to HM with vitreous hemorrhage. Post-op vision was 20/50. This patient needed a re-operation because he developed a rhegmatogenous retinal detachment from a very, very tiny break over the tumor.

**Approach:** Laser confluently over the tumor surface and carefully in areas of ischemic retina. We have a low threshold for intravitreal bevacizumab at the end of the case.

**Take home points:** Vitreous hemorrhage in patients with treated melanoma may have significant visual acuity improvements, and complications requiring additional surgery may be more common such as re-bleeding and rhegmatogenous retinal detachment.

**Case Presentation: Exudative RD**

A young woman 1.5 yrs after brachytherapy. They actually had the plaque plus silicone oil treatment. After the silicone oil was removed, the patient developed a severe exudative retinal detachment. The patient did not want surgical intervention right away and went on to have a nearly total, very severe, exudative retinal detachment with massive retinal exudates.

She was starting to develop NVG and at this point she agreed to intervention mainly for globe salvage. She actually was NLP after surgery and went for enucleation for discomfort.

**Take home points:** Early intervention probably allows for better visual outcomes. You can salvage globes even late. There may be a role for earlier vitrectomy and there is a small series published in 2009. 6 patients where they had significant exudative retinal detachment at presentation and in these cases there was vitrectomy, internal drainage at the time of plaque placement, and with one year follow up they saw no recurrent detachments and they had visual improvement.

**Prevention:**

There may also be a role for earlier pharmacologic therapy after radiation, a small series showed that giving triamcinolone at the time of plaque removal may be more effective than bevacizumab. A group did show that prophylactic bevacizumab for patients with baseline retinal detachments reduces rates of NVG and helps retinal reattachment. Then there’s a small study suggesting that there is resolution or reduction of exudative retinal detachment in some cases with the use of the dexamethasone implant.

**DISCUSSION**

**Q:** Would there be any real contraindication for an ERM peel in symptomatic patients with prior radiation? Or is there a factor that we have to look for that would prevent us from even offering that?

**A:** As long as there are no comorbidities in the macula I think it’s fine to offer. You want to rehabilitate vision once the tumor is treated, and after 2.5 years we know it’s very unlikely to recur.

**Q:** Can you describe your technique for repairing the post treatment exudative RD?

**A:** If it’s a small exudative retinal detachment, displace it and laser the tumor, and put a tamponade in. If it’s a complex exudative retinal detachment drain it and then drain over the tumor surface in these cases and I’m going to laser that space anyway and you’re going to tamponade them. I would not go to an external drainage approach because if there’s a possibility of trouble I don’t want to go there.
Q: One complication of endoresection that you mentioned is the gas embolisms. You hear about these reports every once in a while, what’s the data on this and how can we prevent it?

A: It really scared me when Tom Albini actually reproduced it in his pig model. The practical statement isn’t for endoresection because I doubt anyone in this room is going to do that. But there were some very practical points that came out of Albini and Flynn’s studies, which was 100% confirmation of where your infusion line is placed when you go to air. The way that they reproduced that was not by over pressurizing the vitreous, they had to directly infuse into the suprachoroidal space.

C: There is a recommendation that for every air fluid exchange, there be a mini timeout to verify where the cannula is. Because with small gauge, with unsutured cannulas, with people beveling them to various degrees, these can slip backwards.
**Indications**

- Complications after irradiation
  - Vitreous hemorrhage
    - Tumor vessels
    - Proliferative radiation retinopathy
  - Exudative detachment
    - “Toxic tumor syndrome”

**PRIMARY TUMOR MANAGEMENT**

**Silicone Oil**

- Investigational
  - Difference in VA not statistically significant in retrospective case-control analysis
  - Less macular edema
  - Fewer “abnormal maculas”
- Complications
  - Intraocular retinal tears
  - Tethered RD
  - Macular hole
  - Macular pucker

**Biopsy**

- Transscleral
  - Needle
  - Vitreous cutter
- Transvitreal
  - Indirect ophthalmoscopy
  - Microscope
    - 2 port vs. 1 port
    - Needle vs. vitreous cutter

**Endoresection**

- Controversial
  - +/- radiotherapy
  - Reported complications
    - Retinal detachment: ~9-30%
    - Tumor recurrence: ~2-7%
  - Death

**Indications for Vitrectomy after Radiation for Choroidal Melanoma**

- Complications after irradiation
  - Vitreous hemorrhage
  - Tumor vessels
  - Proliferative radiation retinopathy
  - Exudative detachment
    - “Toxic tumor syndrome”
- Safety has been demonstrated
  - Largest series N=47
**Exudative Retinal Detachment**
- Pharmacological intervention not consistently effective
  - Intravitreal triamcinolone more effective than bevacizumab when administered at time of plaque removal

**Outcomes**
- Any visual acuity improvement: 5/13 (38%)
  - 4/13 > 3 lines (Snellen)
    - 3 vit retn
    - 1 exudative RD
  - 3/5 with VA improvement were pts with vitreous hemorrhage

**Patient Characteristics**
- 13 patients
  - 5 with vitreous hemorrhage
  - 8 with persistent exudative retinal detachment
- Surgery between 2007-2017
- Proton beam irradiation
  - 1996-2014
  - 836 patients treated with PBI between 2006-2014
    - 12/836 = 1.4%

