MEETING NOTES FROM THE 44TH ANNUAL MEETING OF THE ARDS

The complexities of modern retina care make it seem as though 21st century practice greatly outpaces that of 20th century norms. In some ways, this is true: we have more pharmacologic options and surgical equipment from which to choose, and modern communication has thawed the once frozen pipes through which information is disseminated. A tweet with a journal article link, after all, flies to the world; a print version of that same article sits relegated to a dust-collecting tabletop.

But this reductive view of 21st century patterns neglects common contemporary practice traits that have their basis in tradition. Retina specialists rely on clinical trial data just as much today as they did in the 1990s. Imaging for retinal disease is as much a staple today as it was during the days of nascent optical coherence tomography (OCT).

The Aspen Retinal Detachment Society (ARDS) annual meeting marries the concepts of tradition with the spirit of innovation, bridging the old school with the modern. Below, Basil K. Williams Jr, MD, summarizes two talks that embody that marriage: a discussion of the Diabetic Retinopathy Clinical Research Network (DRCR.net), which harnesses the power of modern communication to connect researchers across the country, and a discussion of OCT angiography (OCTA), an imaging platform whose clinical utility becomes more solidified as its application widens.

—Timothy G. Murray, MD, MBA

Impact of DRCR.net Studies on Management of Diabetic Retinopathy

By Basil K. Williams Jr, MD

At the 2016 ARDS annual meeting, Neil Bressler, MD, described the origin of the DRCR.net and impact of some of the group's work on the management of diabetic retinopathy.

ORIGIN STORY

The DRCR.net came to be, Dr. Bressler said, to facilitate clinical research in diabetes, including diabetic retinopathy. In 2010, according to the US Centers for Disease Control and Prevention (CDC), more than 25% of people in some regions of the United States were obese. Additionally, CDC data indicated that 10% of these people older than age 18 years had diabetes mellitus. This prevalence likely was related in part to the dietary habits of the country and the deleterious effects of certain diets on health at the time, Dr. Bressler said.

With increased attention on diabetes, leaders in medicine and advocacy groups for people with diabetes, such as the Juvenile Diabetes Research Foundation, encouraged Congress to provide additional funds to research diabetes and care for patients with diabetes. As a result, Congress provided approximately $150 million per year in new research funding to the National Institutes of Health (NIH), managed by the National Institute of Diabetes and Digestive and Kidney Diseases and including approximately $5 million to the National Eye Institute (NEI), which was used to create the DRCR.net. The DRCR.net would be designed to test new therapies rapidly by centers and patients across the country. One goal of the DRCR.net was to move from study concept to initiation of a trial within a year. To date, approximately one third of every retina practice in the nation likely has been involved in the DRCR.net at some point, Dr. Bressler said, and the DRCR.net has initiated more than 20 protocols, including numerous randomized clinical trials.

BACKGROUND OF PROTOCOL S

Protocol S was designed to examine whether anti-VEGF therapy could be used instead of panretinal photocoagulation (PRP) in the treatment of proliferative diabetic retinopathy (PDR). Despite 40 years of successful treatment use of panretinal PRP, an alternative was desired because PRP is inherently destructive, damages peripheral visual fields and night vision, and can exacerbate diabetic macular edema (DME). Additionally, approximately 5% of people treated with PRP still develop severe vision loss that might require vitrectomy.

Protocol I laid the groundwork for Protocol S by demonstrating that some people receiving anti-VEGF therapy for DME with PDR had less worsening of PDR than those receiving focal/grid laser for DME. Protocol I was designed to compare laser alone,

corticosteroids with laser, and anti-VEGF (ranibizumab; Lucentis, Genentech) therapy with prompt or deferred focal/grid laser for the treatment of DME. The trial found that ranibizumab with prompt or deferred laser was superior to either corticosteroids with prompt laser or prompt laser alone.

In assessing some of the data from Protocol I, investigators noted that treatment with anti-VEGF therapy had reduced the risk of worsening of PDR. Worsening of PDR was determined by study participants receiving PRP or having a new vitreous hemorrhage or vitrectomy for complications of PDR while being followed for treatment of DME.

