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CME ACTIVITY

Retina 2014 – Highlights and Hallmarks

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CONTENT VALIDATION:

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STATEMENT OF NEED:

Advancements in treatment possibilities and technology have amplified the opportunity for improved outcomes for many vitreoretinal diseases. Results from new research is continuously adding to the available evidence in helping inform management approaches for treatment of retinal diseases. The clinical management of retinal diseases, such as AMD and DME, continues to evolve rapidly as novel therapies and new clinical trial outcomes expand and refine practice patterns. Retina specialists and comprehensive ophthalmologists are faced with the challenge of understanding and implementing the most up-to-date information as presented to them within the literature and at meetings. Like other medical professionals, ophthalmologists routinely turn to expert colleagues for knowledge that will help them to develop the most effective therapeutic strategies.

Although new treatments may be approved for disease states and presented study outcomes may demonstrate statistical significance, clinicians may not have access to the methodology or limitations of the information. Expert opinions regarding emerging clinical data can help close the learning and practice gap, allowing more patients to benefit from technology advancements that can improve treatment outcomes.

This CME activity will provide expert, prospective knowledge from a panel of vitreoretinal specialists. This panel of experts will examine the latest topics in retina, weigh the evidence, clarify the latest information and deliberate its validity and impact on the optimal management of the related retinal diseases. The activity will also provide expert opinion to help clinicians plan for near-term future developments in this area.

TARGET AUDIENCE:

This certified CME activity is designed for retina specialists and general ophthalmologists involved in the management of retinal disease.

LEARNING OBJECTIVES:

At the end of this activity, participants will be able to:

- Discuss the differences in dosing regimens and outcomes for anti-VEGF treatments for DME.
- Describe how anti-VEGF is being used in clinical practice, as compared to dosing regimens of large phase 3 trials.
- Identify new developments and recommendations for the use of vitamin supplementation for patients with AMD as it relates to genetic polymorphisms.
- Summarize current trials and the anticipated trial results relating to retinal diseases expected in 2015.

METHOD OF INSTRUCTION:

After reviewing the material in its entirety, 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 www.dulaneyfoundation.org and click "Online Courses." Upon completing the activity and achieving a passing score of higher than 70% on the self-assessment test, you may print out a CME credit letter awarding 1.0 AMA PRA Category 1 Credit.™ The estimated time to complete this activity is 1.0 hour.

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FACULTY CREDENTIALS:

Rishi Singh, MD, is a staff surgeon at the Cole Eye Institute, Cleveland Clinic and assistant professor of ophthalmology at the Lerner College of Medicine in Cleveland, Ohio. He also currently serves as the medical director of informatics at the Cleveland Clinic. He specializes in the treatment of medical and surgical retinal disease such as diabetic retinopathy and age related macular degeneration. Dr. Singh has authored more than 60 peer-reviewed publications, books, and book chapters and serves as the principal investigator of numerous national clinical trials advancing the treatment of retinal disease. He is a frequent invited speaker at national and international meeting as well as continuing medical education seminars. Dr. Singh is also a reviewer for various ophthalmology and diabetes medical publications, including *Archives of Ophthalmology, American Journal of Ophthalmology, IOVS,* and *Ophthalmology*. He maintains a strong relationship with drug development and commercial entities by serving on scientific advisory boards. He received his medical degree from Boston University in the prestigious accelerated medical program and completed his residency at the Massachusetts Eye and Infirmary Harvard Combined Program in Boston. Dr. Singh then completed a medical and surgical fellowship at the Cole Eye Institute in Cleveland. Dr. Singh's current work focuses on the electronic medical records implementation, lean process improvement, and decision support modules for clinical practice. He operates the Cleveland Clinic Electronic

Health Record Consulting program. He has been honored with several research recognitions such as the Alpha Omega Alpha Research Award and the American Society of Retina Specialists Senior Honor Award.

Dean Eliott, MD, is the associate director of the Retina Service at Massachusetts Eye and Ear Infirmary, and the Stelios Evangelos Gragoudas Associate Professor at Harvard Medical School in Boston. He is also director of the Vitreoretinal Fellowship and co-director of the Diabetic Eye Disease Center of Excellence at Harvard Medical School. His special interests include treating retinal detachment, diabetic retinopathy, nondiabetic retinal vascular disease, trauma, and complex surgical problems. Dr. Eliott received his medical training from Vanderbilt University School of Medicine and completed his ophthalmology residency at Wilmer Eye Institute/Johns Hopkins Hospital. This was followed by a vitreoretinal fellowship at Duke University, where he was also chief resident and a faculty member. Dr. Eliott then spent 12 years on the faculty at Kresge Eye Institute in Detroit, where he was director of the Retina Service and Retina Fellowship Director. Prior to joining Massachusetts Eye and Ear, Dr. Eliott was professor of ophthalmology, director of clinical affairs, and director of the Vitreoretinal Fellowship at the University of Southern California Keck School of Medicine's Doheny Eye Institute in Los Angeles.

