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New and Emerging Treatment Paradigms for Macular Edema in Retinal Vein Occlusion and Diabetic Retinopathy

A ROUNDTABLE DISCUSSION FEATURING:

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TARGET AUDIENCE

This activity is designed for retina specialists and other ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

1. Understand the types of macular edema and their corresponding treatments
2. Apply current therapies and practices for treating macular edema
3. Understand the relative utility of laser, steroid and anti-VEGF therapies for treating macular edema
4. Understand the efficacy and side effects of steroid preparations in retinal disease
5. Understand the use of implantable drug delivery systems for treating macular edema
6. Implement current and future strategies (both short- and long-term) for macular edema

METHOD OF INSTRUCTION

Participants should read the continuing medical education (CME) activity in its entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions, and the course evaluation. To answer these questions online and receive real-time results, please visit http://www.dulaneyfoundation.org and click "Online Courses." Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1.5 *AMA PRA Category 1 Credits*.™ The estimated time to complete this activity is 1 hour.

ACCREDITATION AND DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dulaney Foundation and *Retina Today.* The Dulaney Foundation is accredited by the ACCME to provide continuing education for physicians. The Dulaney Foundation designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

CONTENT VALIDATION

In compliance with ACCME standards for commercial support and the Dulaney Foundation's policy and procedure for resolving conflicts of interest, this CME activity was peer reviewed for clinical content validity to ensure the activity's materials are fair, balanced, and free of bias; the activity materials represent a standard of practice within the medical profession; and any studies cited in the materials upon which recommendations are based are scientifically objective and conform to research principles generally accepted by the scientific community.

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DISCLOSURE

In accordance with the disclosure policies of the Dulaney Foundation and to conform with ACCME and FDA guidelines, anyone in a position to affect the content of a CME activity is required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services; and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Dr. Boyer has received grant/research support from Alcon, Allergan, Genentech and Novartis. He is a consultant and speaker for Alcon Laboratories, Inc., Genentech, Inc., Novartis, and Pfizer, Inc.

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Dr. Singer states that he is on the speaker's bureau for Allergan, Inc. and Neovista, Inc.

All of those involved in the planning, editing, and peer review of this educational activity have indicated that they have no financial relationships to disclose.

STATEMENT OF NEED

Given the current and predicted impact of poor health in our aging society,[1-8] a significant burden exists for physicians to remain aware of current and emerging clinical science that impacts their patients. One area of recent and continued interest in the field of ophthalmology is the development of new treatment strategies for retinal vein occlusion (RVO) and diabetic macular edema (DME).[9-11]

RVO and DME are common ocular diseases that remain poorly understood due to the multifactorial nature of the presentation and contributing systemic factors. Several associated systemic factors have been identified and continue to be studied for their impact on RVO, including hypertension, diabetes, hypercholesterolemia, thyroid disorder, and ischemic heart disease. Increased intraocular pressure and axial length are other factors that play roles in this disease.[12]

Common current methods of clinical treatment for RVO and DME include laser photocoagulation and corticosteroid injections that may not provide optimal impact on patient visual recovery following an occlusive event with subsequent macular edema.[13-15] The short and long-term visual acuity outcomes of patients undergoing these treatments continue to be discussed in relation to potential new treatment methods aimed at enhanced retinal perfusion and sustainable improvements in visual acuity.

Additionally, new treatment strategies are under study and there is emerging clinical evidence that practicing retinal specialists must consider in the management of macular edema in these patients. The use of combination treatments involving laser photocoagulation, intraocular steroid injections, and therapeutics targeting vascular endothelial growth factor (VEGF) continues to be a topic of great importance among retinal specialists. As the range of available therapeutics in this area evolves, treatment patterns and timing of therapeutic intervention must be addressed by experts in the field in order to best determine effective methods of patient management.[14,15]

Increasingly, corticosteroids have been employed to treat macular edema. Recently, intravitreal injection of triamcinolone acetonide has become a popular treatment. Subsequently, corticosteroid-based intravitreal implants have been developed to provide sustained release of drug and make repeated intravitreal injections unnecessary.

Drug delivery via intravitreal implant is not a novel concept. The first intravitreal implant used a pars plana approach to deliver ganciclovir for the treatment of cytomegalovirus (CMV) retinitis. The implant provided sustained therapeutic drug levels for up to 6 to 8 months; over 10,000 implants have been implanted.

Recently, the dexamethasone biodegradable implant (Ozurdex; Allergan, Inc., Irvine, CA) was approved by the US Food and Drug Administration for treatment of macular edema secondary to branch retinal vein occlusion (BRVO) and central retina vein occlusion (CRVO). This device is also under development for DME. The other device that is currently in development for RVO and DME is the injectable fluocinolone acetonide–based device (Iluvien; Alimera Sciences, Alpharetta, GA).

Inhibition of inflammation with corticosteroids and inhibition of VEGF have become topics of interest in recent years in the treatment of age-related macular degeneration (AMD). The permeability and proliferative properties of VEGF, and the consequences of its inhibition, also suggest a role for this approach in the management of DME.

Blockade of many if not all involved growth factors will likely be necessary to suppress all of the detrimental effects of ischemia, but even isolated blockade of VEGF may have beneficial effects on RVO and DME. VEGF increases vascular permeability by relaxing endothelial cell junctions, which increases permeability and leakage. Inhibition of VEGF blocks this effect to some extent, as demonstrated in several recent clinical trials and case series employing the anti-VEGF molecules pegaptanib sodium (Macugen, OSI/Eyetech), ranibizumab (Lucentis, Genentech), and bevacizumab (Avastin, Genentech).

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New and Emerging Treatment Paradigms for Macular Edema in Retinal Vein Occlusion and Diabetic Retinopathy

Scott W. Cousins, MD: Retinal vein occlusion (RVO) can cause significant visual loss[1] in our patients and historically, we have had limited treatment options available to us.