The data observed in Protocol I raised the possibility that anti-VEGF therapy could be given instead of PRP for PDR and at least prevent worsening. If it was determined that visual acuity was no worse with anti-VEGF therapy compared with PRP for PDR, many secondary questions would be of increased relevance. Is visual acuity over 2 years (area under the curve) better with anti-VEGF therapy or PRP? Are there other benefits to considering anti-VEGF therapy instead of laser, such as preservation of peripheral visual fields? Would anti-VEGF therapy prevent DME in eyes that did not have it at baseline? Would there be a reduction in the number of vitrectomies? These questions led to the design and execution of Protocol S.

Q&A WITH DRCR.NET PROTOCOLS

Each DRCR.net study asked a clinically relevant question and generated an answer. Results were more nuanced than the notes below, but here is a quick reference that will come in handy when reading this summary of Dr. Bressler's talk.

PROTOCOL I

Question: Among the treatment options for DME, which works best: laser alone, corticosteroids with laser, or ranibizumab injections with prompt or deferred laser?

Answer: Ranibizumab was superior to both corticosteroids with laser and laser alone.

PROTOCOL S

Question: Is PRP or ranibizumab therapy best for patients with PDR?

Answer: Ranibizumab therapy is a viable alternative therapy for some patients with PDR.

PROTOCOL T

Question: In a head-to-head-to-head trial, which anti-VEGF agent would produce the best results for patients with DME: aflibercept, bevacizumab, or ranibizumab?

Answer: At the 1-year endpoint, aflibercept was superior to bevacizumab and ranibizumab in patients with 20/50 or worse vision at baseline; over the course of 2 years, aflibercept was still superior to bevacizumab. In patients with 20/32 to 20/40 vision at baseline, no significant difference among the three agents, on average, was detected at the 1-year or 2-year endpoints.

PROTOCOL S DESIGN AND RESULTS

Protocol S randomly assigned patients with PDR to be treated with either PRP or ranibizumab therapy. Patients in either group with DME at baseline involving the center of the macula with vision impairment would receive anti-VEGF treatment for the DME. The patients who received anti-VEGF therapy for their PDR had a median 22 visits over the 2 years of the study, while those treated with PRP had a median 16 visits.

The results of the study demonstrated that visual acuity results in the anti-VEGF group at 2 years were not inferior to those in the PRP group. In fact, the area-under-the-curve analysis of visual acuity was significantly better over 2 years in the anti-VEGF group. Those treated with anti-VEGF therapy also had a reduced incidence of DME with vision loss among eyes without this at baseline, had less peripheral visual field loss, and required fewer vitrectomies.

Visual acuity was very good initially in both groups (mean 20/32), and about 40% had high-risk PDR at baseline in both groups. About 20% of people had DME for which anti-VEGF treatment was required at baseline.

If neovascularization increased at follow-up after completion of PRP, more PRP was added. The PRP was completed in one visit in more than half of patients. About 35% of patients had DME at baseline, but some were 20/20 and did not require any treatment.

In the anti-VEGF group, participants typically received six initial monthly injections unless no neovascularization was present at the 4- or 5-month visits. Injections were stopped at the 6-month mark if the patient stabilized (no progression of neovascularization). If there was continued improvement, then injections were continued until stabilized. If DME or PDR worsened after deferring injections, then injections were restarted. There was a median of nine injections in year 1 (typically six in the first 6 months) and five in year 2 for those with DME. In eyes without DME, there was a median of seven injections in year 1 (typically six in the first 6 months), with six of these given in the first 6 months. There was a median of three additional injections in year 2 for this subgroup with no DME at baseline that would require anti-VEGF treatment for the DME.

Only 6% of patients in the anti-VEGF group required PRP, which was indicated in patients who had growth of neovascularization or bleeding despite persistent injections. Eight of the 12 patients who required laser treatment had the laser done in the operating room at the time of vitrectomy.

Visual acuity, on average, did not worsen in the PRP group over 2 years. In the anti-VEGF group, visual acuity on average initially improved, but improvement regressed toward, but did not completely return to, baseline at 2 years. Overall, the visual acuity in

the anti-VEGF group was not worse than in the PRP group.

Interestingly, the combination of PRP and anti-VEGF therapy led to worse visual acuity results, on average, in participants with DME and PDR at baseline than did anti-VEGF therapy alone. In the anti-VEGF group, visual acuity, on average, even improved in patients without DME. This might mean that some patients had DME with minimal thickening or excellent visual acuity, and the injections were actually treating the DME too. Development of DME with visual acuity loss was three times more likely in the PRP group than in the anti-VEGF group (occurring in 28% and 10%, respectively).