Philip Ferrone, MD, is a vitreoretinal specialist at Long Island Vitreoretinal Consultants in New York. Dr. Ferrone earned his Bachelors of Science from Union College graduating magna cum laude, and received his M.D. from Harvard Medical School, graduating cum laude with special honors. He completed a medical/surgical internship at Newton-Wellesley Hospital in Massachusetts and his residency in ophthalmology at Duke University Eye Center. He subsequently completed a fellowship in vitreoretinal disease and surgery at Associated Retinal Consultants in Royal Oak, Michigan. He was chief resident and on faculty at the Duke University Eye Center, where he gained extensive experience in ocular trauma. Dr. Ferrone is on the board of directors of the American Society of Retinal Specialists.

Szilárd Kiss, MD, is the director of clinical research and an associate professor of ophthalmology at Weill Cornell Medical College and an associate attending physician at The New York/Presbyterian Hospital in New York. Dr. Kiss's training began in New York, where he received his undergraduate degree with honors from Columbia College and medical school training at Columbia University College of Physicians & Surgeons. He then moved to Boston to complete his ophthalmology residency and surgical vitreoretinal fellowship, both at Harvard Medical School and the Massachusetts Eye & Ear Infirmary. At Harvard, Dr. Kiss was chosen to serve as chief fellow. Dr. Kiss has participated as a principal investigator in numerous prospective clinical trials and laboratory investigations. He has authored nearly 200 scientific publications, given more than 100 invited lectureships worldwide, and serves on the editorial board and as a scientific reviewer to a number of major journals. Dr. Kiss has won numerous academic and scientific awards including the Heed Ophthalmic Foundation Fellowship, the Ronald G. Michels Foundation Fellowship, the Paul Kayser International Fellowship, and the Research to Prevent Blindness Physician-Scientists Award. Additionally, Dr. Kiss has been named to several regional and national top doctors lists.

FACULTY/STAFF DISCLOSURES:

Dean Eliott, MD, has had a financial agreement or affiliation during the past year with the following: Acucela; Alcon; Allergan; Alimeria Sciences; Bausch + Lomb; Genentech; Regeneron Pharmaceuticals; and ThromboGenics.

Philip Ferrone MD, has had a financial agreement or affiliation during the past year with the following: Alcon; Allergan; Arctic DX; Genentech; and Regeneron Pharmaceuticals.

Szilárd Kiss, MD, has had a financial agreement or affiliation during the past year with the following: Alcon; Allergan; Alimeria Sciences; Genentech; and Regeneron Pharmaceuticals.

Rishi P. Singh, MD, has had a financial agreement or affiliation during the past year with the following: Alcon; Allergan; Genentech; Regeneron Pharmaceuticals; and ThromboGenics.

All of those involved in the planning, editing, and peer review of this educational activity report no relevant financial relationships.

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DISCLAIMER:

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Retina 2014 – Highlights and Hallmarks

A roundtable discussion with Rishi P. Singh, MD; Dean Eliott, MD; Philip Ferrone MD; and Szilárd Kiss, MD.

ANTI-VEGF TREATMENT FOR DIABETIC MACULAR EDEMA: THE VISTA & VIVID STUDIES

VISTA and VIVID are 2 phase 3, double-masked, randomized trials that performed a head-to-head comparison of intravitreal aflibercept injection, a vascular endothelial growth factor blocker, and laser for treatment of diabetic macular edema (DME).[1] The study randomly assigned 466 patients 1:1:1 to receive aflibercept 2 mg every 4 weeks, aflibercept (Eylea, Regeneron) 2 mg every 8 weeks (after 5 initial consecutive monthly doses), or laser photocoagulation at baseline. Mean change in ETDRS BCVA from baseline to week 52 was assessed as the primary endpoint (Figure 1). The analysis demonstrated significant improvement favoring both the aflibercept 2 mg every 4 weeks and 2 mg every 8 weeks groups in BCVA compared with laser at week 52 (+12.5 letters and +10.7 letters versus +0.2 letters) and maintained the gains in BCVA through week 100. Additionally, more than twice as many patients treated with aflibercept had an improvement of 2 or more steps in the Diabetic Retinopathy Severity Score, as compared with controls (37% versus 15.6%). Inflammatory events were uncommon (0.2%, 0.1%, and 0.4% for the aflibercept 2 mg every 4 weeks, aflibercept 2 mg every 8 weeks, and focal laser treated groups, respectively).

These findings were discussed in comparison to the 2-year results from the RISE and RIDE trials, published in 2012.[2] RISE and RIDE demonstrated that ranibizumab, when compared to sham injection, improved vision and macular edema in patients with DME and reduced the risk of further visual loss. Although identical in design, the RISE study showed that the proportion of patients with 15 or more letter gain was greatest in the 0.3-mg group at 24 months, whereas in the RIDE study this was greatest in the 0.5-mg group.