In June of 2009, the US Food and Drug Administration (FDA) granted approval to the sustained-release dexamethasone device (Ozurdex; Allergan, Inc., Irvine, CA) for the treatment of macular edema secondary to RVO. This is the first drug device that has been approved for vein occlusions and provides an alternative to observation and laser photocoagulation for branch vein retinal occlusion (BRVO) and central retinal vein occlusion (CRVO).

The standard of care for diabetic macular edema (DME) continues to be laser photocoagulation and the recent study showing grid/focal laser to be superior intravitreal triamcinolone acetonide over 2- and 3-year follow-up supports this.[2,3] Some of our patients, however, do not respond to laser and so we continue to seek alternative treatments.

What is the history of our treatment of these diseases and what are your current treatment strategies?

Pravin U. Dugel, MD: The standard of care for BRVO follows the guidelines from the Branch Vein Occlusion Study (BVOS):[4-6] either grid or central scatter laser photo-

PANEL

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coagulation, depending on whether the patient's vision is 20/40 or lower after 3 months (grid) or more than 5 disc diameters of ischemia (central scatter). Finkelstein[7] sub-analyzed two groups of patients and found that patients with ischemic edema had more frequent spontaneous resolution and improved visual acuity.

For CRVO, we continue to follow the guidelines set forth by the Central Vein Occlusion Study (CVOS),[8-12] which are basically to observe for spontaneous resolution and if the patient does not improve, apply laser after a period of time.

There are a number of patients, however, in whom we cannot perform laser photocoagulation due to hemorrhage. In the past, we would have to wait until the hemorrhaging cleared and in that time, the patient's vision would deteriorate. Recently, however, the off-label use of steroids or antivascular endothelial growth factor (anti-VEGF) agents for earlier treatment in these patients has been more common.

For DME, I will usually use laser first, but I will use steroids for patients who are not responding to laser.

Jeffrey S. Heier, MD: Years ago, when we began looking at surgical interventions for RVO, we viewed patients with diffuse edema and visual acuity worse than 20/200 unlikely to ever recover. Subramanian, et al[13] from our group in Boston published a review showing that patients with preoperative visual acuities worse than 20/200 could respond positively to laser treatment, as well as experience spontaneous resolution.

David S. Boyer, MD: Laser certainly continues to be the gold standard for BRVO, but we can now be more aggressive with steroids or anti-VEGF agents to treat hemorrhaging.

Michael A. Singer, MD: Because we now have a variety of modalities at our disposal, we can mix and match, depending on the clinical course of the patient. For example, we might choose to inject a steroid first and then use laser.

I use pharmacologic agents more frequently in CRVO than laser, mostly because the results of the CVOS showed no significant benefit to laser treatment.

Dr. Dugel: I personally think that steroids are more effective than anti-VEGF in CRVO. Because of potential safety issues with intravitreal steroids, however, in the past I started with an anti-VEGF agent and then, if the patient failed to respond to the anti-VEGF therapy, I would not hesitate to begin steroids. Now that we have a sustained-release dexamethasone device available, however, I no longer have to worry about the side effects of the intravitreal steroid injection.

Dr. Cousins: What imaging methods do you employ for RVO?

Miguel A. Busquets, MD, FACS: I find that fluorescein angiography (FA) is essential in determining which patients will benefit from what type of pharmacotherapy. For example, if I see that a patient has significant capillary dropout and ischemia, he or she might have a greater benefit from an anti-VEGF agent vs a steroid.

Dr. Boyer: I use both FA and optical coherence tomography (OCT). If I have it available, I will also do a wide-field angiogram as well. I agree that patients with a large amount of capillary dropout will respond better to anti-VEGF agent, but I have also found that they also respond very well to selective laser of the ischemic areas.

Dr. Heier: We recently started performing more wide-field angiography (Heidelberg Engineering, Heidelberg, Germany) with the Stuarenghi lens. I think it is particularly important to get a wide-view image for patients who have not responded well to laser or injections. It is common to see significant amounts of peripheral nonperfusion in these patients.

Dr. Cousins: It is clear that the standard of care will most likely evolve from studies that were performed approximately 20 years ago showing that laser was the only effective treatment to pharmacological agents.

APPLYING THE DRCR.NET STUDY DATA

Dr. Cousins: Since the publication of the 2- and 3-year data from the Diabetic Retinopathy Clinical Research Network (DRCR.net),[2,3] there has been much discussion regarding the efficacy of steroids for DME and RVO. The study authors concluded that further study on steroids as an alternative to laser are not warranted, however, the recent approval of the sustained-release dexamethasone implant would suggest that steroids still hold value for patients with macular edema.

Dr. Dugel: The DRCR.net study was certainly important; however, every study has its flaws. We learned from this study that laser is effective for treating DME but I did not interpret this study to mean that steroids are not effective and it did not change the way that I practice. From both the 2- and 3-year data, it appears that at 4 months, patients receiving 1 mg and 4 mg of triamcinolone acetonide did better than laser, but starting at

month 16, there was a statistically significant advantage from laser vs steroids. The improved outcomes with laser holds to month 36 in their data. There are several factors, however, that influence the way that I view these results.

First, I am not sure that I would use steroids in the same manner as in this study. Most often, I am using steroids in my patients who have failed to respond to laser photocoagulation. Second, the formulation that was used in the DRCR.net study was a hydrogel triamcinolone acetonide formulation (Trivaris, Allergan, Inc.), which may or may not have different pharmacokinetics than the triamcinolone acetonide (Kenalog, Bristol-Myers Squibb) that is most commonly used. Third, in the study, patients were eligible for triamcinolone injections every 4 months. The mean frequency of injections was 2.3 injections of the 1 mg dose, and 2.1 of the 4 mg dose in year 1. In year two, the frequency was 3.5 injections of the 1 mg dose and 3.1 injections of the 4 mg dose, so patients got an average of 1 injection in the second year. In my opinion, the patients in this study were severely undertreated. Pharmacokinetics data show that measurable concentrations of triamcinolone acetonide are only present for 3 to 4 months after intravitreal injection in eyes that have not been vitrectomized.[14,15] Based on these data, one would certainly assume that there will be no detectable concentration at 1 year.