The study demonstrated that peripheral visual field loss was minimal in the anti-VEGF group, and significantly less than in the PRP group. Another complication noted was a threefold increase in vitrectomy in the PRP group compared with the anti-VEGF group (15% and 4%, respectively), and a threefold increase in developing DME with visual acuity loss among eyes without DME at baseline in the PRP group compared with the anti-VEGF group. There appeared to be no difference in systemic effects identified between the two treatment groups.

Advantages of PRP treatment are that it can typically be completed in one or two sessions and that it is often long-lasting. However, 40% of patients needed additional PRP after initial completion, at a median of 7 months. Also, laser costs less than multiple anti-VEGF injections, and there is no risk of endophthalmitis. The advantages of anti-VEGF therapy are superior visual acuity results over 2 years, less peripheral visual field loss, less development of DME, and reduced need for vitrectomy. The 0.5 mg dose of ranibizumab was used in Protocol S because that was the dose used in Protocol I that showed potential benefits for PDR; it is not known whether the 0.3 mg dose would work as well.

PROTOCOL T 2-YEAR DATA

Protocol T was designed to compare the effects of three anti-VEGF agents—aflibercept (Eylea, Regeneron), bevacizumab (Avastin, Genentech), and ranibizumab—in patients with DME. At 1 year, all three agents worked well to prevent DME, but aflibercept on average had a stronger effect than bevacizumab or ranibizumab in eyes with visual acuity worse than 20/50 at baseline.

The injection regimen typically consisted of six monthly injections (only four if the retina had normalized), which were eventually withheld when the DME was stabilized or resolved. After treatment was withheld, treatment was restarted if worsening in visual acuity from DME or worsening DME on OCT was seen.

In year 2, the number of visits started to decrease, as did the number of injections. However, the number of treatments given was similar among the treatment arms. Among the eyes with visual acuity at baseline that was 20/50 or worse, at 2 years aflibercept no longer had an advantage compared with ranibizumab, only compared with bevacizumab, but over 2 years aflibercept remained superior to the other two agents.

In regard to systemic effects, patients with or without previous myocardial infarction or stroke who underwent injection with ranibizumab had the most Antiplatelet Trialists' Collaboration events. Based on previous studies using ranibizumab, it is possible that this result was an outlier. This is something to pay attention to in future studies, Dr. Bressler said, but, given that this result is not consistent with other trials, chance is a reasonable explanation for the differences seen.

Dr. Bressler said future reports would discuss the incremental cost-effectiveness ratio of aflibercept or ranibizumab relative to bevacizumab, or aflibercept relative to ranibizumab; (note: this has been published in the August 2016 issue of *JAMA Ophthalmology*) and additional manuscripts describing other clinically relevant outcomes are planned over the next year.

WATCH IT NOW

OCT Angiography

By Basil K. Williams Jr, MD

In a presentation on OCTA, Giovanni Staurenghi, MD, of Milan, Italy, discussed some of the pitfalls of using the new technology and the continuation of multimodality imaging support.

Data in OCTA devices undergo specialized analysis to yield the image desired. Images taken at two time points are needed in order to yield an image; if the two time points are too fast or too slow, no image can be obtained.

Each company that makes instrumentation for OCTA uses a different algorithm, Dr. Staurenghi said. As a result, when images from different instruments are compared, the superficial and deep layers are not the same. Although some machines provide more information than others, there is an unclear relationship between information volume and clinical utility—that is, difficult-to-analyze information may not guide clinical decision-making, and it appears that increased information volume yields diminishing returns for the physician analyzing OCTA images.

MAKE SURE THE MODALITY FITS THE SITUATION

Dr. Staurenghi explained that different imaging modalities provide different types of information. Therefore, doctors should

consider the nuances of a particular disease when choosing an imaging modality. For example, in a patient with a retinal vein occlusion (RVO), if a vein is imaged with fluorescein angiography (FA) after laser treatment, the vein may appear to be occluded. The flow may be demonstrable on OCTA, however, because of the difference in size between the lumen and the wall of the vessel. In this scenario, OCTA may be a better imaging modality.

Dr. Staurenghi offered another example: a patient treated with anti-VEGF and anti–platelet-derived growth factor (PDGF) medications who may appear on OCTA to have a reduction in lesion size when in fact the lesion may just not be filling. OCTA may not be the best modality to evaluate this type of lesion.