Larger doses of ranibizumab have also been studied in patients with clinically significant DME. Ferrone and Jonisch have presented 2-year findings from 42 eyes/patients, treated with either 0.5 mg or 1.0 mg of ranibizumab.[3] The number of injections did not differ significantly between the 2 groups, but they found a statistically significant improvement in overall ETDRS visual acuity from baseline and a significant difference between the 2 groups. The 1.0-mg dose group demonstrated improved resolution of macular edema when compared with the 0.5 mg ranibizumab group at 2 years.

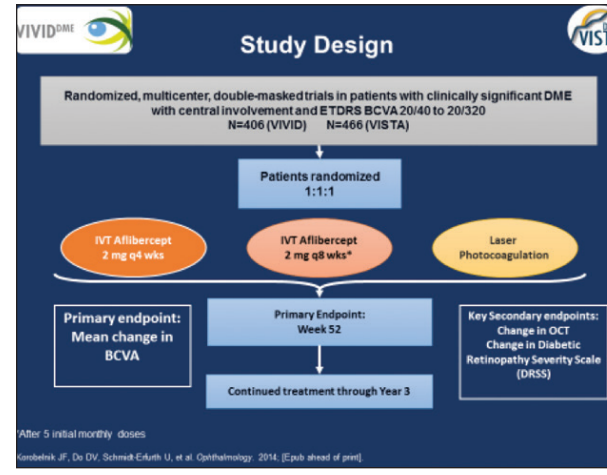

Figure 1. Study Schematic of VISTA and VIVID Studies, comparing intravitreal aflibercept injection and laser, for treatment of DME.

The trial design of VISTA and VIVID differed from other recent anti-VEGF DME trials, like RISE and RIDE, particularly in its inclusion patient population. The trials included larger proportion of multiethnic populations, and more than 40% of study eyes in VISTA were not entirely naïve to previous anti-VEGF therapy. As well, the active anti-VEGF agent, aflibercept, was compared with an active control group (laser), whereas the RISE/RIDE trials compared ranibizumab (Lucentis, Genentech) with a sham injection.[2]

The group discussed the outcomes from VISTA and VIVID and the impact that the results may have to clinical practice. They agreed that the study end points were relevant and reflective of clinical practice. Of important note was that laser may still be appropriate in some patient types (eg, demographics, location, compliance), and that it laser itself is not often a single "1 and done" treatment; often requiring 2 to 3 treatments, as was demonstrated in the laser group in VISTA and VIVID, receiving an average of 2.7 and 2.1 laser treatments, respectively, over the study duration.[1]

Figure 2. Retinal image of a 45-year-old patient with DME and proliferative diabetic retinopathy.

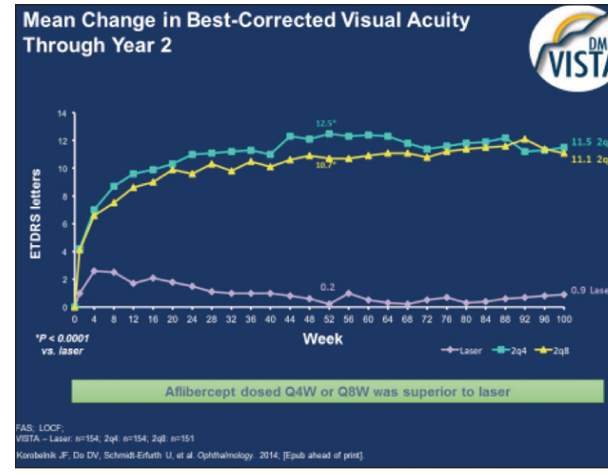

Figure 3. Mean change in BCVA (ETDRS letters) over 2 years after treatment for DME with either aflibercept or focal laser.

> For eyes with a poor response, I tend to change drugs first, and rarely opt for laser, except in cases of circinate lipid with microaneurysms.
> — *Dean Eliott, MD*

Rishi Singh, MD: It is clear when looking at optical coherence tomography (OCT) data from RISE and RIDE and VIVID/VISTA, that all treatments result in a reduction of retinal thickness and a dryer retina (Figure 2). What advantages does VIVID/VISTA offer us for insight into the treatment of DME?

Philip Ferrone, MD: To have a head-to-head comparison with laser, without treatment mixing, is valuable.

Dr. Singh: Do you feel that loading doses matter in DME? Consider the as-needed treatment arm in CATT, loading doses did not benefit the final outcome at least in the setting of exudative AMD.[4]

Szilárd Kiss, MD: The concept of a loading dose may not be valid clinically, more so in a study environment. I do not use a loading dose, rather, I treat depending on the patient's visual acuity and evidence of activity on exam and on OCT.

Dr. Ferrone: I do not clinically utilize a loading dose per se either. Instead, I initially treat patients more intensively (monthly) to dry out the macula, and once it is dry, I move to a schedule, similar to the "treat and extend" format used in AMD.

