MEETING NOTES FROM THE 44TH ANNUAL MEETING OF THE ARDS

The 44th annual meeting of the Aspen Retinal Detachment Society (ARDS) lived up to its participants' high expectations. Two hallmarks of the ARDS meeting—long-form lectures that invite audience participation and expert panels who dissect interesting topics in retina—joined the Founders Lecture (this year delivered by Mark W. Johnson, MD, and summarized below) and Taylor Smith Lecture (awarded to Neil M. Bressler, MD, to be summarized in a future installment of this column) to create a dynamic, world-class meeting.

As in years past, the ARDS has joined forces with Retina Today *to provide thorough summaries of some of the talks at the meeting. This year, meeting scribes Irene Rusu, MD, and Basil K. Williams, MD, will review lectures from a variety of speakers. Below, Dr. Rusu reviews a lecture by Szilárd Kiss, MD, on the future of ocular gene therapy, and Dr. Williams reviews the aforementioned Founders Lecture.*

—Timothy G. Murray, MD, MBA

Promising New Treatments for Retinal Diseases: Gene Therapy and Engineered Cells

By Irene Rusu, MD

In a presentation on promising new treatments for retinal diseases, Szilárd Kiss, MD, discussed gene therapy and engineered cells. He described ocular gene therapy and its application in wet age-related macular degeneration (AMD), as well as novel cellular therapies and immune modulation techniques for other eye diseases. Finally, he drew upon his experience at Weill Cornell Medical Center to describe treatments for patients with cytomegalovirus (CMV) retinitis.

OCULAR GENE THERAPY

The concept of gene therapy using viral vectors has been around since the early 1980s. Recently, monogenetic disorders of the eye have been targeted with gene therapy approaches. Dr. Kiss began his discussion on gene therapy by pointing out that such an approach is attractive for diseases for which no other treatments are available. Ten monogenetic disorders are now being addressed in clinical trials using gene therapy. These trials may demonstrate proof of concept, Dr. Kiss suggested, but it is in diseases that are currently treated with repeated intravitreal injections where gene therapy may have its greatest impact.

To realize the promise of gene therapy, multiple factors must be addressed, including capsid diversity, gene cassette optimization, formulation, and vector administration. Different promoters and enhancers will result in greater or less expression of a particular protein. "The formulation, especially when using viral vectors, is also important because viruses love to stick to things, including surgical instrumentation," said Dr. Kiss. The final challenge is administration of the gene therapy to target tissues, which currently requires subretinal placement. As Dr. Kiss emphasized, "for the typical retina practice, it would be nice if we could treat AMD with gene therapy using an in-office procedure."

GENE THERAPY FOR WET AMD

Companies developing genetic therapies targeting wet AMD include Avalanche Biotechnologies (now Adverum Biotechnologies), AGTC, Spark Therapeutics, and Regenxbio, Dr. Kiss said.

Avalanche was the first company to enter clinical trials with its product AVA-101. The Avalanche approach used the soluble FLT-1 protein with an A82 vector, administered by subretinal injection. "These trials were unsuccessful, and one of the reasons for this has to do with the macular anatomy of wet AMD," Dr. Kiss said. "The choroidal neovascular membrane [CNVM] is actually taking up the area where gene therapy targets need to be delivered," he explained.

This is very different from what happened in the Spark trials, during which the macular anatomy was relatively normal. The Spark trials investigated gene therapy for retinal conditions caused by mutations in the gene RPE65 such as Leber congenital amaurosis and retinitis pigmentosa. In the wet AMD gene therapy trials, the heterogeneity of the macular pathology includes both the size of the CNVM and the size of the bleb carrying the gene therapy targets.

LESSONS FROM THE AVALANCHE TRIAL

"Subretinal injection is not difficult, but there is a learning curve," Dr. Kiss said. Subretinal gene therapy with active CNVM is safe but less predictable than subretinal administration in a macula that is relatively normal, such as in the Spark trial discussed above. Subretinal injection results in outer retinal changes that may persist. Dr. Kiss emphasized that standardization of technique is key in order for clinical trials to be internally valid.

CELLULAR THERAPY

There are two basic ways that stem cells can potentially be used in therapy for retinal disorders. According to Dr. Kiss, "You could use the cells to regenerate whatever tissue you need, or you can take these cells and use the trophic factors that they produce to stimulate tissue regeneration."

