MEETING NOTES FROM THE 44TH ANNUAL MEETING OF THE ARDS

Retina specialists have earned a reputation for bravery. Our anterior segment surgical colleagues commonly consult us during intraoperative complications, and we are the first (and most eager) surgeons to take on a complex case. We thrive on challenge, and we are proud of it.

The same goes for medical retina. One of the most confounding diseases in ophthalmology—indeed, in any medical specialty—is uveitis. Heterogeneous disease manifestation and differing responses to therapy frustrate specialists charged with managing patients with this disease. Combine those biologic facts with the time required to treat uveitis patients—some of whom may have many questions about their disease and how it is treated—and it becomes apparent why retina specialists are eager to find more effective therapies to treat uveitis.

Just as retina specialists do not shy away from the challenges uveitis presents, the Aspen Retinal Detachment Society (ARDS) meeting does not shy away from discussing the disease and its complexities. This year, Glenn J. Jaffe, MD, reviewed the state of uveitis as it presently exists in our field, and discussed a number of new treatments that may offer relief to patients with suboptimal responses to previous therapy. Basil K. Williams, MD, summaries his presentation below.

—Timothy G. Murray, MD, MBA

New Treatments for Uveitis

By Basil K. Williams Jr, MD

Glenn J. Jaffe, MD, gave a presentation at ARDS on treatments for uveitis, including some new therapies that may be coming to the clinic soon. He explained that the treatment goals in uveitis are similar to those for any type of retinal disease, with the additional goal of relieving symptoms. Treatment methods include topical applications, periocular injections, intravitreal sustained drug delivery systems, intravitreal drug injections, and systemic therapies. His talk focused on new treatment options in the last three of those categories.

INTRAVITREAL SUSTAINED DRUG DELIVERY SYSTEMS

Dr. Jaffe explained that local drug delivery has disadvantages. Uveitis often has a course of many years, and patients may be required to self-administer a medication for the duration of the disease process. Appropriate levels of medication may be reached, but they may have limited duration and may produce unacceptable side effects.

Drug delivery systems can be tailored to particular diseases. When a sustained-release medication can be surgically implanted or injected, compliance becomes less of a risk factor. Delivery systems in use or in development include transscleral, suprachoroidal, intravitreal, and subretinal routes of delivery.

Uveitis specialists are already using some scleral-fixated and injected implants. In nonbiodegradable implants, a polymer surrounds the drug, and the drug is delivered through a port, allowing linear delivery. This permits sustained treatment potentially lasting years, but the devices are retained in the eye after the drug is depleted.

The fluocinolone acetonide intravitreal implant 0.59 mg (Retisert, Bausch + Lomb) is the nonbiodegradable implant retina specialists are probably most familiar with, Dr. Jaffe noted. Among biodegradable implants, the one clinicians are most familiar with is the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan), which is indicated for treatment of noninfectious uveitis, macular edema secondary to retinal vein occlusion, and diabetic macular edema (DME).

Dr. Jaffe then discussed his recent work evaluating the injectable fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences) in the treatment of uveitis. This implant is currently indicated for treatment of chronic DME.

Dr. Jaffe and colleagues performed an individual, investigator-sponsored clinical study, with randomization between low and high doses.[1] The investigators assessed the efficacy and safety of the fluocinolone acetonide 0.19 mg in treatment of uveitis over a 2-year period. This implant can be implanted in an in-clinic procedure, as compared to the larger fluocinolone implant, which requires surgical implantation. The formulation of the smaller implant is in a polyamide tube similar in design to the dexamethasone intravitreal implant. It is 3 mm in length and can be inserted through a 25-gauge modified needle injector, and it can release drug for up to 3 years.

Eleven eyes of 11 patients with chronic uveitis were enrolled. The main outcome measure was recurrence of inflammation, but visual acuity, inflammation, medication use, and retinal thickness on optical coherence tomography were also assessed. In the 1 year prior to implant placement, patients experienced 17 recurrences, but there were no recurrences in the 2 years after implantation. Among 10 patients who had bilateral uveitis, there were recurrences in six of the 10 fellow eyes, which had less disease at baseline.