Dr. Singh: What has been your clinical experience with aflibercept for DME?

Dr. Ferrone: I have switched several patients from ranibizumab to aflibercept, but I have only given 1 or 2 doses thus far, so it is too early to make a conclusive decision. Using 0.3-mg ranibizumab has not delivered an impressive response, in my opinion, even though safety profile is great.

Dr. Singh: Agreed, I had a similar experience with ranibizumab 0.3 mg. I had been using 0.5-mg ranibizumab in compassionate cases prior to its approval, and that dose delivered better results than 0.3 mg. I do understand how 0.3 mg was approved for safety profile.

Another interesting finding when comparing these trials is that with aflibercept, visual acuity is increased to a plateau phase earlier than what was seen in RISE/RIDE with Lucentis.[1]

Dr. Kiss: I have a similar opinion with ranibizumab for DME and how it is different from wet AMD. I have not seen a quick "wow" factor, as in AMD and the results for DME require long-term usage. I have switched some patients from ranibizumab to aflibercept with good response, but it is too early to tell if 1 treatment is definitively better than the other; it is nice to have another option.

Dean Eliott, MD: My clinical experience with aflibercept has shown comparable response to ranibizumab, but at this point it is too early to know. I am pleased with the results so far. For eyes with a poor response, I tend to change drugs first, and rarely opt for laser, except in cases of circinate lipid with microaneurysms.

Dr. Kiss: The VIVID/VISTA data provides the third

source confirming that laser is not the optimal primary approach for most patients with DME[2,5] (Figure 3).

Dr. Singh: I believe that the results of these trials have led to a real paradigm shift. For 30 years, laser has stabilized vision, but now the expectation is to gain vision with treatments and avoid the destructiveness of laser. Even though OCT may improve with laser, visual acuity may not. Do you notice a see-saw effect on OCT and vision when treating patients with anti-VEGF agents?

Dr. Ferrone: I do not find that, likely because I am using a treat-and-extend dosing format.

Dr. Kiss: I treat using the true as-needed approach, or PRN, for DME, RVO, and AMD, and even though DME is more forgiving, rebound edema still occurs. There always seems to be a lag between OCT findings and visual acuity; I have found it is even worse in terms of correlation of vision and OCT findings in DME compared with AMD and RVO.

Dr. Singh: We are expecting results shortly from trials that will compare the outcomes of different anti-VEGF treatments. What are the key things that you are looking for in these trials? What would be the results that would make changes to your practice? I am particularly interested in differences in dosing and the side effects.

Dr. Kiss: For me, a 3- to 5-letter improvement in visual acuity would be compelling; 1 to 2 letters is not as impressive.

Dr. Ferrone: For a 5-letter or greater letter gain (1 line), I would make a change to the more favorable agent, although 3 to 4 letters may start to sway my decision.

Dr. Eliott: I agree with the previous comments regarding visual acuity gains; however, safety is even more important. I look forward to the results of Protocol T,[6] as the study may demonstrate a difference in visual acuity gains between the 3 drugs or it may uncover a safety concern.

Dr. Ferrone: We know that diabetic patients have an inherent increased risk of stroke, and in RISE and RIDE, rates of stroke over 3 years were higher in the 0.5-mg group (4.8%) compared with the 0.3-mg group (2.0%) or sham/0.5 mg-group (2.4%), prompting Genentech to seek FDA approval of the 0.3-mg dose for DME.[7]

Dr. Singh: At the end of 2014, Avery and colleagues published their findings of the pharmacodynamics and systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab, or aflibercept.[8] They found notable differences among anti-VEGF treatments after intravitreal administration with all 3 agents rapidly moving into the bloodstream, but ranibizumab clearing very quickly compared with bevacizumab and aflibercept, which demonstrated greater systemic exposure and produced a marked reduction in plasma-free VEGF in patients with neovascular AMD. Thus far, this has not correlated clinically in the multicenter randomized trials that evaluated these agents. We anticipate that the results from Protocol T should provide some of that answer, but I wonder how the results will be interpreted and have opinions already been formed by release of preliminary data from competing press releases.

For a 5-letter or greater letter gain (1 line), I would make a change to the more favorable agent, although 3 to 4 letters may start to sway my decision.
— Philip Ferrone, MD

REAL WORLD USE OF ANTI-VEGF

In 2014, several investigators looked at the utilization of anti-VEGF agents and disease monitoring patterns in clinical practice how this real-world application compares and contrasts to dosing regimens of large validated phase 3 trials. Holekamp and colleagues found that in clinical practice, patients with neovascular AMD received fewer bevacizumab or ranibizumab injections and less-frequent monitoring from 2006 to mid-2011.[9]