**Visual Acuity Outcomes**

<table>
<thead>
<tr>
<th>Baseline VA</th>
<th>VA at last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HM</td>
<td>20/50</td>
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<tr>
<td>HM</td>
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<td>LP</td>
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<td>NLP*</td>
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<tr>
<td>CF</td>
<td>CF</td>
</tr>
<tr>
<td>HM</td>
<td>20/10</td>
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</tbody>
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* N=10

**Baseline Characteristics**

<table>
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<tr>
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<th>Value</th>
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<tbody>
<tr>
<td>Mean Age</td>
<td>63 yrs</td>
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<tr>
<td>Male Gender</td>
<td>9/13 (69%)</td>
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<tr>
<td>Mean Tumor Height</td>
<td>5.2 mm</td>
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<tr>
<td>Mean Largest Basal Diameter</td>
<td>13.5 mm</td>
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<tr>
<td>Posterior Tumor Location</td>
<td>10/13 (77%)</td>
</tr>
<tr>
<td>Mean Time to Surgery after PBI</td>
<td>35 mo</td>
</tr>
<tr>
<td>Mean Follow-up</td>
<td>17.6 mo</td>
</tr>
</tbody>
</table>

**Vitreous Hemorrhage Cases**
- N=5
- 3 patients with VA improvement
  - 2 with > 3 lines improvement
- 3 required additional procedures
  - 2 recurrent vit retn
  - 1 rhegmatogenous retinal detachment
- 1 developed exudative RD
- 1 required enucleation for neovascular glaucoma

**Surgical Procedure**
- Vitreous Haemorrhage
  - PPV
  - Endolaser over tumor and ischemic retina
  - Intravitreal Trasnetron given in 1 case
- Exudative Detachment
  - PPV
  - Pneu/IOI or PPL in all phakic patients except 1
  - Drainage vitreotomy or peripheral retinotomy when needed
  - SB in 1 patient
  - Silicone oil in all cases

**1 year p PBI: HM**
**Exudative RD Cases**

- N=8
- 2 patients with VA improvement
- 6 pts with attached retina at last follow-up
- 1 enucleation

**Vitreous Hemorrhage**

- Patients may have significant visual acuity improvements
- Complications requiring additional surgery may be more common
  - Re-bleeding
  - Rhegmatogenous RD
- Considerations:
  - Posterior
  - Laser
  - Tumor surface
  - Ischemic area
  - Role of intravitreal agents?
    - Anti-VEGF
    - Steroid

**Exudative Retinal Detachment**

- 2 patients with VA improvement had relatively early PPV
  - RD observed for <6 months
- Globe salvage achieved 7/8 cases with control of NVG
  - Majority of cases in this series with very chronic RD and poor baseline VA
- Endoresection not performed

**Role for Early Vitrectomy?**

- At time of plaque placement
  - Gibran and Kapoor, 2009
    - 6 patients
    - Vitrectomy, endodrainage via retinotomy, silicone oil
  - 1 year follow-up
    - VA improvements
    - No recurrent RDs

**Summary**

- Vitreoretinal surgery techniques have an expanding role in management of uveal melanoma patients
- Biopsy for molecular prognostic testing is routine
- Some vision threatening complications may be amenable to surgical intervention
- Surgical approaches for primary treatment are still controversial

**Pharmacotherapy for Exudative RD**

- There may be role for pharmacologic therapy early after radiation
  - Intravitreal triamcinolone more effective than bevacizumab when administered at time of plaque removal
  - Prophylactic bevacizumab for patients with baseline RD reduces rate of rebleeding and hastens retinal reattachment
  - Resolution/reduction of RD seen in Ozurdex
Management of Exudative RD

- Patients with visually significant baseline RD
  - Consider pharmacologic therapy soon after radiation
    - Steroid vs. anti-VEGF
  - Worsening of RD after treatment and/or no resolution after 3-6 months
    - Tumor stable/regressed
    - Consider PPV

Thank You
3D Viewing and the Future of Vitreoretinal Surgery

ALLEN C. HO, MD

SUMMARY
Our tools and technologies to manipulate tissue in the posterior segment of the eye and our ability to create a controlled surgical environment are highly evolved; however, surgical visualization and pharmacosurgical therapy has lagged. The optical microscope is based on 300-year-old principles of the Galilean telescope and has evolved in limited fashion from its initiation in ocular surgery in the 1950s; furthermore, the optical microscope is more suited for anterior segment surgery than it is for posterior segment vitreoretinal surgery.

Vitreoretinal surgery has different imaging requirements and the future of vitreoretinal surgical video imaging will be digital. Digitally assisted vitreoretinal surgery has evolved from substandard surgical displays and video with image lag to full immersion 3 dimension 4K ultra high definition display monitors with enhanced depth of focus and virtually no perceptible video display lag during live surgery. Surgeons are freed from the microscope oculars and can enjoy real time surgical display with their surgical assistants and trainees.

Digital imaging affords high definition and magnification, enhanced depth of field and focus, and peripheral acuity. A reduction in endo illumination and 3D digital guidance systems may also afford improved safety. Other digital imaging input can be displayed simultaneously with the traditional surgeon’s view display to improve surgical facility and techniques.

NOTES
Dr. Ho has been looking at this system since 2008. At that time, it wasn’t ready. It wasn’t ready then, but at the point of this presentation, is it ready now.

Visualization is an unmet need in retinal surgery. We’ve been a little complacent because we’ve relied upon the optical microscope, and it’s really served cataract surgeons well, but not the retina physicians. Consider what imaging you get in the office. Consider the resolution, the quality of digital imaging, color imaging, wide field imaging, OCT imaging, versus what we have in the operating room. There’s a real disconnect in what information we have in the operating room, which is typically inferior.