The implant also reduced or eliminated the need for systemic therapy. Visual acuity improved from a mean of 20/70 at baseline to 20/30 at the 2-year endpoint, while visual acuity in the fellow eye was either unchanged or significantly worse. Complications included hypotony in two eyes despite aggressive therapy, initiation of new glaucoma drops in two patients, and

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Uveitis Update From ARDS

placement of a glaucoma drainage device in two patients.

This study demonstrated promise for use of the implant in patients with uveitis, Dr. Jaffe said. A press release from pSivida detailing 6-month data from the study indicated favorable results.[2]

INTRAVITREAL INJECTIONS

Dr. Jaffe discussed the use of intravitreal injection of sirolimus (also known as rapamycin; Rapamune, Pfizer) in the treatment of uveitis. Sirolimus is a macrolide antibiotic with a ring structure that acts as an inhibitor of the mammalian target of rapamycin (mTOR) and blocks T cell and B cell activation and antigen-presenting cells such as dendritic cells. A depot-forming formulation of sirolimus for intravitreal injection is being developed by Santen and is being evaluated in the phase 3 SAKURA studies for treatment of noninfectious uveitis of the posterior segment. The first SAKURA study has been completed,[3] and a second is ongoing. The completed trial evaluated three doses of sirolimus, with a primary endpoint of complete elimination of vitreous haze at 5 months follow-up. The intermediate dose (440 µg) group demonstrated the best result, with improvement in ocular inflammation and preservation of visual acuity. There was no difference in improved visual acuity in patients whose vision was 20/40 or better at entry, but the 440 µg group demonstrated better visual acuity improvement in patients with less than 20/120 vision at entry, Dr. Jaffe said.

SYSTEMIC THERAPIES

Some new systemic immunosuppressive therapies are close to regulatory approval. Typically, systemic medications are given to patients with panuveitis, intermediate or posterior uveitis, or very severe iridocyclitis.

Dr. Jaffe explained the conditions in which systemic immunosuppression might be used. For patients with anterior segment uveitis, it is often recommended due to difficulty controlling the intraocular pressure. Additional indications include the need for frequent periocular steroid injections, intolerance of periocular therapies, inadequate disease control, or severe visual consequences of recurrence.

The four main systemic drug classes for treatment of uveitis are alkylating agents, antimetabolites, calcineurin inhibitors, and biologic agents. At the time of the ARDS meeting, there were no approved immunomodulating agents other than steroids to treat uveitis, but there were many failed trials, Dr. Jaffe noted.

Voclosporin (Aurinia), a next-generation calcineurin inhibitor, and gevokizumab (Xoma), a biologic and an interleukin (IL)-1 inhibitor, were each evaluated for treatment of uveitis, but results were disappointing and neither is currently being further tested for that indication.

Tocilizumab (Actemra, Genentech) is an IL-6 inhibitor that is indicated for treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Dr. Jaffe said that he has used it successfully in a few patients with chronic cystoid macular edema. It has been tested in animal models as an intravitreal injection, but it is currently given as an intravenous medication in humans. Toxicities include infections and gastrointestinal disturbances. Since ARDS, promising results of the phase 2 SATURN study of an IL-6 inhibitor, sarilumab, given subcutaneously to treat posterior noninfectious uveitis have been reported at the 2016 meeting of the American Society of Retina Specialists and the Retina Society.

Tumor necrosis factor (TNF) inhibitors have shown promise, despite potential toxicities, Dr. Jaffe said. He warned that it is crucial to ensure that a demyelinating disease or tuberculosis is not present in any patient prior to administering a TNF inhibitor.

Dr. Jaffe then discussed adalimumab (Humira, AbbVie), which since the ARDS meeting has become the first biologic approved for uveitis. It was evaluated for treatment of active noninfectious uveitis in the VISUAL-1 study,[4,5] and it is being examined for inactive disease to prevent recurrence in the VISUAL-2 study. In VISUAL-1, it was used as a steroid-sparing agent, given with bursts of steroids. The primary endpoint was time to treatment failure, with treatment failure defined as a multicomponent endpoint that included development of new lesions, anterior chamber cells, vitreous haze, and visual acuity. The drug met its primary endpoint, and treatment never failed in many patients, Dr. Jaffe said. In all instances of treatment failure, the study drug had a greater effect than the control. The side effect profile in the trial was the same as when it is used to treat rheumatologic disease, he said.

