Meeting Notes From the 43rd Annual Meeting of the ARDS

In this and the next three issues of Retina Today, *brief summaries of selected lectures from the 43rd Annual Meeting of the Aspen Retinal Detachment Society (ARDS) will be presented as a refresher for those who attended and as a service for those who were unable to attend. The goal of the ARDS meeting is to address professional practice gaps by offering activities to enhance competence in the fields of vitreoretinal diseases, surgery, and practice management.*

This installment of ARDS meeting coverage includes a synopsis of a presentation by Baruch D. Kuppermann, MD, PhD, who reviews the safety and efficacy of intraocular steroids. His talk could not come at a more timely moment, as regulatory approvals of steroid treatments have added steroids to retina specialists' treatment options for patients with retinal disease.

When we think of pharmacologic vitreolysis, we often imagine adult patients. After all, these are the patients in whom vitreomacular traction distorts vision. However, as a recap of a talk by Kimberly Drenser, MD, PhD, reminds us, pediatric patients can also benefit from pharmacologic vitreolysis. Employing such therapy before retinal detachment surgery may result in better outcomes for patients in whom successful surgery is integral to living a productive life.

The 44th Annual Meeting of the ARDS will take place from March 5 to March 9, 2016, in Snowmass, Colorado. More information about the meeting is located at aspenretina.com.

—Timothy G. Murray, MD, MBA

Ocular Steroids: A Review

Baruch D. Kuppermann, MD, PhD

In a review of steroid options for treating macular edema, Baruch D. Kuppermann, MD, PhD, noted that this mode of therapy has the capacity to affect multiple steps of the inflammatory process.

"Steroids have an ability to control components within the cascade of events that lead to macular edema, regardless of whether it is primary inflammation or VEGF-mediated inflammation," he said.

He noted that there is always a concern about side effects in patients treated with steroids, but that those side effects must be placed in the context of disease severity and the ability to correct the side effect. Cataract development and increased intraocular pressure (IOP) are two of the chief side effects that concern retina physicians, and associated rates of cataract surgery and IOP-lowering treatments should be considered before choosing a steroid to manage macular edema.

TRIAMCINOLONE ACETONIDE

Dr. Kuppermann, a professor, chief of the retina service, and vice chairman of clinical research at the Gavin Herbert Eye Institute at the University of

At a Glance

- Ophthalmic triamcinolone formulations have varying particle sizes, pharmacokinetics, and pharmacodynamics.
- Studies in animal models suggest that the triamcinolone formulation with the largest particle size has the longest duration and greatest influence on edema reduction.
- Cataract and elevated IOP occur after use of all sustained-release steroid devices, and each option offers unique advantages and disadvantages associated with its respective pharmacodynamic and pharmacokinetic profiles.

Video: Corticosteroid Implants

California, Irvine, outlined a history of ocular steroids, beginning with triamcinolone acetonide.

Dr. Kuppermann reviewed the results of two studies in which he participated that assessed the pharmacokinetics and pharmacodynamics of four ophthalmic formulations of triamcinolone acetonide: Trivaris (Allergan), Kenalog (Bristol-Myers Squibb), Triesence (Alcon), and a preservative-free formulation from Leiter's Compounding Pharmacy. In one study, researchers injected each of the formulations into vitrectomized rabbit eyes. In these models, Kenalog lasted the longest, followed by Triesence, Leiter's, and Trivaris.

In a second study, researchers injected VEGF-165 into rabbits to create a leporine model of diabetic retinopathy. Eyes were later injected with one of the triamcinolone formulations, and the degree of inflammation was graded after treatment. The Kenalog formulation resulted in the largest reduction in edema.