With the digital viewing system, you’ll see improved resolution, magnification, depth and peripheral acuity. In other words, surgical performance is enhanced, and that will help patient care.

Even Machemer, who did the first vitrectomy in 1970, knew of unmet posterior segment visualization needs. Machemer’s recommendation to Zeiss in 1970 was, “We need xy movement.” He recognized that there were visual needs in the posterior segment, that weren’t being addressed by the optical microscope. The microscope has not kept pace with the other surgical advancements.

The current OR optical microscope, was first introduced in the 1950s, and is really optimized for the front of the eye. Integrating digital technologies is why the digital microscope is where you want to be for retinal surgery.

Galileo. Astronomer, scientist, engineer, philosopher, mathematician. The foundation of the OR microscope is really Galilean. It’s over 350 years old. There was an interesting book written on the history of cataract surgery by Charlie Kelman in 1998.

“Surprisingly, the OR microscope was not initially accepted. Despite a number of prominent proponents, as well as success in other specialties, ENT, neurosurgery, etc, the technique only caught on very slowly. This was especially surprising, since ophthalmologists use this type of magnification for diagnostic purposes, yet they were reluctant to try it for surgery. One of the causes for skepticism among the eye surgeons in the 1950’s was the likelihood that a new instrument would change their surgery techniques. Standard and time tested techniques.”

The surgical microscope has basically remained the same. It’s now motorized, there’s different light bulbs that are used, but it’s basically the same as it was in 1950. It’s optimized for cataract surgeons and people that do work in the front of the eye.

NGENUITY:
The foundation is a 3D, high dynamic range, digital camera. A digital camera takes light and focuses it via lens onto a sensor. This is kind of like what an eye does. The sensor is made of silicone, it’s a grid, and the tiny photosites are sensitive to light. Each individual photosite is called a pixel. There are millions of these individual pixels in the sensor of a digital camera. There are millions of photoreceptors that are sensors in the back of an eye. But we don’t have the ability in the eye to manipulate the information digitally. Just based on your experience with your phone, and the billion digital
pictures that are taken around the world every day, you know that there’s potential power in the digital world. The digital camera is hooked up to the microscope to the two oculars, so there are two feeds. The information is displayed on a very large, ultra-high definition 4K, oled monitor. What’s different from 2008, when it first debuted, was that previously there was tremendous delay. Now, the digital graphics processors have improved. The cameras have improved as well, but the processors have improved so that the lag between the image and what’s projected is really almost imperceptible when you first try the machine.

You have movie theater 3D glasses to view this on the monitor. The microscope is still there, but you’re now ocular free, untethered to the microscope, and then you have the display somewhere that’s easy to look at, at the foot of the bed.

**Benefits of NGENUITY:**
The true vision feed, is a little bit more detailed, it’s a little better resolution, the contrast is better, and the depth perception is better. There’s a hyper-stereopsis that makes it very good for macular surgery.

Surgical education, collaboration. Everyone’s on the same page. George Williams has been with the same scrub nurse for 35 years and she said to him, “Finally I understand what you’re doing in the eye.” Everyone is on the same page, and therefore of course it’s good for teaching, for those who don’t have fellows, it’s good for your surgical team.

85% of retina surgeons have neck and back pain. There are some ergonomic advantages. I can imagine over time that this might be a potential benefit for those that are in pain.

What the digital nature allows is remote real time collaboration. If someone wanted to set up a surgical consultation practice, you could actually get the information to them in real time.

Peripheral acuity, I think the best example of this is when you’re operating on a diabetic traction retinal detachment and you’re focused with the flat lens on the particular pegs that are causing the traction retinal detachment, but your efforts there are also causing problems out in the mid-peripheral/equatorial zone. With digital viewing, you can have better peripheral surgical acuity.

There’s a potential for improved safety. You can reduce the illumination significantly, and perhaps reduce the possibility of photo toxicity.

Digital filters can enhance tissue visualization, maybe red free for surface membranes. Vitreous visualization, it remains to be seen if digital filters can improve this, but vitreous visualization is important.

Then the fun part of this is thinking about integrating other digital technologies to create a surgical cockpit for us. For example, OCT imaging, instrument tracking, 2D or 3D localization in the posterior segment, navigated laser guidance, voice command, mapping techniques allowing robot assisted surgery (e.g. for cannulation of vessels).

The technology is here, it’s time.

**DISCUSSION**

Q: How can I convince the guy that put the money in the hospital to buy these?

A: Obviously each institution hospital has its own unique capital budget procedure and process. I would say if you had an administrator that is a decision maker, I would bring them into the operating room when the unit is there for demonstration, and have them take a look for themselves. It is a “WOW” moment; I mean it truly is a “WOW” moment when people look at that screen.

C: I make the claim that the finest maneuver done by the human hand is ILM Peeling. In all of surgery you all do the finest maneuver and we do it, but when you try these cases you are able to do it safer. This is going to give us the next jump for surgery of the macula I believe.