At the 2014 American Society of Retina Specialists Meeting in San Diego, Szilárd Kiss, MD, presented a paper titled "The Pattern of Anti-VEGF Use in Neovascular Age-Related Macular Degeneration and Diabetic Macular Edema: A US Claims Analysis to evaluate anti-VEGF utilization patterns from Claims data."[10] The studies included in this presentation found that the frequency of intravitreal injections and subsequent visual acuity improvement in clinical practice was lower than improvements reported in large randomized trials, linking less frequent anti-VEGF injections to less visual acuity improvement.[10-13]

Further analysis showed that bevacizumab was the main anti-VEGF therapy used in clinical practice for BRVO, CRVO, and DME, and that patients treated with bevacizumab were monitored less frequently and received fewer injections than patients in major clinical trials of ranibizumab.[13] Using EMR data (closed system database) the UK Age-Related Macular Degeneration EMR Users Group study looked at mean visual acuity improvement with the number of injections and found that the real-world visual outcomes achieved at a large number of centers across the United Kingdom did not match the results achieved in

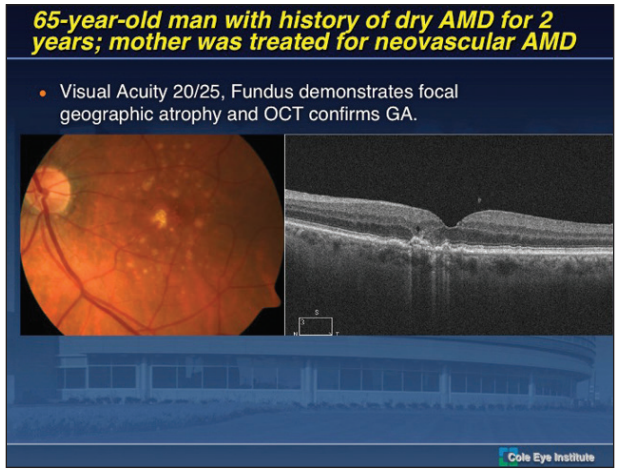

Figure 4. Retinal Image and OCT of a 65-year-old male with a 2-year history of dry AMD. Note the focal geographic atrophy. His mother had received treatment for neovascular AMD.

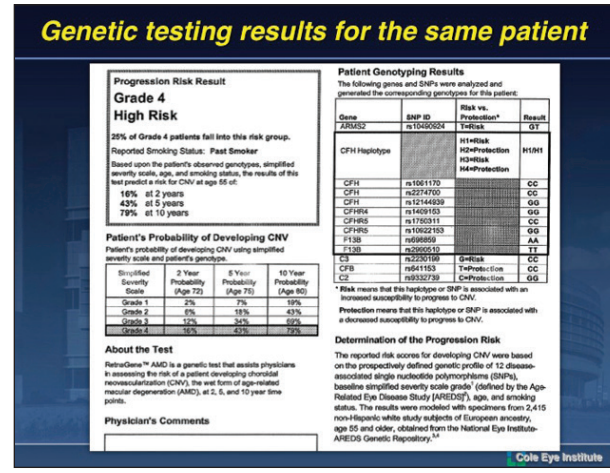

Figure 5. Genetic test results for patient depicted in Figure 4 using RetnaGene AMD test (Sequenom), noting patient's probability of developing choroidal neovascularization.

most randomized trials, but they were delivered with substantially fewer injections and hospital visits.[15] A subanalysis of the claims data was also presented by Dr. Kiss at ASRS and reported on the rate of endophthalmitis in AMD and RVO patients treated with ranibizumab or aflibercept.[10] They found that the risk of developing endophthalmitis (sterile and nonsterile) was significantly higher with aflibercept compared with ranibizumab in AMD (1.7 versus 0.8 per 1,000 injections [($P < 0.001$)) and RVO (3.8 versus 0.4 per 1,000 injections [$P < 0.001$]).[10]

Dr. Kiss: The claims analysis work done by Allergan 4 to 5 years ago is similar to recent findings, all pointing to undertreatment. The hypothesis is that physicians are tailoring treatment to the individual patient. In few other fields do physicians deviate to such a great extent from prospective trials to what is being seen with anti-VEGF therapy and RVO, DME, and AMD treatment.

Dr. Kiss: The limitations of claims data analysis are (1) pre-defined look back period may eliminate some patients from analysis based solely on follow-up status; (2) data based on Medicare or commercial insurance, therefore demographics are based on insurance buying, or database buying; (3) there is no outcome data (eg, visual acuity, OCT, etc.); and (4) coding by physicians (which is the foundation of claims data) may not reflective of the actual patient pathology.

Dr. Singh: So, it appears we have a consensus from the group, that at a national level, clinicians are acutely aware that they are undertreating, at some level. This undertreatment with anti-VEGFs for DME was similar to the realization of the undertreatment for AMD seen in the SEVEN-UP study.[16] Perhaps the undertreatment of DME is not a reflection of the physician but rather related to the burden of care for diabetic patients.