Dr. Kuppermann explained that Trivaris, an ophthalmic formulation of triamcinolone acetonide, was developed at the request of the National Institutes of Health. Trivaris concentrated 4.0 mg of drug in a 50-µL solution, compared with the usual concentration of 4.0 mg in a 100-µL solution. A high rate of cataract formation was found in patients treated with the drug: After 2 years of treatment, 55% of patients required cataract surgery. Pseudophakic patients injected with the drug had visual acuity results equal to patients treated with ranibizumab (Lucentis, Genentech). Elevated IOP levels, too, concerned many physicians. After 2 years of treatment with this triamcinolone formulation, approximately 40% of eyes had IOP elevation.

Dr. Kuppermann concluded this section of his talk by discussing the particle size of the formulations. Kenalog had the largest particle size (47 µm), followed by Triesence (26 µm), then Leiter's compounded triamcinolone acetonide and Trivaris (both 22 µm).

"It looks like the Kenalog formulation has a larger mean particle size, which may be the reason for the difference" seen in the rabbit models, he explained. "Not all triamcinolone acetonide formulations are the same."

SUSTAINED-RELEASE STEROID IMPLANTS

Dr. Kuppermann also discussed sustained-release steroid implants. He pointed out that the same side effects seen after bolus steroid injection are also commonly seen in patients receiving sustained-release steroid treatment, although at different rates. Cataract development, in particular, is ubiquitous. "I'm not here to try to argue between a 60% and 80% cataract rate," he said. "[The cataract rate across all steroid implants] is high."

Regarding elevated IOP levels, Dr. Kuppermann said close management of this side effect is a necessity to ensure safe patient outcomes. He also encouraged retina subspecialists to seek help elsewhere in the ophthalmic community for management of elevated IOP as necessary. He suggested involving "our glaucoma friends" to help manage elevated IOP, as "management could be tricky."

Dr. Kuppermann outlined the characteristics of each commercially available sustained-release steroid device, beginning with the first such device, the 0.59-mg fluocinolone acetonide implant (Retisert, Bausch + Lomb). Approved by the US Food and Drug Administration (FDA) for treatment of chronic noninfectious uveitis affecting the posterior segment of the eye, the implant has a high side effect profile, he said. High rates of elevated IOP resulted in approximately 40% of eyes in a pivotal clinical trial of the device undergoing incisional surgery. Still, Dr. Kuppermann noted, an implant, which lasts up to 2.5 years, is an effective method for treating patients with chronic uveitis.

The 0.19-mg fluocinolone acetonide implant (Iluvien, Alimera Sciences), indicated for treating diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and who did not have a clinically significant rise in IOP, was approved by the FDA in September 2014. The implant, which is smaller than a grain of rice, is nonbiodegradable. After the 3-year period over which it releases therapy, he said although there is "an empty husk sitting in the inferior vitreous space," the used device "doesn't seem to cause any harm."

The device releases 0.25 µg of drug per day during its initial phase and eventually maintains a release rate of between 0.1 µg and 0.2 µg per day over 3 years. In the FAME trial, which evaluated the safety and efficacy of the 0.19-mg fluocinolone acetonide implant in patients with persistent DME, 28% of patients gained 3 or more lines of visual acuity at 36 months, Dr. Kuppermann said. Additionally, roughly 25% of patients in a study evaluating

the 0.19-mg fluocinolone acetonide implant in patients with nonchronic DME had gains of 3 lines or more.

Approximately 5% of patients receiving the device in the FAME trials required incisional surgery to lower IOP. That rate is high, Dr. Kuppermann admitted, but it is an improvement from the 40% seen in patients using the 0.59-mg implant. Approximately 40% of patients had elevated IOP levels, and 38% of them required IOP-lowering medications.

The dexamethasone intravitreal implant (Ozurdex, Allergan) is approved by the FDA for the treatment of macular edema following branch or central retinal vein occlusion, noninfectious posterior uveitis, and DME. This implant, like the 0.59-mg fluocinolone acetonide implant, is biodegradable. Dr. Kuppermann explained that the release rate of the drug has a three-phase process. The first phase lasts about 2 months, during which bulk erosion of the drug results in high exposure to the therapeutic agent. During the second phase of 4 to 8 weeks, surface area is reduced, and the patient is exposed to moderate levels of the therapeutic agent. In the third phase, the patient is exposed to subtherapeutic levels. Still, he noted, some patients respond to below-average levels of pharmacologic exposure (likely due to an interruption in the inflammatory cascade), whereas other patients require retreatment around the 4-month point due to low response to subtherapeutic drug levels.

