NOTES FROM THE 46TH ANNUAL ARDS MEETING

Medicine is a continually evolving field, and ophthalmology—specifically retina—provides a great example of the speed at which technology and innovation occur. The core principles of the annual Aspen Retinal Detachment Society (ARDS) meeting include maintaining high standards in teaching, providing innovative and in-depth presentations, and sparking intense dialogue between speakers and attendees.

Each year, the ARDS meeting presentations and discussions are scribed by a group of young vitreoretinal surgeons and published for the society. A handful of these summarized talks are chosen for inclusion in Retina Today's *last four issues of each year. In this annual tradition, please enjoy the first of this year's series of ARDS summaries below.*

At the 2018 meeting, Daniel F. Martin, MD, and Carl C. Awh, MD, demonstrated in their presentations how the field continues to move forward. Dr. Martin spoke about his involvement in the development of intravitreal drug delivery, and Dr. Awh described the use of ultrasonic power to remove the vitreous. Below, Neepa B. Shah, MD, and Kimberly D. Tran, MD, provide overviews of these two presentations.

—Timothy G. Murray, MD, MBA

INTRAVITREAL THERAPY FOR RETINAL DISEASES: A BRIEF LOOK

Charting the emergence and growth of this approach to treatment and its future potential.

By Neepa B. Shah, MD

The Taylor Smith and Victor Curtin Lecture is one of two named lectures given at the ARDS meeting each year. Daniel F. Martin, MD, who was privileged to give the lecture this year, has many honors and accolades to his name, but one of his most significant contributions to the field has been in clinical trial development. His lecture focused on his experiences, particularly those pertaining to targeted retinal therapy using intravitreal drug delivery, from ganciclovir (Zirgan, Bausch + Lomb) for cytomegalovirus (CMV) retinitis to anti-VEGF agents for age-related macular degeneration (AMD). Following is my brief summary of his lecture.

GROWTH OF INTRAVITREAL THERAPY

According to Medicare claims data, the intravitreal injection rate has risen from 2,000 injections per year in 1993 to more than 500,000 injections in 2016.[1] Intravitreal injections were first popularized in the 1980s for the treatment of endophthalmitis, but they were typically administered only once to treat the acute disease.

The idea of using multiple repeated intravitreal injections to treat a chronic retinal disease did not come about until the AIDS era. During that time, CMV retinitis became the most common opportunistic infection in patients with CD4 counts of less than 50 cells/mm^3. At that time, only two treatments were available for CMV retinitis: intravenous ganciclovir and intravenous foscarnet (Foscavir, Pfizer). These medications were not ideal for several reasons: They required long-term intravenous catheterization, which led to frequent infection; they were associated with significant systemic toxicities, such as myelosuppression; and they were expensive. In search of a safer, more affordable option, a group of individuals explored the use of intravitreal ganciclovir delivery.

Because ganciclovir has a short half-life, it requires weekly injections, but it was found to be highly effective in the treatment of patients with CMV retinitis—so much so that some clinics adopted repeated intravitreal ganciclovir as primary therapy for these individuals. Dr. Martin worked in one of these clinics, and at one point before the advent of highly active antiretroviral therapy he was administering 30 injections a day. Because some patients were not able to come in for weekly injections, a sustained drug delivery device, the ganciclovir intravitreal implant (Vitrasert, EyePoint Pharmaceuticals, formerly pSivida and Control Delivery Systems), was developed and received US FDA approval for the treatment of viral retinitis. Rates of CMV retinitis rapidly declined with the advent of highly active antiretroviral therapy, and previous options grew obsolete. However, the importance of ganciclovir as an antecedent to modern intravitreal injection therapy remains.

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THE ERA OF ANTI-VEGF THERAPY AND THE CATT TRIAL

Dr. Martin recalled that in 2006, the results of the MARINA trial showed remarkable visual acuity gains with ranibizumab (Lucentis, Genentech) in the treatment of AMD.[2] Although the efficacy of ranibizumab fostered excitement, its cost raised concern. Retina specialists nationwide sought alternatives, and bevacizumab (Avastin, Genentech) was identified as a cost-effective substitute.

Dr. Martin spearheaded the landmark CATT trial as one of the chairs of the CATT Research Group.[3] He touched on some of the challenges his team faced coordinating the study, such as how to pay for an expensive drug (ranibizumab) in a trial using public money, and how to find a supplier and distributor for a medication used off-label (bevacizumab). Due to regulations, an act of Congress was needed to change existing Medicare policy to allow the CATT to proceed. Fortunately, some of these policy changes have also benefitted other clinical trials in medicine since then.

The main conclusion of the CATT was that ranibizumab and bevacizumab were equivalent in the treatment of AMD. This finding has been supported by other randomized clinical trials, including IVAN.[4] Other key take-home points from the CATT include these:

• Because 14% of patients need only three injections to resolve their choroidal neovascularization and do not experience recurrence, all patients should be initially treated as needed (prn). If choroidal neovascularization recurs, then treatment should be continued on a treat-and-extend or monthly regimen.

• The number of injections required per patient is heterogeneous. The CATT team was not able to find any baseline variables clearly associated with greater or less need for injection other than retinal angiomatous proliferation lesions, which may require less injection therapy.

• The better the patient's visual acuity at baseline, the better the visual acuity at 1 year.

• Patients who had subretinal hemorrhage did well with injection therapy alone.

• Intraretinal fluid is worse than subretinal or sub–retinal pigment epithelium fluid.