Another important point that was evaluated within some of these claims studies was the rates of intraocular inflammation.[10] I have found that these published endophthalmitis numbers are not reflective of practice. This result was surprising if true.

Dr. Kiss: The results were based on coding by physicians; the definition of endophthalmitis was strictly defined as a code for endophthalmitis submitted within 30 days after injection. There was definitely a difference between ranibizumab and aflibercept in terms of all types of inflammation; when we cast a broader net of codes and included inflammation, like iritis and vitritis, that difference between the drugs held up. Importantly, ocular culture results are not included in claims data. We have another study pending with the analysis showing no difference in cultures positive endophthalmitis between anti-VEGF agents.

Dr. Ferrone: Keep in mind that infection is still a rare occurrence; of the 1.3 million injections from the Medicare data, 0.07% endophthalmitis is considered rare and in most cases the eye is effectively injected with antibiotics, preserving a good visual outcome. In many other studies included in a large meta-analysis, the average rate was 1 per 2,000 injections.[17]

GENETICS OF AMD AND PERSONALIZED VITAMIN THERAPY FOR AMD

The role of genetic testing, commercially available tests and their clinical utility, particularly in retinal diseases, was a prominent topic of discussion and study in 2014. Specific to nutritional supplementation for AMD, a recent report from the AREDS group[18] determined that AREDS supplements

> I do not currently use any genetic testing, and I strongly believe that there is currently no clinical utility outside of a research setting to offer genetic testing for AMD.
> — *Szilárd Kiss, MD*

reduced the rate of AMD progression across all genotype groups and, specifically, genotypes at the CFH and ARMS2 loci did not statistically significantly alter the observed benefits of AREDS supplements, concluding that adopting variations in vitamin formulations based on genotype should not be done at this time.[18] These conclusions are in contrast to a 2013 study by Awh and colleagues that showed CFH and ARMS2 genetic polymorphisms predicted response to antioxidants and zinc in patients with AMD in the AREDS population.[19] In addition, they reported that patients with no CFH risk alleles and with 1 or 2 ARMS2 risk alleles derived maximum benefit from zinc-only supplementation and patients with 1 or 2 CFH risk alleles and no ARMS2 risk alleles derived maximum benefit from antioxidant-only supplementation, adding that treatment with zinc was associated with increased progression to advanced AMD.[20] These results are contradictory to the nonsignificant association between CFH and ARMS2 genotype response to supplements from AREDS, further adding that genetic testing provides no benefits in managing nutritional supplementation for patients at risk of late AMD (Figures 4 and 5).[18]

Dr. Singh: We know that genes do matter in AMD and testing is now available, but how does this panel implement genetic testing in their practice?

Dr. Kiss: I do not currently use any genetic testing, and I strongly believe that there is currently no clinical utility outside of a research setting to offer genetic testing for AMD. Outside of the debatable clinical utility of the current tests, there are also certain restrictions around genetic testing – in New York State, for example, genetic counseling is a mandatory step prior to any genetic testing.

Dr. Singh: Also, according to AREDS, addressing modifiable risk factors such as smoking status and diet are much more important than increasing antioxidant use. How do you recommend vitamin use in your practice?

Dr. Kiss: I do not routinely recommend vitamins for my AMD patients. Many of my patients do ask about diet and supplements–I then use the data from AREDS and AREDS2 to guide my discussion.

Dr. Eliott: I recommend according to AREDS2.

Dr. Ferrone: I also recommend according to AREDS2.

Dr. Singh: I, too, recommend according to AREDS2. However, I think it is estimated that only 30% of patients actually take supplement and it is an issue of compliance.

Dr. Eliott: Even though the AREDS studies demonstrated a modest benefit from antioxidant vitamins and minerals, recent studies raise the possibility that this regimen may be harming subsets of patients with certain genetic polymorphisms. Further study is needed to look at genetic stratification.

Dr. Kiss: There may be some benefit ultimately with the AREDS vitamins, but it is also important to consider that these patients may also be taking other supplements and have variable diets which can impact the results from these supplements.

Dr. Singh: Yes, in these sorts of studies there are always concerns with standardizing the patient population, and diet is certainly 1 of those confounding issues.

Dr. Kiss: It is important to remember that just because polymorphisms indicate a predisposition, it does not mean that the condition is drugable. Predisposition is not the same as defect, indicating 100% certainly of an event happening. I cannot think of an SNP study that has led to a drugable intervention. Also, the interpretation of results of genetic testing can be really complicated and made more so by conflicting interests such as NEI and IP holders. Outside of a research setting, patients may not know what to make of results, and many physicians are confused even about the proper terminology.

Dr. Ferrone: Genetic testing may have a role for a patient with drusen who is aged 50 or 60 years, which may convince the clinician to monitor them more closely. These patients may notice reduced vision, and think they need refractive correction, but it is really the beginning of AMD. In that scenario, patients with a high-risk eye in addition to a high-risk genetic profile will be seen earlier and more often, ideally. I do think that in some situations genetic testing makes sense.