Dr. Boyer: The DRCR.net was an excellent study, but as Dr. Dugel points out, the way it was designed is not necessarily how we treat our patients in day-to-day practice. Another example I would add is that in order to be eligible for the study, the investigator had to have evidence that laser photocoagulation would be beneficial to patients. As Dr. Dugel stated, we often are using steroids for patients who do not respond to laser.

Dr. Heier: I agree that this study did not show that steroids are ineffective. It did, however, show that laser continues to be the standard of care for DME.

Dr. Cousins: So how do you make a decision about whether to laser, use a steroid, or an anti-VEGF agent in DME?

Dr. Singer: With DME, I will always start with laser first, assuming there is good perfusion. If the macular edema

SIX-MONTH RESULTS FROM THE SUSTAINED-DELIVERY DEXAMETHASONE DEVICE PHASE 3 TRIAL

A sustained-delivery intravitreal 0.7-mg dexamethasone implant (Ozurdex, Allergan, Inc.) was well-tolerated and significantly improved vision in patients treated early compared with sham, according to data from identical multicenter, double-masked, randomized, parallel phase 3 trials presented by Julia Haller, MD, at the Retina Congress.[1]

The dexamethasone implant received US Food and Drug Administration approval in June for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). The dexamethasone implant is a biodegradable implant administered by intravitreal injection that delivers dexamethasone to the vitreous cavity via a solid polymer delivery system, which enables extended release and sustained effects of dexamethasone.

Patients were randomly assigned to receive either a single treatment with dexamethasone 0.7 mg or sham injection. About two-thirds of patients had BRVO and one-third patients had CRVO, with duration of disease over 3 months for approximately 85% of patients and greater than 6 months for 30%.

Pooled data showed that more patients in the dexamethasone group gained three lines of vision significantly faster compared with sham, with 20% to 30% of dexamethasone -treated patients (n=427) gaining three lines within 1 to 2 months compared with 7% to 12% of sham-treated patients (n=426).

Improvement peaked at day 60, with 29.3% of patients in the dexamethasone group gaining three or more lines compared with 11.3% of patients in the sham group ($P<.001$). A significant difference was seen between the Ozurdex and sham groups through day 90 ($P<.001$). Relative to duration of disease and treatment response, 42% of patients with BRVO for 90 days or less achieved a three-line improvement in visual acuity by day 60, which is more than 50% better than patients who had more chronic disease.

By day 180, 0.2% of patients treated with dexamethasone had an intraocular pressure of 35 mm Hg or greater and 1.2% of patients had an intraocular pressure of 25 mm Hg or greater. In the dexamethasone group (n=421), 29.7% of patients received medication for intraocular pressure at day 90, and 0.7% of patients required surgery.

1. Haller JA. 6-month randomized controlled clinical trial of an intravitreal dexamethasone implant in macular edema associated with retinal vein occlusion. Paper presented at: Retina Congress 2009; October 4, 2009; New York, NY.

does not resolve, I will initiate pharmacotherapy. For refractory macular edema, I have a completely different strategy.

Dr. Heier: I agree. For refractory cases, I try to get rid of the edema with pharmacotherapy and then apply a lighter laser pattern over areas of previous laser. Bandello et al[16] recently evaluated posterior juxtascleral infusion of modified triamcinolone acetonide in 22 eyes for refractory DME and the improvements in central macular thickness were significant. It will be interesting to see data from larger clinical studies.

DATA ON PHARMACOTHERAPY FOR RVO AND DME

Dr. Cousins: Let's discuss the rationale for pharmacotherapy in RVO and DME.

Dr. Boyer: I think we can safely say that, prior to the availability of the sustained-release dexamethasone device and our off-label use of pharmacotherapy, we had no effective treatments for CRVO. The CVOS study showed no impressive improvement with laser and steroids and anti-VEGF agents both seem to work well.

Dr. Heier: In the clinical studies for the sustained-release dexamethasone device, patients with BRVO and CRVO achieved equal to or better than 15 letters of vision in a significantly shorter period of time than sham ($P<.01$).[17]

Genentech, Inc. (South San Francisco, CA) released top-line data[18] in July 2009 for the BRAVO (A phase 3, multicenter, randomized, sham injection-controlled study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema secondary to BRVO) and CRUISE (A phase 3, multicenter, randomized, sham injection-controlled study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema secondary to CRVO) studies. Both studies randomized patients to receive monthly injections of either 0.3 mg or 0.5 mg ranibizumab (Lucentis) or sham for 6 months. A 6-month observation period followed, during which time patients could receive injections as needed. BRAVO allowed rescue therapy with laser at 9, 10, and 11 months. The data that have been released show that at 6 months, best-corrected visual acuity was improved in the treatment groups over sham for both studies, with an early and sustained response seen with ranibizumab treatment in CRUISE.

Earlier this month, the complete 12-month results from the SCORE (Standard Care vs Corticosteroid for Retina Vein Occlusion) study were published in the *Archives of Ophthalmology*. The 1-year analysis of overall vision improvement revealed that 29% of patients who were assigned to standard of care (grid laser photocoagulation unless hemorrhaging is present, in which case the patient would be observed until laser could be performed) had improvement, 26% of the 1-mg triamcinolone acetonide group had some improvement, and 27% of patients in the 4-mg group.[19] The study authors concluded that the standard of care remains the best option for RVO.

"Prior to the availability of the sustained-release dexamethasone device and our off-label use of pharmacotherapy, we had no effective treatments for CRVO."