ARTIFACTS

Artifacts can appear on OCTA, and these must be factored in before accurate interpretation of the image is possible, Dr. Staurenghi cautioned. The Optovue OCTA device can produce a horizontal scan with white lines, which represent movement of the eye. This change in fixation also prevents a combination of the horizontal and vertical scans, inhibiting map creation. When a patient blinks, the signal is eliminated, resulting in an artificial tartan-like pattern.

Another artifact that is commonly seen on OCTA is a projection artifact, which occurs when there is no reflection at a certain depth level, causing the image to stop and appear deeper. This projection artifact is solely a matter of orientation. The nerve fiber layer (NFL) is not visible on some structural OCTs based on orientation, and, if the angle of the image is switched, then it will reappear.

Projection artifacts can affect interpretation of OCTA. In acute macular neuroretinopathy, the NFL is usually visible. No neovascularization may be present, but a retinal vessel may appear in a deeper location due to the projection effect, explained Dr. Staurenghi. A structural OCT is required to determine whether something has changed in that image. Additionally, there may be areas that appear to have multiple locations of choroidal neovascularization (CNV) with subretinal fluid. Adding a structural OCT, autofluorescence imaging, and early and late FA images can make the lack of retinal pigment epithelium (RPE) noticeable. There is increased transmission of signal and better visualization of the choriocapillaris compared with adjacent areas where the RPE is normal. These artifacts and many more are discussed in detail in a paper by Spaide et al.[1]

Additionally, appropriate use of the slabs can prevent image changes, Dr. Staurenghi said. Because of the projection artifact, the best visualization of the lesion is deeper than where the lesion is actually located. The image can also change based on the size of the slab. The thickness of the slab changes, and that affects the amount of contrast, making the lesion appear in a completely different manner.

The differences between imaging modalities can be demonstrated by analyzing choroidal neovascularization with OCTA, FA, and indocyanine green (ICG) imaging. ICG fluoresces more when a greater amount of dye is used. This information is an important supplement to the OCTA, which may show increased signal. This increase may be theorized to result from increased flow; however, depending on the slab location, the contrast and visualization changes. This makes assessing flow based on OCTA alone somewhat difficult, Dr. Staurenghi emphasized.

IMAGING SPEED

Dr. Staurenghi said speed of imaging also makes a big difference. In branch RVO, a high contrast FA using the confocal digital ophthalmoscope can demonstrate microaneurysms and areas of nonperfused retina. By overlapping the OCTA one can see whether the retina is perfused or not. Side-by-side microaneurysms are not shown on OCTA because the flow is too slow to show up. If the flow was faster they may be able to be seen. Vessels may also show up differently for the same reason.

Looking at video FA and ICG angiography, the feeding and draining vessel can be seen. The lesion looks the same on OCTA as it would on ICG angiography, but because the fill cannot be visualized one cannot definitively tell which is the feeder and which is the draining vessel. The draining vessel is often more prominent.

ATROPHY IDENTIFICATION

One particular benefit of OCTA is that it is extremely useful for identifying and analyzing different types of atrophy. In Stargardt disease, ICG angiography demonstrates a dark area not visible in age-related macular degeneration, where there is an isofluorescent area of central atrophy. Based on these findings, Dr. Staurenghi asked, is it possible that the choriocapillaris is nonexistent in patients with Stargardt disease? The choriocapillaris is not visible on a structural OCT, but OCTA does have the capability to image it. Using OCTA, it has been shown that the choriocapillaris is absent in Stargardt disease but is present, albeit rarefied, in geographic atrophy associated with age-related macular degeneration.

Similarly, autofluorescence allows the physician to visualize areas where the RPE is present or absent. A dark choroidal vessel can appear white on OCTA. An individual B-scan can demonstrate the lack of RPE compared with the structural OCT. Light penetration in the absence of RPE yields a black image deep to the vessel due to projection artifact, Dr. Staurenghi said. If the RPE is in place, however, the projection of the areas deep to the choroidal vessel will appear white.

OCTA is a new imaging modality that comes with a learning curve, Dr. Staurenghi explained. Still, he stressed, physicians should become comfortable with the technology, as the importance of multimodal imaging will increase as we begin to understand and treat geographic atrophy.

1. Spaide RF, Fujimoto JG, Waheed NK. Image artifacts in optical coherence tomography angiography. *Retina*. 2015;35(11):2163-2180.

Basil K. Williams Jr, MD
- chief resident, co-director of ocular trauma, Bascom Palmer Eye Institute, Miami
- financial interest: none acknowledged
- b.williams9@med.miami.edu