Dr. Kuppermann noted that some diseases respond better to low levels of dexamethasone exposure. "In the uveitis trial [for the dexamethasone implant], they found an effect out to 6 months," he said. "That's because, in a primary inflammation-mediated disease, even a little bit of dexamethasone can control things." But in more a complex inflammation cascade, such as inflammation associated with DME, he advised "having more steroid on board."

In a study examining the efficacy of the dexamethasone intravitreal implant in patients with DME, 22% of patients gained 3 or more lines of vision. Although this was less than the 28% rate of 3-line gainers seen in the study of the 19-mg fluocinolone acetonide implant in patients with DME, Dr. Kuppermann cautioned against placing too much emphasis on the difference. "It is only one study," he reminded attendees.

One benefit to the dexamethasone implant, according to Dr. Kuppermann, concerns safety. Although the rates of cataract (60%) and need for IOP-lowering medication (40%) seen in pivotal studies were higher than expected, patients benefited from the drug's quick turnover rate. "Of the three steroids…, this is the easiest one to manage because of the pharmacokinetics of the drug," he said. "The eyes taper themselves off, and you do not need to keep patients on IOP-lowering medications for long."

Ocriplasmin in Pediatric Patients

Kimberly Drenser, MD, PhD

Kimberly Drenser, MD, PhD, delivered a talk on pharmacologic vitreolysis in pediatric patients. Her presentation discussed use of presurgical ocriplasmin (Jetrea, ThromboGenics) in pediatric patients undergoing repair for retinal detachments and retinoschisis.

Dr. Drenser, the director of ophthalmic research at the Beaumont Eye Institute in Royal Oak, Michigan, began her presentation with a number of warnings vis-à-vis pediatric surgery. Throughout the presentation, she repeated a mantra—"Children are not little adults"—that stressed the complexity of pediatric surgery, reminding retina specialists that pediatric patients are at increased risk for redetachment and proliferative vitreoretinopathy (PVR) after surgery. She also discussed tamponade considerations, which are important, given that positioning regimens can be a challenge with pediatric patients.

Dr. Drenser made clear that the goals of surgery are different in pediatric and adult patients. "The goal [in children] is not to have the cleanest, prettiest-looking eye at the end of surgery," she said. "The goal is to address the pathology." The presence of postsurgical subretinal fluid in a pediatric patient, for example, should not concern the surgeon as much as it would in an adult patient. Subretinal fluid frequently resorbs, she said, and surgeons should be more concerned about relieving tractional forces and repairing ocular structures than about making an ideal postsurgical eye.

Inducement of posterior vitreous detachment (PVD) via ocriplasmin injection can be a useful adjunct to surgery, Dr. Drenser said. She discussed tractional retinal detachments (TRDs), which can arise as complications in diseases such as retinopathy of prematurity (ROP), Coats disease, and familial exudative vitreoretinopathy. Surgery in these eyes requires examination under anesthesia, Dr. Drenser noted, because unrecognized congenital pathology is often present. Warning parents of patients with TRDs that further procedures may be necessary

At a Glance

- Pediatric patients may benefit from presurgical pharmacologic vitreolysis.
- The goals of pediatric eye surgeries are often different from those of adult eye surgeries.
- Even if a surgeon uses presurgical pharmacologic vitreolysis, follow-up surgery to maintain structural integrity may be required.

Video: Pharmacologic Vitreolysis

during surgery prepares them for the possibility that the surgeon may employ prophylactic laser or some other measure in the eye.