• Geographic atrophy is a real finding, but the risk of vision loss is likely greater from undertreatment rather than overtreatment.

Photo courtesy of Kevin Caldwell

Daniel F. Martin, MD, presenting the Taylor Smith and Victor Curtin Lecture at ARDS.

IT'S ONLY JUST BEGUN

The number of intravitreal drugs available and the diseases they can treat continues to grow, and it is unlikely that the curve of injections performed per year will dip any time soon. Additionally, long-acting drug delivery systems are in development, and while their trials are ongoing there is hope for a future when injection frequency may decrease.

1. Erie JC, Barkmeier AJ, Hodge DO, Mahr MA. High variation of intravitreal injection rates and Medicare anti-vascular endothelial growth factor payments per injection in the United States. *Ophthalmology*. 2016;123(6):1257–1262.
2. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419–1431.
3. Maguire MG, Martin DF, Ying G, et al; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group Writing Committee. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration. *Ophthalmology*. 2016;123(8):1751–1761.
4. Chakravarthy U, Harding SP, Rogers CA, et al; IVAN Study Investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*. 2012;119(7):1399–1411.

HYPERSONIC VITRECTOMY

The future looks promising for this new technology.

By Kimberly D. Tran, MD

Vitreous cutter technology has evolved dramatically from the original 16-gauge prototype of Robert Machemer, MD, made from a model airplane motor, drill bit, syringe, and tubing, to today's 27-gauge pneumatic-driven cutters. Hypersonic vitrectomy is a new method of vitreous removal in which ultrasonic power is used to actuate the vitrectomy probe. Carl C. Awh, MD, spoke about this new technology at the ARDS meeting, and highlights from his presentation follow.

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VITRECTOMY: THE NEXT GENERATION

Flow through a vitreous cutter is dependent on pressure differences, cutter and tubing geometries, the mechanical properties of the aspirated material, and the duty cycle. The duty cycles of conventional cutters are constrained by the guillotine-like cutting mechanisms used.

In 2013, Dr. Awh presented preliminary work with an ultrasound-driven cutter, which had a 100% duty cycle (ie, the port is always open). Vibrating at 1.7 million cpm, this prototype demonstrated continuous flow. Dr. Awh and Kevin J. Blinder, MD, presented data in a porcine model demonstrating no histopathologic changes in the retina with the use of a pneumatic versus a hypersonic cutter. Paulo E. Stanga, MD, similarly demonstrated no significant clinical or histopathologic differences in cadaveric (porcine and human) and live porcine eyes with the use of a pneumatic cutter versus a hypersonic cutter.[1]

In electron microscopy studies by Dr. Stanga and colleagues, the vitreous collagen was shown to be pulverized, a phenomenon now termed *hypersonic liquefaction*, and flow increased linearly with vacuum and with power level.[2] Flow is also improved because the hypersonic vitrector has a larger inner lumen due to the absence of an inner sleeve. Additionally, hypersonic liquefaction appears to occur only at the outer margins of the port, allowing the use of different port geometries and locations, including a curved cutter. In the guillotine cutter, flow is dependent on vacuum, infusion pressure, and cut rate. With the hypersonic vitrector, *stroke*, rather than cut rate, affects flow. Stroke is the longitudinal amplitude of tip oscillation, which in the current device varies from 0 to 60 µm. Hypersonic vitrectors allow a much greater range of vitreous flow than pneumatic guillotine cutters.

HYPERSONIC PIONEERS

Dr. Awh related that Dr. Stanga; Amar Agarwal, MS, FRCS, FRCOphth; and Anusha Venkataraman, MD, FRCS(Glasg), FICO, performed the first 22 operations in 20 patients with the hypersonic vitrector in India in July 2017. Maneuvers successfully performed with the new instrumentation included induction of posterior vitreous detachment, core and peripheral vitrectomy, removal of dense vitreous hemorrhage and lens cortex, and posterior capsulotomy. The first cases using the instrument in the United States were performed by Drs. Awh and Blinder and Sunir J. Garg, MD, in September 2017.

Dr. Awh described his experience performing 31 cases for indications including macular hole, epiretinal membrane, rhegmatogenous retinal detachment, retained lens material, vitreomacular traction, and retained silicone oil. He said complications included one iatrogenic retinal break in detached retina (out of eight retinal detachment cases), and one incidence of pitting an intraocular lens during posterior capsulotomy (out of nine cases that included posterior capsulotomy). He attributed the iatrogenic retinal break to his learning curve with the new instrument. He has since learned to limit flow by reducing the amount of stroke when working near detached retina. Dr. Awh reports that the device is capable of removing dense lens nucleus and even 5000 cs silicone oil, which is not possible with a guillotine cutter.

Photo courtesy of Kevin Caldwell

Carl C. Awh, MD, on stage at ARDS discussing hypersonic vitrectomy.

FINE TUNING

The hypersonic cutter is being refined based on results of the initial cases performed in the United States. New port designs and 25-gauge and 27-gauge devices are in development. It will be exciting to see the capabilities of this next generation of vitrectomy instruments. ■

1. Stanga PE, Pastor-Idoate S, Zambrano I, et al. Performance analysis of a new hypersonic vitrector system. *PLoS One*. 2017;12(6):e0178462.
2. Pastor-Idoate S, Bonshek R, Irion L, et al. Ultrastructural and histopathologic findings after pars plana vitrectomy with a new hypersonic vitrector system. Qualitative preliminary assessment. *PLoS One*. 2017;12(4):e0173883.

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