In a trial conducted by Astellas Institute for Regenerative Medicine (formerly Ocata, formerly Advanced Cell Technology), patients with either Stargardt disease or dry AMD received a subretinal injection of human embryonic stem cells with the goal of replacing retinal cells via the regeneration mechanism. "Although this therapy was not a cure for Stargardt disease or dry AMD, it was a step toward understanding how we may be able to use stem cells in the future," Dr. Kiss said.

The other way to use stem cells is the trophic approach. Dr. Kiss explained that researchers with the Janssen BetaLogics group at Johnson & Johnson recently injected adult umbilical cord stem cells into the subretinal space in patients with atrophic AMD. They used an external approach with a catheter to place the cells in areas of geographic atrophy in the hope that the cells would provide a milieu for retinal growth or decreased degeneration. As in other trials, a limitation to success in this study was the surgical procedure. "The surgical technique itself was an integral part of actually delivering this therapy," Dr. Kiss explained. He predicted that there will be a phase 2b clinical trial of the same therapy in which the surgical procedure will be "completely revamped."

COMBINING GENE AND CELLULAR THERAPY

Encapsulated cell therapy (ECT; Neurotech) combines gene and cellular therapy, Dr. Kiss explained. "The concept here is to put a gene of choice into cells and then place these engineered cells into the eye," he said. A third-generation ECT (NT-503) was investigated in a phase 2 clinical trial in patients with wet AMD. In this form of ECT, a cylinder containing modified RPE cells that produced an anti-VEGF molecule was implanted in the eyes of patients with the goal of decreasing anti-VEGF injection frequency. The trial was discontinued because a larger number of patients than anticipated required rescue therapy.

HARVESTING THE POWER OF THE IMMUNE SYSTEM

Dr. Kiss and his team at Weill Cornell Medical Center and Memorial Sloan Kettering have been harvesting T cells to develop a therapy to treat CMV retinitis. He explained the concept as follows.

Cytotoxic T cells float around the body ignoring cells that express self-antigens. But if they encounter a cell that is expressing a foreign antigen on its surface, the cytotoxic T cells activate a series of mechanisms resulting in apoptosis of the abnormal cell.

"We obtain donor T cells from CMV-seropositive patients and use these to generate CMV-specific cytotoxic T cell lines, resulting in a library of T cell lines," Dr. Kiss explained. "This library has a variety of major histocompatibility complex (MHC) class 1 and class 2 phenotypes. Then, given a patient with CMV retinitis, these cells are made to look like self-cells if two of eight of these alleles are matched. These engineered self-cells are amplified and then infused into the patient." Exactly what happens next is under investigation, but it is believed that the infused T cells help some of the body's other T cells become activated to also recognize the same antigen.

WATCH IT NOW

From ARDS 2016:

Dr. Kiss talks about treatments using gene therapy and engineered cells.

Ocriplasmin Retinopathy

By Basil K. Williams, MD

Ocriplasmin (Jetrea, ThromboGenics) is a recombinant protease indicated for the treatment of symptomatic vitreomacular adhesion. It dissolves the proteins that connect the vitreous to the macula, with the aim of inducing posterior vitreous detachment (PVD) and alleviating vitreomacular traction (VMT).[1,2]

Mark W. Johnson, MD, and colleagues have described a complication dubbed *acute ocriplasmin retinopathy*, a range of abnormalities occurring after ocriplasmin injection that can include severe loss of vision and other sequelae.[3] Dr. Johnson gave

a lecture on ocriplasmin retinopathy at the 2016 ARDS Annual Meeting with the stated goal of answering four questions:

- What are the structural and functional characteristics of acute ocriplasmin retinopathy?
- What is the pathogenic mechanism?
- How often does it occur?
- What is the time course of extended recovery from the acute injury?

STRUCTURAL AND FUNCTIONAL CHARACTERISTICS

The signs and symptoms of acute ocriplasmin retinopathy can include visual acuity loss (rarely to as low as light perception), bizarre photopsias unrelated to a PVD, dyschromatopsia, nyctalopia, visual field constriction, afferent pupillary defect (APD) or anisocoria, retinal vascular attenuation, and macular hole enlargement.

One of the less frequently discussed complications is macular detachment. These cases demonstrate either frank detachments or multiple small blebs without significant macular detachment, as if the retina is trying to separate. The electroretinogram (ERG) responses are well known: Reduction of the A or B wave can be seen, sometimes to the point of being completely flat. Diffuse autofluorescence changes may be present, lasting as long as 5 months after injection with an accompanying APD. Cases of delayed zonular dehiscence have also been reported.