-DAVID S. BOYER, MD

In a second report, however, it was noted that 1 mg triamcinolone may be worth considering instead of observation and natural history when laser cannot be used. At 1 year, significant visual acuity improvement was seen in 7% in the observation group, 27% in the 1-mg triamcinolone acetonide group, and 26% in the 4-mg triamcinolone acetonide group.[20] Those who were treated received injections every 4 months for 1 year, unless there was reason not to treat. The patients in the 4 mg group had a higher rate of cataracts and intraocular pressure spikes (IOP), but the side effect profiles for the observation group and the 1-mg group were similar.[20]

The 3- and 6-month data for the sustained-delivery fluocinolone device (Iluvien; Alpheretta, GA) were presented at the Association for Research in Vision and Ophthalmology Annual Meeting this past May. The 6-month results showed a mean improvement in visual acuity from baseline in the 0.2-µg/day group of 2.7 letters, ±2.5; in the 0.5-µg/day group the improvement was 6.9 letters, ±3.1. Center subfield thickness at 6 months was reduced by 87 µm (±22.1) in the 0.2-µg group and by 179 µm (±50.7) in the 0.5-µg group.[21]

COMPARING CORTICOSTEROIDS FOR OCULAR USE

Dr. Cousins: What are the distinctions between the different triamcinolone acetonide preparations, dexamethasone, and fluocinolone in terms of solubility and strength?

Dr. Dugel: Triamcinolone acetonide is insoluble and

thus serves as its own drug depot. Dexamethasone is more potent than triamcinolone acetonide, but because it is highly soluble, it has a short half-life—approximately 3 hours after injection.[22] Fluocinolone has a similar potency and solubility profile as triamcinolone.

The actual real-life potency of these steroids, however, is hard to compare. For example, if you look at the studies by Kuppermann et al,[23,24] dexamethasone is potent, but it is hard to quantify the potency based on solubility and receptor binding. In my opinion, the

"In the phase 2 study for the dexamethasone-sustained delivery device, there was a relatively lower incidence of pressure spikes than with injected triamcinolone."

-SCOTT W. COUSINS, MD

12-MONTH RESULTS FROM THE SCORE CRVO AND BRVO TRIALS

The SCORE Study, sponsored by the National Eye Institute (NEI), consists of two multicenter, randomized, phase 3 clinical trials comparing the safety and efficacy of standard care with preservative-free intravitreal triamcinolone acetonide (IVTA) in either a 1-mg or a 4-mg dose for vision loss associated with macular edema secondary to CRVO or BRVO. The primary objective of the study is to compare visual acuity outcomes among those who are randomly assigned to receive standard care and those randomly assigned to receive one of two doses of IVTA for treatment of macular edema secondary to CRVO or BRVO.

In the SCORE-CRVO trial,1 intravitreal triamcinolone was superior to observation for treating vision loss associated with macular edema secondary to central retinal vein occlusion (CRVO).[1] The data, presented by Michael S. Ip, MD, revealed that the 1-mg dose of intravitreal triamcinolone has a safety profile superior to that of the 4-mg dose.

The randomized clinical trial included 271 participants with macular edema from CRVO. Of these, 92 individuals were assigned to receive 1 mg of intravitreal triamcinolone, 91 received 4 mg of intravitreal triamcinolone, and 88 were assigned to an observation group. Participants were evaluated every 4 months for 12 months, and those in the triamcinolone groups received additional injections at each follow-up visit unless there was a specific reason not to re-treat them.

Seven percent of patients in the observation group, 27% in the 1-mg group, and 26% in the 4-mg group achieved a gain in visual acuity letter score of 15 or more from baseline to month 12. Patients who received the 1-mg dose were five times more likely to achieve improved vision than the observation group (P=.001). Patients in the 4-mg group were also five times more likely to achieve the primary outcome than the observation group (P=.001). A difference between the 1- and 4-mg groups (P=.97) was not observed; however, the rates of elevated intraocular pressure and cataract were higher in the 4-mg group compared with the 1-mg and observation groups.

The SCORE-BRVO trial[2] compared the safety and efficacy of IVTA with standard care (grid photocoagulation in eyes without dense macular hemorrhage, or deferral of grid photocoagulation until hemorrhage clears in eyes with dense macular hemorrhage) in 411 patients with macular edema secondary to branch retinal vein occlusion (BRVO).[2] Patients received standard care (n=137), a 1-mg dose of intravitreal triamcinolone (n=136), or a 4-mg dose (n=138). Participants were evaluated and re-treated as indicated every 4 months for 12 months.

Results of the study, presented by Ingrid U. Scott, MD, MPH, showed that 29% of participants in the standard care group, 26% in the 1-mg group, and 27% in the 4-mg group achieved the primary outcome of a gain in visual acuity letter score of 15 or more gain from baseline to 12 months. All three groups had an approximate gain of four to six letters in mean visual acuity from baseline to month 12. After month 12, the mean change from baseline in visual acuity score was greater in the standard care group than the triamcinolone groups. Additionally, all three groups showed a decrease in mean OCT-measured center point thickness from baseline throughout follow-up. After month 12, and through the 36-month follow-up, the center point thickness was lowest in the standard care group. At 12 months, the rate of cataract onset or progression, and the rate of initiation of medications to lower intraocular pressure, were significantly lower in the standard care group compared to the triamcinolone groups. One case of endophthalmitis occurred in the 4-mg group.

1. Ip MS. The SCORE Study CRVO Trial: A randomized trial to compare the efficacy and safety of intravitreal triamcinolone with standard care to treat CRVO. Paper presented at: Retina Congress 2009; October 4, 2009; New York, NY.
2. Scott IU. The SCORE Study BRVO Trial: A randomized trial to compare the efficacy and safety of intravitreal triamcinolone with standard care to treat BRVO. Paper presented at: Retina Congress 2009; October 4, 2009; New York, NY.

potency issue will be less relevant than the pharmacokinetic profile of these drugs. For example, if a steroid will bind to a receptor in a cytoplasm and bind to the nucleus, it will profoundly change gene expression in a broad manner. The amount necessary to reach complete saturation of the receptor is approximately 100 nM. With 4 mg of triamcinolone acetonide the concentration is 7.5 mM, approximately 10,000 times greater than necessary for saturation. One could argue that more is not better; in fact, a higher concentration may actually down-regulate the receptor, making the drug less effective. Thus, the delivery may be more important to a drug's mechanism and ultimate potency. The disease processes that we are seeking to address with steroids are so complex and so different that I think eventually our goal will be to pinpoint a particular disease and how the steroid and its delivery targets a particular stage of that disease, rather than differences in the potency of the steroids themselves.