C: It took no time to learn. The first case I did was a macular hole, and I was kind of nervous about that. And I actually let the fellow do the core vitrectomy. And so, the first time I ever sat in front of that thing, the very first maneuver I did was peel the ILM, it’s the very first thing I did, and it was so easy. I was pretty stunned that 30 seconds, and I was like, “oh yeah, this is not a big deal.”
3D VIEWING AND THE FUTURE OF VR SURGERY – HO

Disclosures

- A0epio (C)
- Alcon (C, S)
- Allegan (C, G)
- Aplex (G)
- Beaver EndoOptics (C)
- Covalent (G)
- Digitight (C, O)
- Genetech (C, G)
- Iodine (G)
- Iridex (C, G)
- Janssen (C, G)
- NEI/NIH (G)
- Ots (C, G)
- OME (C, O)
- Ophthotech (C, G)
- Optovue (C)
- PanOptica (C, G)
- PRN (C, G)
- Regentron (C, G, O)
- Reperix (C)
- Second Sight (C, G)

The Future of Vitreoretinal Surgery 2017

Unmet Needs

- Pharmacosurgical Therapy
  - Retinal Detachment / PVR
  - Drug Delivery

- Surgical Visualization: Evolution
  - Differences: Office versus OR Imaging
  - OR Optical Microscope will be Digital
  - Digital Photography to 3D Digital Videography

Brief History of Pars Plana Vitrectomy 19g

- 1970 Dr. Robert Machemer & Swiss engineer Jean Marie Panel – first automated vitreous cutter: Vitreous Infusion Section Cutter (VISIC, 2 port) 19-gauge instrumentation
- 2.3 mm single port scleral access and 3.3 mm fiberoptic illumination
- Recommended to zero its side AY movement into the Upstaging Microscope
- April 20, 1970: The first human PPV: Vitreous Hemorrhage pre-op VA CF:2 feet, post-op VA: 20/40)

Brief History of Pars Plana Vitrectomy 20g

- 1974 O’Malley & Heine – 20-gauge instrumentation (Ocutome)
  - 0.9 mm scleral access using 3 ports

Future of VR Surgery is 3D and Digitally Assisted

Summary

- Visualization is an unmet need in retinal surgery
- Digital Imaging: Consider Office versus OR
- Evolution of the Optical to a Digital OR Microscope
- Improved: Resolution, Magnification, Depth, Peripheral Acuity
- Potential: Improved Safety: Digital Illumination Modulation
- Integrated Digital Surgical technologies: “Surgical cocktail”
  Other digital feeds eg OCT and more

Vitreoretinal Surgical Visualization

Improvements Needed

- OR Optical Microscope
  - Visualization Optimized for Anterior Segment

- Future is Digital Microscope
  - Digitally Assisted VR Surgery
  - Integrated digital technologies
Future of VR Surgery is 3D and Digitally Assisted Summary

- Visualization is an unmet need in retinal surgery
- Digital Imaging: Office versus OR
- Evolution of the Optical to Digital OR Microscope
- Surgical Education and Head’s Up
- Improved: Resolution, Magnification, Depth, Peripheral Acuity
- Potential for Improved Safety: DIMS
- Integrated Digital Surgical technologies: “Surgical cockpit”
  Other digital feeds eg OCT and more

Galileo Galilei 1564 – 1642
Astronomer, Scientist, Engineer, Mathematician, Philosopher
Foundation of the OR optical Microscope is over 300 years old

History of the OR Optical Microscope
1950’s concept derived from Galileo’s 300 year optical design

History of the Operating Microscope
“Optimized for cornea, capsule and lens … ”

History of the Operating Microscope
in History of Cataract Surgery Kelman and Kwitko 1998

Surgical Visualization Optical Evolution
Galileo to Loupes to OR Microscope (1959)

History of the Operating Microscope
“… initially not widely accepted … ”

Vitreoretinal Surgery
Different imaging requirements with unmet needs
Digital 3D Visualization System

- High Dynamic Range 3D
- Curved
- 4K Ultra HD OLED Display
- High-Speed Graphics Processing
- Computer-Generated Polarizing Glasses

Next Generation 3D Digitally Assisted PPV Surgery

Immersive 4K UHD OLED Digital Display

- 55" Ultra HD 4K OLED Display
- Vibrant Colors
- High Contrast Sensitivity
- Excellent Detail

Future of VR Surgery is 3D and Digitally Assisted Summary

- Visualization is an unmet need in retinal surgery
- Digital Imaging: Office versus OR
- OR Optical Microscope will be Digital for retinal surgery
- Surgical Education and Head’s Up
- Improved: Resolution, Magnification, Depth, Peripheral Acuity
- Potential for improved safety: DIMS
- Digital Surgical Apps: Other digital feeds eg OCT and more

Surgical Education and Collaboration

- Surgical Support Staff
- Surgeons in Training
- Visiting Surgeons
- Remote Surgeons
Future of VR Surgery is 3D and Digitally Assisted

- Visualization is an unmet need in retinal surgery
- Digital Imaging: Office versus OR
- OR Optical Microscope will be Digital for retinal surgery
- Surgical Education and Head's Up
- Improved: Resolution, Magnification, Depth, Peripheral Acuity
- Potential for Improved Safety: Digital Illumination Modulation
- Integrated Digital Surgical technologies: “Surgical cockpit”
  
  Other digital feeds eg OCT and more

3D Digital “Surgical Cockpit”
Integrating Other Potential Digital Technologies

- Enhanced visualization and guidance systems:
  - PIP imaging
  - Collision avoidance
  - Rotation of surgical planes
  - Navigated laser guidance
  - Voice command
  - Robotic guidance

  - Future digital ideas ....