Retina surgeons may feel comfortable addressing rhegmatogenous retinal detachments (RRDs) in children because these surgical cases often resemble those a surgeon might see in an adult. Despite the surgery's straightforward nature, Dr. Drenser warned, 20% to 30% of patients require a second or third surgery for ultimate structural success, and many have a high risk of developing postsurgical PVR. She advised employing a "belt and suspenders" approach to repairs for RRDs: that is, vitrectomy followed by scleral buckling.

Dr. Drenser said that incomplete hyaloid dissociation is a common cause for surgical failure in pediatric patients, frequently resulting in the patient returning for further surgery. She presented a series of cases involving RRD or TRD in which pharmacologic vitreolysis resulted in safe, successful surgery.

Dr. Drenser first discussed an 8-year-old patient with an RRD. (The case was from approximately 20 years ago, and the agent used for pharmacologic vitreolysis was autologous plasmin injection.) Nineteen hours after injection, surgeons observed a partial PVD, liquefied vitreous, and a loosened junction of the hyaloid to the posterior cortex. The surgeon in this case employed cryotherapy to the break and, after application of a scleral buckle, used a gas bubble as tamponade.

The second case Dr. Drenser presented concerned a pediatric patient with an avascular retina with a ridge of tissue due to an inherited dysgenic disorder. The patient presented with a peripheral superior break. Surgeons induced vitreolysis in the patient and 30 minutes later, they observed a partial PVD. Surgeons treated the break with cryotherapy and a gas bubble tamponade; they left subretinal fluid in the eye, which had resorbed by 1 month postoperative.

Dr. Drenser also presented two cases in which retina surgeons used pharmacologic vitreolysis before TRD repair. In one case, Dr. Drenser used optical coherence tomography images to demonstrate the difficulty of finding a single operable plane during surgery due to the complex layering of tissue secondary to familiar exudative vitreoretinopathy. The use of an enzymatic vitreolytic agent loosened the hyaloid junction and allowed the surgeon to identify a plane for dissection.

In a final case, Dr. Drenser presented the details of a patient with stage 5 ROP. Initially the patient was treated with an anti-VEGF agent, but the patient eventually had significant dragging of the posterior pole and severe peripheral tension. After ocriplasmin-assisted vitrectomy, the patient showed improved structure and stable vision despite the presence of a macular scar.

Dr. Drenser discussed the use of pharmacologic vitreolysis in patients undergoing surgery for retinoschisis. These patients, she explained, may have tight vitreoretinal junctions. Surgery for retinoschisis has a low success rate, and removal of the hyaloid during surgery can result in extended schisis. During these surgeries, Dr. Drenser said, the surgeon must avoid extending the schisis during PVD induction, especially if the schisis cavity is near the macula.

Injecting ocriplasmin before surgery for retinoschisis may loosen the junction over the schisis cavity in some patients, allowing the surgeon to remove the hyaloid and avoid performing an inner wall retinectomy. If the surgeon is able to remove the hyaloid, the fluid in the retina (which, Dr. Drenser said, "is surprisingly aqueous") should be removed with a 42-gauge needle. In these cases, a long-term tamponade is integral to maintaining a successful structure.

Dr. Drenser detailed the structure and inclusion/exclusion criteria for the Microplasmin in Children, or MIC, trial (NCT00986362). This phase 2 randomized trial enrolled 22 pediatric patients (24 eyes) scheduled for vitrectomy; surgeons were masked as to which patients received treatment and placebo. Patients were excluded if they had stage 1, 2, 3, or 5 ROP; cataract; or dense vitreous hemorrhage. Patients were injected with ocriplasmin 30 minutes before surgery. Surgeons in the trial were asked to rate on a scale of 1 to 4 the quality of the vitreous; a higher score indicated a more aqueous consistency. The results are awaiting publication.

Dr. Drenser pointed to reduced retinal trauma and increased plane visibility during such surgeries as indications that ocriplasmin can serve as a useful tool for surgeons in selected pediatric cases. Still, she reminded the audience that pharmacologic vitreolysis itself is not a substitute for surgery for TRD, RRD, or retinoschisis. "[Ocriplasmin] is really a surgical adjunct," she said. "It's not a slam dunk." ■