Dr. Heier: I am not sure there is that much of a difference in the triamcinolone profiles because their suspensions are the same. Currently in phase 1 study, Nova63035 (Novagali Pharma; http://clinicaltrials.gov/ct2/show/NCT00665106), uses a different type of suspension and delivery system, so the drug diffuses slowly over a period of time.

There are data to show that the location of where the steroid is delivered has an effect on both efficacy and incidence of side effects,[25] suggesting that a more posterior location of delivery may be beneficial.

MANAGING IOP INCREASES

Dr. Cousins: Does the chemistry of a steroid have an effect on the associated complications?

In the phase 2 study for the dexamethasone sustained delivery device, there was a relatively lower incidence of pressure spikes than with injected triamcinolone.[15,16]

Dr. Boyer: I think the difference is the lower dose that is delivered over a 6-month period. The sustained-release dexamethasone device and the sustained-delivery fluocinolone device deliver a lower dose of steroid over a longer period of time than a free injection of steroid.

Dr. Heier: The two main complications with the sustained-release dexamethasone device are cataract and IOP increase.[23,24] In the DRCR.net study comparing triamcinolone acetonide with laser photocoagulation for diabetic macular edema (DME), there was a dose-dependent elevation in IOP.[2] In that study, the IOP was raised by approximately 16% in the 1-mg group and 33% in the 4-mg group. Twenty-three percent of phakic patients in the 1-mg group developed cataracts that required surgery vs 51% in the 4-mg group.

In my opinion, the cataract side effect is not as troubling as glaucoma. In many cases, these patients have visually debilitating RVO disease that is not responsive to laser or anti-VEGF agents. Having cataract surgery is an acceptable consequence of treating the disease. The pressure rises are more serious, but if they can be controlled with topical glaucoma medications, the trade off may be more manageable.

Dr. Dugel: In the 3-year follow-up in Protocol B of the DRCR.net study the cataract side effect figures are even more dramatic: 83% in the 4-mg group that require cataract surgery, 46% in the 1-mg group, and 31% in the laser group.[3]

Dr. Boyer: In some patients, the IOP effect can be short-lived with the effect of the steroid wearing off.

"The delivery may be more important to a drug's mechanism [than concentration] and ultimate potency."

-PRAVIN U. DUGEL, MD

Dr. Singer: I agree. If we have pressure spikes that we can control with medicines, we may be able to ride it out. When the pressure increase is severe, it presents more of a problem.

Dr. Busquets: In all cases of IOP spikes with steroid treatment, I think it is important to co-manage with a glaucoma specialist. Many patients can tolerate a pressure rise of 5 mm Hg, and even 10 mm Hg, depending on the status of their optic nerve.

Dr. Dugel: The combined 6-month data on the sustained-delivery dexamethasone device showed increased IOP in 25% of patients, with 0.7% requiring laser or surgical intervention for the increased IOP.[17]

The 18-month results for the sustained-delivery fluocinolone device show that no patients in the open-label phase 2 FAME (Fluocinolone Acetonide in Diabetic Macular Edema) study who were assigned to the lower dose of fluocinolone (approximately 0.23 µg/day) had IOP increases of more than 30 mm Hg.[26] The higher

dose group (approximately 0.45 µg/day) did have some incidences of pressure over 30 mm Hg.

Dr. Cousins: From the available data, it seems that patients with advanced glaucoma would not be considered suitable for either a steroid injection or a sustained-release implant.

Dr. Boyer: I agree. Advanced glaucoma is definitely a contraindication. But I also tend to be hesitant in patients with earlier-stage glaucoma and higher pressures. For example, if a patient presents with IOP higher than 17 mm Hg and is taking one or two topical glaucoma medication, I am reluctant to give a steroid. I will usually start with an anti-VEGF, resorting to a steroid

A RANDOMIZED TRIAL COMPARING INTRAVITREAL TRIAMCINOLONE ACETONIDE AND LASER PHOTOCOAGULATION FOR DIABETIC MACULAR EDEMA*

PURPOSE

1. To determine whether intravitreal triamcinolone acetonide injections at doses of 1 mg or 4 mg produce greater benefit, with an acceptable safety profile, than macular laser photocoagulation in the treatment of diabetic macular edema.
2. To compare the efficacy and safety of the 1 mg and 4 mg triamcinolone acetonide doses.

EVALUATION METHODS

In the trial, 4 mg and 1 mg doses will be evaluated. The former will be used because it is the dose that is currently most commonly used in clinical practice and the latter because there is reasonable evidence for efficacy and the potential for lower risk. Although there is good reason to believe that a 1 mg dose will reduce the macular edema, it is possible that the retreatment rate will be higher with this dose compared with 4 mg because the latter will remain active in the eye for a longer duration than the former. Insufficient data are available to warrant evaluating a dose higher than 4 mg at this time.