Digital 2D or 3D Guidance System
Digital Laser Guidance System

Aspen Retinal Detachment Society 2017

THANK YOU

The Future of Vitreoretinal Surgery 2017
3D Digital Assisted VR Surgery

Current Next Generation 3-D digital surgery features include:
1. 3-D ultra-high-definition 4K display
2. Passive 3-D visualization glasses
3. Ocular free surgeon viewing
4. Enhanced depth of field and peripheral acuity
5. All of the above

future of vr surgery is 3d and digitally assisted summary

1. OR Optical Microscope will be Digital for retinal surgery
2. Surgical Education and Head's Up, Ocular free
3. Improved: Resolution, Magnification, Depth, Peripheral Acuity
4. Potential for Improved Safety: DIMS
5. Integrated Digital Surgical technologies: "Surgical cockpit"
   Other digital feeds eg OCT and more

ARS2017

ARS2017

All of the following are true regarding 3D Digital visualization systems except:
1. Incorporate other digital information such as OCT imaging
2. Digital-free for tissue visualization
3. Permit enhanced depth of field and high magnification performance
4. Permit enhanced depth of field and high magnification performance
Masquerades of Posterior Uveitis

DEBRA A. GOLDSTEIN, MD

SUMMARY
Many cancers can present in the eye, sometimes as obvious tumors and in other cases as mimickers of other ocular conditions. The most common malignant masquerader of uveitis is lymphoma. Lymphoma in the eye can be broadly characterized as systemic lymphoma, with ocular metastases, typically to the choroid, and primary vitreoretinal (or primary intraocular) lymphoma, which is related to primary CNS lymphoma. Both types may present to the retinal specialist prior to a known diagnosis of cancer. Timely diagnosis is important both for preservation of visual function, but also to allow for appropriate systemic diagnosis and management. This talk will focus on clinical and imaging clues to the diagnosis of intraocular lymphoma and other masqueraders of uveitis.

NOTES
There are in general two kinds of lymphoma. We’re all taught that systemic lymphoma metastasizes to the choroid, and primary vitreoretinal lymphoma or primary intraocular lymphoma is really a subset of primary CNS lymphoma. However, there are some variations to that classic teaching.

Case 1:
77-year-old Caucasian male with two weeks of floaters in both eyes. In 2011, he was diagnosed with systemic diffuse large b-cell lymphoma. Visual acuity was normal. Slit lamp examination was unremarkable.

Fundus exam demonstrated punched out, atrophic-looking lesions in the periphery OU. The posterior pole had active choroidal infiltrates. On the OCT images there is a focal choroidal infiltrate, but there’s some overlying disruption of the RPE in the outer retina. FAF showed hyper and hypo-autofluorescent lesions.

This is metastatic choroidal lymphoma. We didn’t know if this meant he failed Rituximab or is this new disease. He was started on rituximab and observed. Over 6 weeks he had dramatic resolution of the lesions. He improved and the only treatment was systemic rituximab.

Key Points:
• This is a very classic presentation of metastatic systemic lymphoma.
• Autofluorescence patterns are variable with choroidal lymphoma, depending on the overlying RPE involvement.
• Ocular disease responded well to systemic therapy.

Case 2:
47-year-old male with three days of vision loss. He was previously diagnosed with diffuse large cell lymphoma, with testicular involvement. This makes the diffuse large cell lymphoma more likely to metastasize to the brain. He had repeated CSF analysis and MRIs, all were negative. He was treated with high dose systemic chemotherapy, but got prophylactic intrathecal methotrexate because of the testicular involvement.

Visual acuity was CF OD with an APD. He had two plus AC cell. He had a diffuse infiltrate in the macula that seemed to be coming out from along the vessels.

His OCT was really not what you expect with somebody with systemic lymphoma. There was diffuse involvement of the outer retina, really almost absence of the outer retina. FAF had hypautofluorescence.

He was tested for syphilis, because syphilis can give you retinal infiltrates. It’s hard to imagine while you’re getting chemo for lymphoma that you get yourself syphilis, but it’s always possible. Then the question is, is this atypical lymphoma metastasis or is this some kind of infection?

We got imaging of his brain and he had a new lesion. A chorioretinal biopsy showed sheets of atypical lymphocytes classic for lymphoma, mostly in the retina with some infiltration of the choroid. This goes against the classic teaching that systemic lymphoma metastasizes to the choroid. This was primary retinal involvement with systemic lymphoma.

He had weekly intravitreal methotrexate and Rituximab until his stem cell transplant. He no longer has an APD and his vision is 20/100.

Key Points:
• When you see lymphoma cells in the anterior chamber, you see a lot of large cell. We don’t see a lot of flare. We don’t get posterior synechiae.
• This is a case of metastatic disease in a 47 year old with the primary site of metastasis to the retina and not the choroid.

Case 3:
71-year-old woman, referred for atypical drusen. She has lesions along the arcade that look like extrafoveal drusen. The OCT had widespread photoreceptor involvement but there were little ex crescences, some of which were under the RPE, some of which were on top of the RPE. On IR, the lesions were all uniformly hyperreflective. On FAF, they were less symmetric, but they’re all uniformly hypautofluorescent.

She also had two to three plus large white cells in the vitreous in both eyes. Two months prior, she’d had some paresthesias and balance issues. MRIs showed a cerebellar
lesion. That lesion was biopsied and consistent with primary CNS lymphoma.

She was treated with systemic chemotherapy, including rituximab and methotrexate. With treatment, she had remarkable reduction in the hyper autofluorescent lesions. And you see the same thing on OCT with improvement of the outer segments and excretions.

