TACKLING DIABETES AT ARDS 2023

Experts came together in Snowmass Village to discuss the nuances of treating diabetic eye disease.

BY MOHAMMAD ALI SADIQ, MD

The Aspen Retinal Detachment Society (ARDS) meeting in Snowmass, Colorado, is always a haven of learning—a place where clinicians come together to discuss new data, therapeutics, and surgical approaches. During the 2023 meeting, held March 4-8, Charles C. Wykoff, MD, PhD; Susan B. Bressler, MD; and Zofia A. Nawrocka, MD, PhD, shared recent findings that have shifted the way we treat patients with diabetic retinopathy (DR) and diabetic macular edema (DME). Here, you can find a summary of their excellent lectures (Figure).

ARDS 2024 is just a few weeks away, set for March 2-6. Visit aspenretina.com to register, find lodging, and prep for another year of top-notch education!

- Timothy G. Murray, MD, MBA

ABOUT THE SPEAKERS

Charles C. Wykoff, MD, PhD
- Director of Research, Retina Consultants of Texas/Retina Consultants of America, Houston; Deputy Chair for Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston
- Editorial Advisory Board Member, *Retina Today*

Susan B. Bressler, MD
- Julia G. Levy, PhD, Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore

Zofia A. Nawrocka, MD, PhD
- Vitreoretinal Specialist, Ophthalmic Clinic, "Jasne Blonia," Lodz, Poland

RETINAL NONPERFUSION IN DR

Dr. Wykoff began his lecture by outlining the evidence for retinal nonperfusion as a biomarker of DR progression. First, a RISE and RIDE post-hoc analysis showed that, over 3 years, the risk of progression to proliferative DR (PDR) was substantially lower in patients treated with monthly ranibizumab (Lucentis, Genentech/Roche) compared with sham.[1] However, despite monthly injections, close to one in five patients still developed PDR. The only baseline factor that helped to predict progression was retinal nonperfusion. Second, the DRCR Protocol AA trial showed that greater baseline nonperfusion on fluorescein angiography was associated with a higher risk of disease worsening.[2] Finally, a post-hoc analysis of the PANORAMA study found that retinal nonperfusion once again played a critical role in progression.[3]

The phase 2 RECOVERY trial studied nonperfusion changes in patients with PDR without DME, Dr. Wykoff said. Patients were treated with aflibercept (Eylea, Regeneron) either monthly or every 3 months, and the 1-year results showed relatively stable nonperfusion with monthly dosing and a 29% worsening with the extended dosing schedule.[4]

Dr. Wykoff then discussed reports of retinal reperfusion in the literature.[5-7] In the RISE, RIDE, and VISTA studies, there was a steady increase of nonperfusion over time in eyes in the sham arm. In the group that received anti-VEGF therapy, the increase in nonperfusion appeared to be blunted.[8,9]

Dr. Wykoff explained that the best evidence we have of reperfusion is the concept of a leukostatic plug. According to the concept, in any hypoxic state, there is an upregulation of VEGF and other cytokines. A downstream effect is the upregulation of the ICAM-1 molecule, a receptor that endothelial cells express to attract white blood cells. White blood cell clumping can then block the blood vessel. Through VEGF inhibition, downstream expression of these molecules is modified, causing a reversal of the breakdown of this plug and improving flow.

Dr. Wykoff concluded his talk with a brief look at therapies in the pipeline working to address retinal reperfusion.

DME MANAGEMENT: STEP THERAPY

Dr. Bressler provided an update on first-line therapy for patients with DME. In DRCR Protocol T, aflibercept, bevacizumab (Avastin, Genentech/Roche), and ranibizumab were all effective in achieving visual improvement through 2 years in patients with center-involving DME (CI-DME).[10] However, a subgroup analysis found that, at 1 year, aflibercept showed superiority for patients with a VA of 20/50 or worse and remained superior to bevacizumab but was statistically similar to ranibizumab at 2 years, Dr. Bressler explained.[11] An area-under-the-curve analysis found that aflibercept

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Figure. During ARDS 2023, Drs. Wykoff (left), Bressler (middle), and Nawrocka (right) share the latest data and treatment approaches for DME.

remained superior to ranibizumab for patients with a presenting VA of 20/50 or worse. It's reasonable to consider aflibercept as the first-line therapy for patients with CI-DME and a VA of 20/50 or worse, she said.

She then moved on to discuss Protocol AC, in which patients with CI-DME with a VA of 20/50 or worse were randomly assigned to either aflibercept monotherapy or bevacizumab and switched if necessary.[12] Within 2 years, 70% of patients who started with bevacizumab had switched to aflibercept, Dr. Bressler noted. Although the net number of injections was similar between the two groups over 2 years, there is a cost savings when starting with bevacizumab, she said, adding that step therapy did not compromise long-term visual outcomes when using the Protocol AC criteria.

She then discussed Protocol V, in which patients with CI-DME with a VA of 20/25 or better were randomly assigned to either anti-VEGF treatment, focal grid laser, or observation until vision loss occurred. Regardless of the strategy, 15% to 19% lost 1 or more lines of vision, Dr. Bressler explained. Within each treatment arm, about half of patients who lost vision lost between 5 and 9 letters. There was no difference between the treatment strategies, she emphasized. At the end of 2 years, 85% maintained a VA of 20/25 or better, regardless of treatment approach.

VITRECTOMY FOR DME

Finally, Dr. Nawrocka discussed vitrectomy as a treatment option for patients with DME. She highlighted her study in which 44 eyes with treatment-naïve DME underwent vitrectomy and experienced an improvement in DME and visual acuity.[13]

She then discussed another study that reported that a subretinal injection of balanced salt solution (BSS) in DME led to a decrease in osmotic pressure and the viscosity of subretinal fluid.[14] This can promote water transport from the subretinal space into the choroid and wash out cytokines and migratory cells. To further test this hypothesis, Nawrocki et al designed a study in which each patient's better-seeing eye (n = 14) was treated with aflibercept and the worse-seeing eye underwent vitrectomy with ILM peeling and a subretinal injection of BSS. The team found that the central subfield thickness decreased similarly in each group, Dr. Nawrocka explained. The delta in visual acuity was similar in each group. A mean of 3 injections were performed over the course of 6 years in half of the vitrectomized eyes, suggesting that these eyes responded well to anti-VGEF treatment, Dr. Nawrocka added.

She concluded by emphasizing that the rate of visual acuity improvement is similar in eyes treated with anti-VEGF injection and those treated with vitrectomy. Performing vitrectomy decreases the possible number of required future anti-VEGF injections, may reduce the density of the superficial foveal avascular zone, and may have a protective effect on future DR complications. ■

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