DESCRIPTION

- The study involves the enrollment of patients over 18 years of age with diabetic macular edema. Patients with one study eye will be randomly assigned (stratified by visual acuity and prior laser) with equal probability to one of the three treatment groups:
  1) Laser photocoagulation
  2) 1mg intravitreal triamcinolone acetonide injection
  3) 4mg intravitreal triamcinolone acetonide injection.
- For patients with two study eyes (both eyes eligible at the time of randomization), the right eye (stratified by visual acuity and prior laser) will be randomly assigned with equal probabilities to one of the three treatment groups listed above. The left eye will be assigned to the alternative treatment (laser or triamcinolone). If the left eye is assigned to triamcinolone, then the dose (1 mg or 4 mg) will be randomly assigned to the left eye with equal probability (stratified by visual acuity and prior laser).
- The study drug, triamcinolone acetonide, has been manufactured as a sterile intravitreal injectable by Allergan. Study eyes assigned to an intravitreal triamcinolone injection will receive a dose of either 1 mg or 4 mg. There is no indication of which treatment regimen will be better.
- Patients enrolled into the study will be followed for three years and will have study visits every 4 months after receiving their assigned study treatment. In addition, standard of care post-treatment visits will be performed at 4 weeks after each intravitreal injection.

PATIENT ELIGIBILITY

- Study Eye Eligibility
  Inclusion
  a. Best corrected E-ETDRS visual acuity score of ≥24 letters (i.e., 20/320 or better) and ≤73 letters (ie, 20/40 or worse). b. Definite retinal thickening due to diabetic macular edema based on clinical exam involving the center of the macula. c. Mean retinal thickness on two OCT measurements ≥250 microns in the central subfield. d. Media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs.

EXCLUSION

- e. Macular edema is considered to be due to a cause other than diabetic macular edema. f. An ocular condition is present such that, in the opinion of the investigator, visual acuity would not improve from resolution of macular edema (eg, foveal atrophy, pigmentary changes, dense subfoveal hard exudates, nonretinal condition). g. An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass Syndrome, etc.) h. Substantial cataract that, in the opinion of the investigator, is likely to be decreasing visual acuity by 3 lines or more (i.e., cataract would be reducing acuity to 20/40 or worse if eye was otherwise normal). i. History of prior treatment with intravitreal corticosteroids. j. History of peribulbar steroid injection within 6 months prior to randomization.. History of focal/grid macular photocoagulation within 15 weeks (3.5 months) prior to randomization. Note: Patients are not required to have had prior macular photocoagulation to be enrolled. If prior macular photocoagulation has been performed, the investigator should believe that the patient may possibly benefit from additional photocoagulation. l. History of panretinal scatter photocoagulation (PRP) within 4 months prior to randomization. m. Anticipated need for PRP in the 4 months following randomization. n. History of prior pars plana vitrectomy. o. History of major ocular surgery (including cataract extraction, scleral buckle, any intraocular surgery, etc.) within prior 6 months or anticipated within the next 6 months following randomization. p. History of YAG capsulotomy performed within 2 months prior to randomization. q. Intraocular pressure ≥25 mm Hg. r. History of open-angle glaucoma (either

only if the patient is unresponsive to the anti-VEGF agent.

Dr. Busquets: It is essential to balance the potential side effects of a drug with the severity of disease and also, if the patient is a known steroid responder, I will most likely start with an anti-VEGF agent.

Dr. Heier: There is no patient for whom I can say that I would never use a steroid. If all other options have been exhausted for a glaucoma patient who has 20/60 vision and macular edema, I will not give a steroid. If, however, it is the patient's only good eye and the vision acuity is poor and I think that a steroid can help them, I will confer with their glaucoma specialist. Many times the glauco-

A RANDOMIZED TRIAL COMPARING INTRAVITREAL TRIAMCINOLONE ACETONIDE AND LASER PHOTOCOAGULATION FOR DIABETIC MACULAR EDEMA* (CONTINUED)

primary open-angle glaucoma or other cause of open-angle glaucoma.) Note: Angle-closure glaucoma is not an exclusion. A history of ocular hypertension is not an exclusion as long as (1) intraocular pressure is <25 mm Hg, (2) the patient is using no more than one topical glaucoma medication, (3) the most recent visual field, performed within the last 12 months, is normal (if abnormalities are present on the visual field they must be attributable to the patient's diabetic retinopathy), and (4) the optic disc does not appear glaucomatous. If the intraocular pressure is 22 to <25 mm Hg, then the above criteria for ocular hypertension eligibility must be met. s. History of steroid-induced intraocular pressure elevation that required IOP-lowering treatment. t. History of prior herpetic ocular infection. u. Exam evidence of ocular toxoplasmosis. v. Aphakia. w. Exam evidence of pseudoexfoliation. x. Exam evidence of external ocular infection, including conjunctivitis, chalazion, or significant blepharitis.

- In patients with only one eye meeting criteria to be a study eye at the time of randomization, the fellow eye must meet the following criteria:
  a. Best corrected E-ETDRS visual acuity score ≥19 letters (ie., 20/400 or better).
  b. No prior treatment with intravitreal corticosteroids.
  c. Intraocular pressure <25 mm Hg.
  d. No history of open-angle glaucoma (either primary open-angle glaucoma or other cause of open-angle glaucoma.)Note: Angle-closure glaucoma is not an exclusion. A history of ocular hypertension is not an exclusion as long as (1) intraocular pressure is <25 mm Hg, (2) the patient is using no more than one topical glaucoma medication, (3) the most recent visual field, performed within the last 12 months, is normal (if abnormalities are present on the visual field they must be attributable to the patient's diabetic retinopathy), and (4) the optic disc does not appear glaucomatous. If the intraocular pressure is 22 to <25 mm Hg, then the above criteria for ocular hypertension eligibility must be met.
  e. No history of steroid-induced intraocular pressure elevation that required IOP-lowering treatment. f. No exam evidence of pseudoexfoliation.

CURRENT STATUS OF STUDY

Completed, with results published. Comments: The Diabetic Retinopathy Clinical Research Network: A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Focal/Grid Photocoagulation for Diabetic Macular Edema. *Am J Ophthalmol.* 2008;115:1447–1449.