She has been treated with systemic chemotherapy only and continues to improve.

Key Points:
• Historical teaching was that systemic chemotherapy did not treat intraocular lymphoma.
• You can see improvement to intraocular disease with high-dose rituximab and methotrexate.
• Lymphoma lesions can be diffusely and consistently hyper-autofluorescent and hyper-reflective on IR.

Case 4:
55-year-old woman initially presented at age 45 years old in 2006 with floaters in both eyes. Had vitrectomies, and the specimens were thrown away.

She finally gets seen at the National Eye Institute and is diagnosed with intraocular lymphoma. On presentation, she had four plus anterior chamber cells and huge tumor-clumps on the cornea.

On OCT she had lesions that are clearly sub-RPE, but others that were in the superficial retina poking up into the vitreous. AC tap showed lymphoma. She was treated with intravitreal methotrexate, plus rituximab. The tumor cells almost went away in one week. It was probably the rituximab in her case. The OCT showed remarkable response.

Now she’s getting scheduled rituximab and methotrexate injections.

Key Points:
• Atypical presentation: presented at age 45, she had lymphoma for 10 years and still has no CNS involvement.
• Don’t do a diagnostic or therapeutic vitrectomy in a uveitis specimen and throw away the specimen. Send the specimen for analysis.

Case 5:
44-year-old male. Initially presented at the age 40 years old elsewhere. Had bilateral PPV for unexplained uveitis and both specimens were thrown away. He had some improvement with local steroid therapy. He presented with two plus large anterior chamber cells and large vitreous cells that looked like lymphoma. He had a huge vitreous skirt and the whole vitreous skirt was infiltrated with huge white cells.

He had a repeat PPV. The sample showed lymphocytes with scant cytoplasm and irregular nuclei with nucleoli and IGHG rearrangement was detected and IL-6 to IL-10.

He was initially treated with high-dose systemic methotrexate and then intermittent intravitreal methotrexate and his vitreous cells went away completely.

He comes back 10 months later and clinically he looks normal but you can only see changes on OCT and autofluorescence. He gets these new hyper-autofluorescent lesions and with treatment the lesions are only appreciated on imaging to go away.

Key Points:
• Another atypical presentation.
• Recurrences would not be picked up without multi-modal imaging as the clinical exam seemed completely normal.
• Almost never see CME in lymphoma, even with significant cell.

DISCUSSION

Q: What I used in the past for isolated ocular disease is focal radiation therapy. Do you ever use radiation?
A: I don’t.

Q: Historically we learned there was a short life expectancy, has this changed with current chemotherapy?
A: It has changed a lot. So when I trained I was told all these guys would be dead in a year, but with current regimens they do remarkably well. It’s impressive to me.

Q: Do you have any treatment guidelines?
A: Not really. I wish I could give you a great guideline. When I trained we did intravitreal methotrexate, and we did it much more frequently than I do now. In patients who responded really well to methotrexate, like the first patients I showed you, I have done just that. If they don’t respond to the methotrexate I’ll just switch them to rituximab.

Q: Do you have any suggestions or tips on how you handle this specimen after the surgery?
C: I always talk to my pathologist and I ask them how they wanted it and a lot of times I would split it up and send it, an undiluted specimen and we will send the entire cassette, and they will do gene rearrangement studies.
Intraocular Lymphoma

Debra A. Goldstein MD
Northwestern University

Ocular Lymphoma

- Primary intraocular/vitreoretinal lymphoma
  - Ocular presentation of primary CNS lymphoma
  - Typical lesions subretinal and intraretinal
  - Vitritis with large white cells is common
- Systemic lymphoma
  - Typically metastasizes to choroid

Case 1: GC

- 77-yr Caucasian male with 2 weeks of floaters OU
- 2011 systemic diffuse large B cell Lymphoma (DLBCL)
- 2013 treated with XRT followed by R-CHOP
- 4/2016 new lymphadenopathy
  - Rituximab started
- No eye exam since diagnosis of DLBCL
- First seen July 2016

- BCVA: OD 20/20, OS 20/25
- IOP: OD 14, OS 16
- SLE: unremarkable

- Inactive and active lesions
- Observe with systemic treatment
  - Weekly rituximab x 6 cycles
• All lesions now inactive on systemic therapy
• Continue maintenance rituximab Q6weeks

Case 2: DM
• 47-yo Caucasian male with 3 days vision loss OD, 10/2016
• 6/2016 diagnosed stage IVb diffuse large B cell lymphoma (DLBCL) on subcutaneous LNI
• Testicular involvement
• CSF and MRI repeatedly negative
• Treatment
  • High dose MTX, R-EPDC, prophylactic intrathecal MTX

• BCVA: OD CF @ 6’  OS 20/20
• IOP: OD 16  OS 12
• Pupils: 2+ APD OD
• SLE OD: 2+ AC cell, minimal flare, 2+ large AV cell
MASQUERADES OF POSTERIOR UVEITIS – GOLDSTEIN

• Syphilis EIA negative
• ?atypical infection, atypical metastatic systemic lymphoma

Case 3 MG
• 71 year old female referred for eye exam 10/2016
• ?drusen

• Metastases to retina via vasculature?
• ? extravasation from small vessels on OCT/FAF
• New CNS lesion
• Oncology needed tissue dx

• BCVA: OD 20/25, OS 20/30
• IOP: OD 12, OS 13
• SLE: No AC cell or flare
Other info...