Dr. Kiss: Many patients being targeted for testing are those that already have significant risk factors—they are older than 55 years, a family history of AMD, have drusen, and pigmentary changes. A clinician may decide to follow

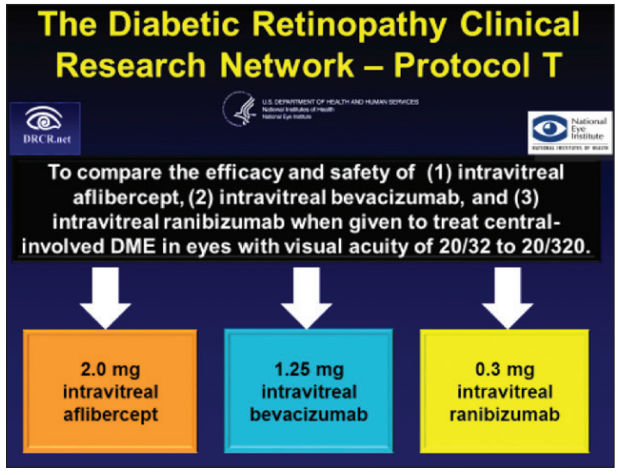

Figure 6. Overview of DRCR.net Protocol T study, comparing the efficacy and safety of intravitreal anti-VEGF agents in the treatment of central-involved DME.

these patients more closely, regardless of the genetic test results that are currently being done.

LOOKING TO 2015, TRIAL RESULTS AND APPROVED INDICATIONS

Editors' Note: *At the time of this discussion, the Diabetic Retinopathy Clinical Research Network's "Protocol T" had not yet been published. Therefore, the clinicians were unable to discuss its findings or its potential impact on patients.*

Dr. Singh: We anticipate 2 new approvals for diabetic retinopathy (DR) in the coming year, but this may be a tough sell for patients: offering frequent anti-VEGF injections in order to avoid laser. It is important to note that the clinical endpoints for DME treatment are very different than for DR. With DME, visual acuity is impacted, while patients with DR tend to have a long way to go until their vision is affected. As well, good treatments for DR already exist, which makes it difficult to rationalize this treatment and the increased number of injections increases risk of endophthalmitis.

Dr. Kiss: In the case for first line for most DME, we have already seen the paradigm shift away from laser photocoagulation to intravitreal anti-VEGF injections. I think that shift will continue. More interestingly, in 2015 and beyond, we may see a shift from laser to pharmacotherapy as a first line for proliferative diabetic retinopathy and severe/pre-proliferative NPDR.

Dr. Eliott: There are always going to be compliance issues, particularly with diabetic patients who have advanced retinopathy.

Dr. Singh: If these patients miss an injection, how much will their disease progress in that time? What will be the visual outcomes? For those patients who are reliable and can afford injections, is this the better option? I think it is completely dependent on the patient population.

DRCR.net Protocol T compared the efficacy and safety of (1) intravitreal aflibercept, (2) intravitreal bevacizumab (Avastin, Genentech), and (3) intravitreal ranibizumab when given to treat center-involving DME in 660 eyes with visual acuity of 20/32 to 20/320 in patients who are aged 18 years and older with type 1 or 2 diabetes (Figure 6). Eyes were excluded from Protocol T if they had a history of intravitreal anti-VEGF within the past 12 months or other DME treatment, such as macular laser within the previous 4 months. Some interim results were released in October 2014. DRCR.net Protocol S will determine if visual acuity outcomes at 2 years in eyes with PDR (with or without concurrent DME) that receive anti-VEGF therapy with deferred PRP are noninferior to those in eyes that receive prompt PRP therapy.

Dr. Singh: When considering the anticipated results of Protocol T and Protocol S, what results would initiate change to your treatment patterns? Recall that with the results of the CATT study, it was anticipated that practice patterns would change, and they have not.

Dr. Ferrone: If the study demonstrates a difference in treatment burden to patients (1 drug shows fewer injections than another drug), if there is a significant difference in duration of effect or a larger change in visual acuity outcomes, then I think practice patterns may change.

Dr. Eliott: Safety is of utmost importance, but efficacy and duration are also meaningful. Preventing even 1 patient from having a stroke is most important.

Dr. Singh: How would the group feel if results show that aflibercept demonstrates twice the benefit, but twice the inflammation?

Dr. Kiss: The benefit of efficacy is more important, since almost all inflammation can be treated. Despite the visual acuity curves in the published data for anti-VEGF in DME, some patients are not getting the expected response and are disappointed.

Dr. Eliott: Anti-VEGF injections will reverse retinopathy, but if injections are stopped after 2 years, for example, will the retinopathy return to its initial status? Will PRP be required as soon as anti-VEGF is stopped?