RESULTS

At 4 months, mean visual acuity was better in the 4-mg triamcinolone group than in either the laser group (*P*<.001) or the 1-mg triamcinolone group (*P*=.001). By 1 year, there were no significant differences among groups in mean visual acuity. At the 16-month visit and extending through the primary outcome visit at 2 years, mean visual acuity was better in the laser group than in the other 2 groups (at 2 years, *P*=.02 comparing the laser and 1-mg groups, *P*=.002 comparing the laser and 4-mg groups, and *P*=.49 comparing the 1-mg and 4-mg groups). Treatment group differences in the visual acuity outcome could not be attributed solely to cataract formation. Optical coherence tomography results generally paralleled the visual acuity results. Intraocular pressure increased from baseline by 10 mm Hg or more at any visit in 4%, 16%, and 33% of eyes in the 3 treatment groups, respectively, and cataract surgery was performed in 13%, 23%, and 51% of eyes in the 3 treatment groups, respectively. Over a 2-year period, focal/grid photocoagulation is more effective and has fewer side effects than 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone for most patients with DME who have characteristics similar to the cohort in this clinical trial. The results of this study also support that focal/grid photocoagulation currently should be the benchmark against which other treatments are compared in clinical trials of DME.

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**Information from National Eye Institute's Clinical Studies Database. http://www.nei.nih.gov/neitrials/viewStudyWeb.aspx?id=105#Resource%20Centers. Accessed September 18, 2009.*

ma specialist will agree that we should be aggressive. If we can maximize their glaucoma medications to get the IOP as low as possible, and have a plan in place to do filtering surgery if necessary to relieve any IOP spikes, I will choose to treat with a steroid.

Dr. Cousins: What IOP increase do you treat vs an IOP increase that you will observe for a time when using a steroid?

Dr. Singer: If a patient's IOP is in the teens, I will most likely observe. If he or she is in the 22- to 24-mm Hg range, I will prescribe a single glaucoma drop, but if the patient's IOP is 30 mm Hg or higher, I will prescribe a combination glaucoma drop.

Dr. Heier: My strategy is dependent on the individual patient. If a patient has a 0.2 or 0.3 cup and the IOP is 24 mm Hg, I will typically ride it out. If the patient's cup is 0.6 or 0.7, and the IOP is 24 mm Hg, or possibly even in the teens, I will treat aggressively.

"It is essential to balance the potential side effects of a drug with the severity of disease."

-MIGUEL A. BUSQUETS MD, FACS

Dr. Boyer: I agree with Dr. Heier. If the patient has increased cupping, I am more inclined to be aggressive about lowering their pressures; I may be reluctant to use a steroid.

Dr. Dugel: When I use a steroid for a patient who has increased IOP, I will have them get their pressures checked every month, either at my office or another physician for 6 months following the injection of the steroid. If the patient is being checked by another office, I prefer to have direct communication with that clinician to ensure the patient is being properly followed.

I will have the patient followed for at least 1 year, but it is interesting to note that Gillies et al, reported that in 5-year follow-up for patients who received steroid injections, 88% of patient treated with 4 mg triamcinolone acetonide required glaucoma medication at some point.[27]

Dr. Busquets: I usually follow these patients for 1 year. I have seen some patients who have IOP spikes 9 or 10 months after injection with a steroid.

Dr. Heier: The sustained-delivery steroid devices have a distinct advantage over steroid injection in that the complication profiles are better in regard to IOP spikes. Currently, our practices are being bombarded with patients who have age-related macular degeneration and are coming in every 6 to 8 weeks for intravitreal anti-VEGF injections. Sustained-delivery devices may make it easier to manage our patients with DME or RVO.

PATIENT SELECTION CRITERIA

Dr. Cousins: We have already talked about patient criteria for using a steroid in DME and we are in agreement that laser is our first line of therapy. If a patient presents with CRVO, significant macular edema on OCT with good vision, good perfusion seen on FA, moderate hemorrhaging, and 20/40 vision, what would you do in this case?

Dr. Busquets: If after a thorough discussion with the patient I find that visual acuity has decreased to where it is having an effect on their ability to maintain their level of activity, I will consider using a steroid. The SCORE data suggest that 1 mg triamcinolone may have an acceptable safety profile. The other option is close observation.

Dr. Heier: Age plays a factor in my decision. If this is a patient in his or her late 50s, 60s, or older I will usually treat first with an anti-VEGF agent because I am still concerned with the side effect profiles of steroids. If the anti-VEGF agent does not work, however, I will go to steroids. For a younger patient, I will probably observe because of the history of spontaneous resolution in this age group.

Dr. Dugel: I am actually more aggressive now because a patient with CRVO and 20/40 vision does not have the same vision as a normal patient with 20/40 vision: Vision with CRVO is essentially as if looking at light in a dark room, which can be very troubling to a patient. I would first try an anti-VEGF agent. Having said that, in my experience, anti-VEGF agents do not seem to work as well for patients who are highly perfused. I will usually end up treating this patient with a steroid, which can be excellent VEGF inhibitors.

Dr. Cousins: How many anti-VEGF injections will you administer before switching to a steroid?

Dr. Dugel: Probably three—after that I can be pretty

certain the patient is not responding if I do not see improvement.

Dr. Heier: I tend not to wait for three, but rather, switch after two injections and no response.

"Sustained-delivery devices may make it easier to manage our patients with DME or RVO."

-JEFFREY S. HEIER, MD

Dr. Busquets: If the patient does respond to anti-VEGF treatment, do you treat monthly until the macula is dry or do you treat and extend once visual acuity stabilizes?

Dr. Dugel: At that point, treating these patients becomes difficult because we have to start talking to them about frequent injections. This is where a sustained-delivery steroid delivery system is attractive. We can inject once and have an effect for up to 6 months, according to the data.

Dr. Boyer: I have one patient who I have to inject every 4 weeks.

Dr. Cousins: Would you consider performing scatter laser in such a patient because the severity of the edema is proportionate to the severity of the non-perfusion, correlating with the VEGF levels in the vitreous?