- SLE also showed 2-3+ large white vitreous cells and clumps
- 3 months ago noted balance problems and paresthesias

- MRI brain showed cerebellar lesion
- Surgical pathology:
  - Large B cell lymphoma
  - CD19+, CD20+, CD5+, and CD10+ positive
- Systemic chemo:
  - Rituximab-MTX/Vincristine/Procarbazine
MASQUERADES OF POSTERIOR UVEITIS – GOLDSTEIN

Case 4: SP
- 55-yr Caucasian female referred to NW December 2016
- Presented with floaters OU in 2006 at age 45
- W/U negative
- Therapeutic PPV 2007/09, specimen discarded
- 12/09 repeat PPV, diagnosed with PIVD
  - Cytology: elevated II-30/4 in vitreous, tigh rearrangement
  - LP/MRI repeatedly negative

PVRL
- Differentiation from druse
- Diffusely/consistently hyper-AF
- Consistently hyper-reflective on near infra red
- May see shadowing on OCT

Course:
- Intravitreal MTX without much effect
- Systemic rituximab, cyclophosphamide, bortezomib without much response
- Adjuvant intravitreal rituximab had some response
- 2014 serum + for multiple ARA
- Intermittent intravitreal RTX
- Seen at NIH, then referred to us December 2016
- Last treatment 5 months prior to our evaluation

- BCVA: OD 20/20 OS 20/50
- IOP: OD 10 OS 13
- Pupils: OS 1+ APD
- SLE: OS 4+ AC and AV large white cells

December 29, 2016
MASQUERADES OF POSTERIOR UVEITIS – GOLDSTEIN

- Lymphoma presented age 45
- Dramatically prolonged course of bilateral PVRL
- No CNS involvement
- Never throw out vitrectomy specimen in case of “uveitis”

Case 5: AM

- 44-yo Hispanic male with floaters and blurred vision for 4 years
- Prior PPV OU, not sent for testing
- Some improvement with local steroid therapy

- BCVA: OD 20/30, OS 20/25
- IOP: OD 20, OS 24
- SLE: 2+ large AC and vitreous cell OU
• Repeat PPV OD, sample sent to NIH
• PVRL
  • “Some lymphocytes have large irregular or segmental nuclei and scanty cytoplasm with prominent granular nucleoli. light gene rearrangement was detected”
• Treated with intermittent systemic MTX and intravitreal MTX, with resolution large vitreous cells

• Monitoring clinical exam and autofluorescence
• Interesting idiosyncratic presentations in each eye
• Young patient (presented first at age 40)
• Treating with PRN intravitreal MTX
• Regular CNS evaluation

**Intraocular lymphoma**

• Variable presentations of systemic and primary vitreoretinal lymphoma
• Multimodal imaging may aid in diagnosis
• Do not throw out PPV specimens!
• Do not discount diagnosis of PVRL in patient younger than 50

• Thanks to Anjum Koreishi and Amani Fawzi
Which of the following factors excludes primary vitreoretinal lymphomas as a diagnosis?

1. Age under 45
2. Female gender
3. Bilaterality
4. Absence of vitreous cells
5. None of the above

Survey:

- Male: 6%
- Female: 92%
- Total: 98%

Which of the following are typical features of primary vitreoretinal lymphomas?

1. Primarily choroidal involvement
2. GME
3. Hyperautofluorescence of lesions
4. Posterior synechiae
5. Retinal neovascularization

Survey:

- Male: 12%
- Female: 33%
- Total: 45%
- Male: 8%
- Female: 21%
- Total: 29%
- Male: 2%
- Female: 2%
- Total: 2%
PANEL 3:
Surgical Approaches, Advanced Viewing and Instrumentation.
Case Presentation.

MODERATOR:
ALLEN C. HO, MD

Panelists:
Ivana Kim, MD
Hugo Quiroz-Mercado, MD
Timothy G. Murray, MD, MBA

SUMMARY
Drs. Kim, Quiroz-Mercado and Murray, MD will discuss their surgical approaches, advanced viewing techniques and use of instrumentation in various vitreoretinal conditions including PVR, dislocated IOL, macular hemorrhage and macular hole, surgical complications and more. The discussion will be focused on current surgical techniques and instrumentation.

NOTES
First Video: Cysticercosis removal
Dr. Quiroz-Mercado presented a patient from Denver. The first-year resident initially presented the case as, “we have a mac ... on RD”. The patient’s visual acuity and pupils were normal, but he had a temporal scotoma. (Video plays with large white cyst consistent with cysticercosis)

The patient had a MRI showing multiple intracranial cysts. Dr. Quiroz-Mercado asked the order of treatment: first treat systemically or first surgical treatment for his eye? The consensus was to treat surgically first because of the large inflammatory reaction that can occur following systemic treatment. In these scenarios, surgery should take place before systemic treatment, followed by immediate systemic treatment. If systemic treatment occurs first, Dr. Quiroz-Mercado stated inflammation occurs and they can’t be removed because they scar down.

The surgical procedure was a PPV, ensuring you get the hyaloid removed. If the hyaloid is not up and removed the retina will detach after contracting around the retinectomy. A retinectomy is made with a MVR blade. The retina is very elastic and the large cyst can come out of a small retinectomy. The cyst is grasped with the soft tip aspiration cannula. The sclerotomy is not enlarged until the cyst is ready to come out in order to prevent turbulence. Dr. Quiroz-Mercado also mentioned you can increase the pressure to help push the cyst out, which can be used in IOFB removals as well.