Dr. Kiss: Also important to note that there are limitations to fluorescein angiography (FA) findings, particularly that an angiographically quiet retina is not necessarily an unviable

retina. Conversely, there can be abnormalities in the retinal vasculature that look completely normal on FA. On a wide-field angiogram of patients with ischemic RVO, for example, a certain portion of the retina can angiographically revascularize, or be angiographically viable as is similar to patients with chronic uveitis and steroid treatment. There is more to consider than the "silent" appearance on FA.

Dr. Singh: What are the study results are you most looking forward to in 2015, or which do you think will have the biggest impact?

Dr. Kiss: For my diabetic patients, I am awaiting the results of DRCR.net Protocol T and S. Protocol T will help guide our thinking on the comparative effectiveness, treatment burden and possible safety profile of the 3 anti-VEGF medications in the treatment of DME. Protocol S may lead to a paradigm shift in the treatment of proliferative disease, with anti-VEGF therapy supplanting panretinal photocoagulation (PRP) as first line for PDR. For my wet AMD patients, I am also excited about the phase 2a data from the gene therapy trials (AVA-101, Avalanche Biotechnology)—with a number of our wet AMD patients now getting close to (or even more than) 100 injections, a treatment such as gene therapy may be the next frontier for the long-term treatment of this disease.

Dr. Ferrone: Protocol T is of most interest for DME, as well other AMD studies evaluating treatments that can reduce subretinal hyperreflective material and the frequency of anti-VEGF injections.

Dr. Eliott: I am looking forward to Protocol T results, as there may be a difference with respect to efficacy, or the study may uncover a safety issue. I think the advances in gene therapy, and possibly even stem cells will be impactful and potential game changers.

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CME QUESTIONS

1 *AMA PRA Category 1 Credit™*
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1. **In the VISTA and VIVID trials, a comparison of intravitreal aflibercept injection and laser for treatment of DME, at 52 weeks, what was the BCVA improvement in the 2q8 group?**
   a. 12.5 letters
   b. 10.7 letters
   c. 5.4 letters
   d. 2.7 letters

2. **How did the patient population of VISTA and VIVID differ from other recent anti-VEGF DME trials?**
   a. larger proportion of multiethnic populations
   b. all eyes were naïve to previous anti-VEGF therapy
   c. large proportion of eyes were not entirely naïve to previous anti-VEGF therapy
   d. a & c

3. **In recent studies of the utilization of anti-VEGF agents in clinical practice as compared with dosing regimens of large validated phase 3 trials, how did the real-world dosing compare?**
   a. anti-VEGF agents tend to be dosed less frequently in clinical practice than in the trials
   b. anti-VEGF agents tend to be dosed more frequently in clinical practice than in the trials
   c. clinical practice seems to adhere to the same dosing regimens of the trials
   d. results were inconclusive

4. **In a large meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents what was the average rate of endophthalmitis?**
   a. 1 per 2,000 injections
   b. 1 per 1,000 injections
   c. 1 per 1,200 injections
   d. 1 per 5,000 injections

5. **Specific to nutritional supplementation for AMD, what were the AREDS Report #38 findings regarding AREDS supplements for specific genotype groups?**
   a. AREDS supplements reduced the rate of AMD progression across all genotype groups
   b. AREDS supplements are not recommended for patients with CFH risk alleles.
   c. CFH and ARMS2 loci did not statistically significantly alter the observed benefits of AREDS supplements
   d. a&c

6. **In order to meet inclusion criteria for DRCR Protocol T, patients had to be at least 18 years old with type 1 or 2 diabetes and have what visual acuity in the study eye?**
   a. Between 20/40 and 20/400
   b. 20/80 or worse
   c. Between 20/32 to 20/320
   d. DRCR Protocol T did not have a visual acuity requirement for inclusion.

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Discuss the differences in dosing regimens and outcomes for anti-VEGF treatments for DME.	_____	_____	_____
Describe how anti-VEGF is being used in clinical practice, as compared with dosing regimens of large phase 3 trials.	_____	_____	_____
Identify new developments and recommendations for the use of vitamin supplementation for patients with AMD as it relates to genetic polymorphisms.	_____	_____	_____
Summarize current trials and the anticipated trial results relating to retinal diseases expected in 2015.	_____	_____	_____

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME). Please complete the following course evaluation and return it via fax to (610) 771-4443.

Name and e-mail _____

Do you feel the program was educationally sound and commercially balanced? ❒ Yes ❒ No

Comments regarding commercial bias:

_____

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Rate your knowledge/skill level prior to participating in this course: **5 = High, 1 = Low** _____

Rate your knowledge/skill level after participating in this course: **5 = High, 1 = Low** _____

Would you recommend this program to a colleague? ❒ Yes ❒ No

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If yes, please specify. We will contact you by e-mail in 1 to 2 months to see if you have made this change.

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If no, please identify the barriers to change.

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Please list any additional topics you would like to have covered in future Dulaney Foundation CME activities or other suggestions or comments.

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