PATHOGENIC MECHANISM

Toxicology studies in rabbits demonstrated zonular dehiscence starting at doses of 25 µg ocriplasmin. There is suppression at lower doses, but persistent change after 90 days with higher doses. It is unlikely that transient increase in VMT is the cause of the issue. It is more likely the molecule itself is causing these effects.

Ocriplasmin is a nonspecific protease that digests dozens of proteins (including laminin and fibronectin), many of which are found in the vitreous, retina, and zonules. It is a relatively small molecule capable of penetrating all retinal layers, making it likely that enzymatic degradation or cleavage of inter-retinal proteins is responsible for the retinal damage. These proteins may then reconstitute, which explains why some of these changes are reversible over time.

While many proteins are digested by ocriplasmin, there may be a key role for laminin degradation, Dr. Johnson suggested. Laminin is found in the vitreous gel, in the zonules, and in multiple retinal layers, including the internal limiting membrane, the outer plexiform layer, the external limiting membrane (ELM), and the inner photoreceptor matrix. It is especially important in the outer plexiform layer, where it localizes the synapses between photoreceptors and bipolar cells.

In rat eyes, intravitreal ocriplasmin degrades laminin and fibronectin at the vitreoretinal interface and in the outer retina. ERG B-wave depression has been demonstrated in these rat eyes, potentially resulting from laminin degradation in the outer plexiform layer because of the disruption of the synapses between the bipolar cells and the photoreceptors.

Degradation of laminin in the ELM could explain the loss of the ELM signal on optical coherence tomography (OCT). Acuity loss, APD, dyschromatopsia, nyctalopia, field constriction, ERG A-wave suppression, decreased retinal adhesion, and submacular fluid could all result from degradation in the inner photoreceptor matrix. Lastly, degradation in the lens zonules could cause lens subluxation.

FREQUENCY

The phase 3 studies of ocriplasmin did not employ either ERG or spectral-domain (SD) OCT. Published reports of consecutive eyes imaged with SD-OCT demonstrate outer retinal signal changes in 30% to 50% of eyes. The prospective OASIS study, presented at the 2015 American Academy of Ophthalmology Annual Meeting, found ERG changes in 40% of eyes. In the OASIS Study, ERG changes were found in nonstudy eyes or sham-injected eyes 5% of the time.

RECOVERY

Animal toxicology studies suggest that the acute findings of ocriplasmin retinopathy were mostly reversible over time, but there was persistence beyond 8 weeks in eyes receiving the dose used in humans. In humans, retinal adverse effects typically resolve within 2 to 3 months. Most patients return to baseline visual acuity or better. Even severe vision and visual field loss have been reported to resolve completely over extended periods of up

WATCH IT NOW

From ARDS 2016:

Dr. Johnson explains acute ocriplasmin retinopathy.

From the BMC Archive

***NRMD* at the Meetings**
44th Annual Aspen Retinal Detachment Society Meeting
New Retina MD Volume 7, Issue 2
Find it online at: bit.ly/nrmd0716

to 3 years. There is a major concern that some changes persist beyond 6 months. In the OASIS trial, changes persisted for up to 2 years in some patients.

Although many eyes recover from acute ocriplasmin retinopathy with good vision, aggregate visual outcomes are somewhat disappointing. In the phase 3 clinical trials, the mean change in visual acuity at 6 months did not differ between the placebo and ocriplasmin groups despite the higher rate of VMT release in treated eyes. In the OASIS study, there was no significant difference between the ocriplasmin and the sham group in the percentage of patients gaining visual acuity at 2 years. Published studies have shown that mean final visual acuity is typically the same as or only modestly better than the mean pretreatment visual acuity. This means that many patients have final visual outcomes that are worse than expected for the condition they are being treated for, even if the acuity is not decreased from baseline.

SUMMARY

Ocriplasmin can cause retinopathy that is sometimes undetectable, sometimes mild and reversible, but occasionally severe and at least at times persistent. At present, it is difficult to predict which patients are susceptible to significant damage. Until ongoing phase 4 studies are able to provide additional safety data, ocriplasmin should be used with caution. ■

1. Jetrea [package insert]. Thrombogenics. 2012. http://jetrea.com/wp-content/uploads/JETREAPrescribingInformation.pdf. Accessed July 15, 2016.
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3. Johnson MW, Fahim AT, Rao RC. Acute ocriplasmin retinopathy. *Retina*. 2015;35(6):1055-1058.

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