Dr. Dugel: The downside to scatter laser in this scenario is that the laser will remove a fair amount of peripheral vision.

DRUG DELIVERY SYSTEMS

Dr. Cousins: There are several different delivery systems for steroids that are either available or under investigation: free injection, biodegradable, and sutured or injectable. What are the pros and cons of each?

Dr. Singer: The sustained-delivery dexamethasone device is an extended dexamethasone biodegradable delivery system and is injected into the eye using a 22-gauge needle applicator. It is implanted in the office using local anesthesia. The duration of action is 6 months, based on the pharmacokinetics data that were submitted to the FDA.[23]

Dr. Dugel: The profile of the sustained-delivery dexamethasone device mimics giving an intravitreal injection. As soon as it is injected, the patient receives a burst (approximately 100 ng) of steroid, but then it subsides over the next 60 days to approximately 10 ng and persists in zero-order kinetics thereafter.

At the other end of the spectrum is the sustained-delivery fluocinolone device, which has the lowest release of any steroid delivery system—approximately 0.2 µg over an extended period of time.

The sustained-delivery fluocinolone device is injected with a 25-gauge needle and syringe. It is a non-biodegradable device that essentially has many of the same materials, such as the polyvinyl alcohol polymer that is in the fluocinolone device approved for uveitis (Retisert; Bausch & Lomb, Inc., Rochester, NY), but with the device being investigated for DME, it is wrapped around the fluocinolone tablet itself so that, presumably, it would cause fewer side effects and deliver a steady low dose of steroid.

Regarding biodegradable and nonbiodegradable implants, I think there are some generalizations that we can make about each. Those that are entirely biodegradable are not going to have zero-order of kinetics, because as soon as they are injected, their surface area, shape, and pharmacokinetics will change. The sustained-delivery fluocinolone device, on the other hand, is not biodegradable, and will have more of a zero-order of kinetics.

Dr. Cousins: Dr. Singer, how do you inject the sustained-release dexamethasone device?

Dr. Singer: The sustained-release dexamethasone device is injected through a 22-gauge needle. It is important to construct a wound that will be self-sealing—it cannot be a straight-in wound like what we make for a 27- or 30-gauge needle, but rather a beveled incision. Also, because the needle for injecting the implant is larger, the patient should be administered subconjunctival anesthesia.

So after the patient is given subconjunctival anesthesia and a beveled incision is made, the 22-gauge is inserted via the pars plana, the actuator is pressed, and the pellet is dislodged into the vitreous cavity. After 5 seconds, the needle injector can be pulled out of the incision, following the same path as the entry and at that point, the wound should be self-sealing.

Dr. Cousins: What is the learning curve for this procedure?

Dr. Singer: It is a good idea to get some practice han-

dling the actuator and to become accustomed to making the beveled incision. Most surgeons now have some experience with small-gauge surgery so know how to create a beveled wound. Waiting 5 seconds before removing the actuator through the incision, however, may seem like an eternity to a retina surgeon.

Dr. Heier: It is also important to stabilize the eye during the procedure.

"The sustained-release dexamethasone device is injected through a 22-gauge needle."

-MICHAEL A. SINGER, MD

Dr. Busquets: I use a second instrument to displace the conjunctiva and to stabilize the eye.

Dr. Boyer: I think the learning curve is short. If a surgeon has no small-gauge surgery experience, however, there might be more involved with learning to make the incision.

Dr. Cousins: From our discussion, it is clear that we have many new options on the horizon. It will be interesting to see the final results of all of the studies on new treatments for RVO and DME. Our patients will surely benefit from expanded options and combination strategies for resolving the macular edema that has such deleterious effects on their vision. ■

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New and Emerging Treatment Paradigms for Macular Edema in Retinal Vein Occlusion and Diabetic Retinopathy

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CME QUESTIONS

1. The DRCR.net study comparing intravitreal steroids to grid laser to treat diabetic macular edema (DME) showed :
a. at 4 months, mean visual acuity was better in the 4-mg triamcinolone group than in the laser group
b. at 4 months, mean visual acuity was better in the 4-mg triamcinolone group than in the 1-mg triamcinolone group
c. at 4 months, mean visual acuity was the same in the laser, 4-mg, and 1-mg triamcinolone groups
d. A and B
e. All of the above

2. Treatment group differences in the DRCR.net study with regard to the visual acuity outcome could not be attributed solely to cataract formation.
a. True
b. False

3. The DRCR.net study authors concluded that:
a. steroids are beneficial and should be used as an adjunct to lasers
b. focal/grid laser photocoagulation should be the benchmark against other treatments for DME
c. lasers and steroids are equivalent
d. none of the above

4. In the sustained-delivery dexamethasone device phase 3 trial, the breakdown of patients with branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) is approximately:
a. two-thirds CRVO and one-third BRVO
b. evenly split
c. two-thirds BRVO and one-third CRVO
d. none of the above

5. In the 6-month results of the sustained-delivery dexamethasone device phase 3 trial:
a. more patients in the sustained-delivery dexamethasone group gained three lines of vision compare with sham
b. twenty- to 30% of the treated patients gained three lines within 1 to 2 months
c. seven- to 12% of the patients in the sham arm gained three lines of vision within 1 and 2 months
d. all of the above

6. In the sustained-delivery dexamethasone device phase 3 trial visual acuity improvement peaked at:
a. 30 days
b. 60 days
c. 90 days
d. none of the above

7. In the study by Gillies et al, patients who received steroid injections required glaucoma medications at some point in ____-year follow-up.
a. 3
b. 1
c. 5
d. all of the above

8. The wound construction for injecting the sustained-delivery dexamethasone device should be:
a. straight
b. beveled
c. similar to that with 27- or 30-gauge instruments
d. none of the above

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New and Emerging Treatment Paradigms for Macular Edema in Retinal Vein Occlusion and Diabetic Retinopathy

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