There are a variety of new medications on the horizon for the treatment of uveitis, Dr. Jaffe said in conclusion. These new medications will increase and improve treatment options, lasting longer than current treatment options while also causing fewer side effects. ■

1. Jaffe GJ, Lin P, Keenan RT, et al. Injectable fluocinolone acetonide long-acting implant for noninfectious intermediate uveitis, posterior uveitis, and panuveitis: two-year results. *Ophthalmology*. 2016;123(9):1940-1948.
2. Topline Results from First Phase 3 Trial of pSivida's Medidur Presented at ASRS Annual Meeting [press release]. Watertown, Mass.: pSivida; August 15, 2016.
3. Nguyen QD, Merrill PT, Clark WL, et al; Sirolimus Study Assessing Double-Masked Uveitis Treatment (SAKURA) Study Group. Intravitreal sirolimus for noninfectious uveitis: a phase III sirolimus study assessing double-masked uveitis treatment (SAKURA). *Ophthalmology*. 2016;123(11):2413-2423.
4. Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in patients with active noninfectioius uveitis. *N Engl J Med*. 2016;375(10):932-943.
5. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10050):1183-1193. Erratum in: *Lancet*. 2016;388(10050):1160.

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The ARDS collaborates with Eyetube.net to create an online video database summarizing some of the most important talks from the ARDS meeting. Each year, Timothy G. Murray, MD, MBA, interviews the meeting's guest faculty about their presentations. Much like the articles presented in the Retina Today *print series covering the ARDS meeting, Dr. Murray's collection of interviews serves as an archive for the meeting proceedings. Here, we highlight a few of Dr. Murray's interviews. Access these particular videos by using the URLs below, and visit Eyetube.net to view the entire collection.*

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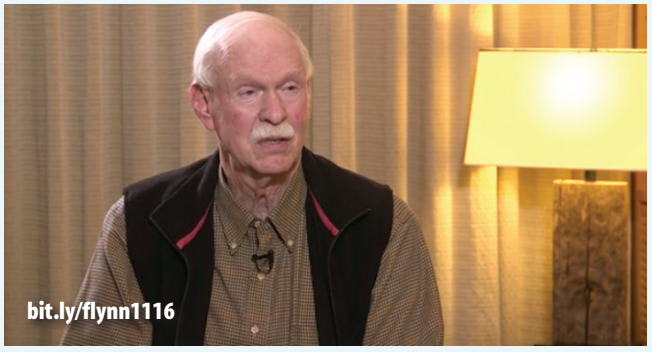
VMT Management: Watch and Wait



Tim Murray, MD, MBA, invites Harry W. Flynn Jr, MD, to summarize his presentation on vitreomacular traction (VMT) management. Dr. Flynn reviews a multicenter clinical trial of 230 eyes managed for at least 6 months, and discusses the positive consequences of observation in VMT patients.

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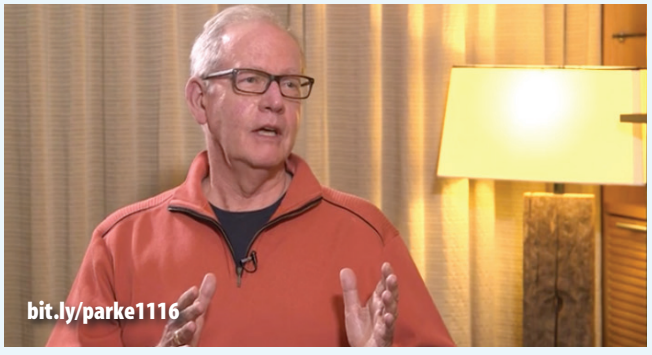
Update on Health Care Policy



David W. Parke II, MD, CEO of the American Academy of Ophthalmology, speaks with Tim Murray, MD, MBA, regarding recent changes to health care policy. Dr. Parke says that ophthalmologists will see more changes to physician payment in the next 5 years than they have in the past 50 years. He explains the direct effects these changes will have on specific procedures and provides insight into what physicians can expect in the future.

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Advances in Pediatric Vitreoretinal Surgery

Tim Murray, MD, MBA, sits down with R.V. Paul Chan, MD, to review advances in pediatric retina. Dr. Chan discusses how the marriage between old knowledge and new imaging devices allows retina surgeons to treat pediatric patients more carefully and thoroughly—two characteristics of treatment that are paramount to success in a vulnerable population.