If the cyst ruptures it is okay but you should try to remove it without rupturing it. You can also eat it with the cutter but Dr. Quiroz-Mercado did not prefer this technique. Other techniques included if the cyst was in the periphery to do a sclerotomy and pop the cyst out. Dr. Quiroz-Mercado also pointed out that you do not need to laser retinotomies in the posterior pole. The patient ended up 20/20.

Second Video: ERM being peeled and then sudden cough by the patient causes retinal touch
The panel discusses the case starting with ways to prevent movement by the patient during macular surgery. Dr. Ivana Kim suggested waking the patient up and engaging them prior to doing the peel so they do not fall asleep and become startled while waking up. The audience suggested taping all cases, because bucking under general anesthesia can occur as well. Also, it can be beneficial to discuss the case with the anesthesiologist prior to starting and explain that you do not want the patient too deep.

The panel then discussed ways to stop bleeding. These included turning the pressure up as the first step for most of the panel. PFO was suggested as an alternative or mechanical pressure with the cutter, which has been shown by Dr. Maria Berrocal. Obtaining good visualization is key.

Dr. Murray suggested to peel ILM to prevent contraction in the site of the retinal touch. Dr. Quiroz-Mercado insisted not doing laser. Dr. Quiroz-Mercado explains to his fellows, “If you remove the macula with a vitrector, it’s a hopeless case. Otherwise, you can fix almost everything. When this occurs the first mistake has occurred, don’t make the next mistake and laser this area”.

Most of the panel would not tamponade in this setting and would close with fluid.

Third Video: Heterochromia, small IOFB in the vitreous base inferiorly
The patient had been hammering >6 months ago. He developed a cataract and then subsequently heterochromia. B-scan picked up an IOFB. The patient had persistent inflammation following cataract surgery. The discussion started with the importance of suspecting and working up for an IOFB in this setting.

The audience was questioned and about 30% would start with a magnet. Dr. Abrams discussed the Bronson ocular magnet used as an external approach, which he uses. A sclerotomy over the IOFB is performed and the magnet is brought onto the field and put to the sclera perpendicularly. The IOFB then comes out of the sclerotomy. These magnets are no longer readily available at most locations.
An audience member recommended a Bausch + Lomb 23 G intraocular magnet. Per the audience this works very well and goes through a 23G sclerotomy. Most other people would use a 19G IOFB magnet. Other audience members recommended forceps or even using the vitrector since it was small and friable.

The video continued with the surgeon grasping the IOFB with forceps and then removing it through an enlarged sclerotomy.

**Forth Video: Exudative RD in previously treated melanoma patient**

Dr. Ivana Kim showed a video of a patient with an exudative retinal detachment. The patient had previously been treated with proton beam irradiation for an amelanotic melanoma. The video showed a PPV with retinotomy away from the melanoma. The fluid was drained. Laser was applied to the melanoma and avascular retina. Oil was placed for the tamponade.

Dr. Kim debates about the retinotomy over the tumor or away from it, but she typically places it over the regressed tumor. Dr. Murray agreed and would also typically place it over the tumor because he will laser that area extensively. Dr. Murray also stated the importance of adequately removing the hyaloid, and oil is his tamponade of choice.

There was a discussion on external drainage and Drs. Kim and Murray do not typically drain externally for these cases, and would not recommend it. Dr. Kim also mentioned that PVR was not frequently seen and felt that prior radiation likely played a role in that observation.

**Fifth Video: Inferior GRT**

Dr. Ho presented a case of an inferior giant retinal tear (GRT) that had a fold under PFO. The audience was initially asked who puts buckles on with GRTs? Very few people raised their hand. Dr. Ho thought it was interesting how the pendulum has swung away from buckles when previously people would insist on buckles and sometimes buckle the other eye prophylactically.

In the video, the retina did not appear to flatten or to have a fold under PFO. The panel was asked what they do if there is persistent fluid or a slip in a GRT. Dr. Quiroz-Mercado stated if he was to use oil he would try to remove the fluid. If he was to use gas he would leave it and have the patient face down.

The way people would remove the fluid included creating another retinotomy, using a snake or a long soft tip, or creating a clover leaf edge. Dr. Abrams also discussed how he would go to oil and use a soft tip to pull the edge up. He stated this can’t be done under air because the surface tension is too high and it will not work. But under oil you can walk the edge of the slipped retina up.

An audience member recommended to fill the eye with PFO and leave it for 2 weeks, then remove it and the retina would be flat at that time. He had left PFO in for up to three weeks. He offered this as an alternative.
Which of the following is least accurate?
1. Gore tenon sutures can be used for more stable than polypropylene sutures.
2. Syphonizing fluid technique may be helpful to remove long subretinal bands.
3. Vortex vitrectomy helps to remove the vitreous from the outer retinal surface.
4. Consider the possibility of trauma and occult intracranial foreign body with dense leakage of internal and chronic inflammation.

Regarding surgical repair of giant retinal tears, which of the following is most accurate:
1. Valved cannulas reduce surgical visualization when using perfluorocarbon liquids by increasing outflow of blood.
2. Tilting the eye away from the giant retinal tear during air fluid exchange reduces trapped subretinal fluid.
3. All giant retinal tear repairs should include an encircling scleral buckle.
4. Direct perfluorocarbon exchange or exchange can reduce posterior vitreous.

ARS2017

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Aspen Retinal Detachment Society Meeting

March 3–7, 2018
The Viceroy Snowmass

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