The DRCR Protocol-T study is the first and only comparative effectiveness study of intravitreal aflibercept (Eylea; Regeneron, Tarrytown, NY), bevacizumab (Avastin; Genentech, South San Francisco, CA), and ranibizumab (Lucentis; Genentech, South San Francisco, CA) for the treatment of diabetic macular edema (DME). This historic study is now complete with 2-year data publicly available. Last year, I charged Charles C. Wykoff, MD, PhD, with the monumental task of analyzing and dissecting the DRCR-T 1-year data. The Practical Retina column presented herein is an update that includes an analysis of the complete 2-year data set.

Dr. Wykoff delves deep into the data, focusing on efficacy, durability, anatomical outcomes, and safety differences between the various agents. Importantly, Dr. Wykoff re-addresses the ethics of offering a patient off-label bevacizumab based on the data and explains the real-world situation when one considers important variables like cost and access to care.

The DRCR Protocol-T study was the result of a tremendous undertaking from our respected retina colleagues around the country and was sponsored by the National Eye Institute. It clearly is a study with great clinical impact, and we are grateful to the DRCR investigators and their patients. Dr. Wykoff’s insights and review of this complex topic will be highly valuable to those of us treating diabetic macular edema.
the only prospective trial directly comparing the three commercially available anti-VEGF agents, Protocol-T: A Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab for DME,8,9 involving 660 patients with center-involved DME causing visual acuity (VA) loss to 20/32 to 20/320 using Early Treatment of Diabetic Retinopathy Study best-corrected visual acuity (ETDRS BCVA).

Year 2 data, publically released on February 27, 2016, revealed that more than 90% of living patients completed the final trial endpoint, with an impressive 98% protocol compliance.9 During year 1, all subjects were evaluated monthly. In year 2, intervals between visits could be extended up to 16 weeks, depending on the extent of prespecified, protocol-determined disease activity; specifically, if injections were repeatedly deferred, the interval between visits was sequentially lengthened. Despite this opportunity for a reduced care burden in the second year, the median number of visits was identical in each treatment group (n = 10) and the mean number of visits was nearly identical in year 1 and year 2, respectively, for aflibercept (9.2 vs. 9.4), bevacizumab (9.7 vs. 9.3), and ranibizumab (9.4 vs. 9.3). Similarly, the median number of intravitreal injections performed during year 2 and during the full trial duration were similar, with no statistical differences between the groups: aflibercept (five vs. 15), bevacizumab (six vs. 16), ranibizumab (six vs. 15).

**VISUAL OUTCOMES**

Among all patients, VA gains achieved at year 1 were maintained through year 2 in all three arms. Aflibercept-, bevacizumab-, and ranibizumab-treated eyes gained 12.8, 10, and 12.3 mean letters respectively at 2 years. The only pairwise comparison that was statistically significant was aflibercept versus bevacizumab (P = .02). The statistical superiority of aflibercept over ranibizumab observed at year 1 was lost at the year 2 endpoint.

One of the key findings from year 1 data was the impact of baseline VA on final VA. Among eyes with mild baseline VA impairment (20/32 to 20/40) mean VA improvements remained similar and not significantly different between the arms at year 2: aflibercept (+7.8), bevacizumab (+6.8), and ranibizumab (+8.6). VA gains for bevacizumab drifted downward, losing 0.7 mean letters from year 1 to year 2, whereas aflibercept and ranibizumab remained closer to their year 1 VA mark. Among patients with baseline VA of 20/50 or worse, mean VA curves converged from year 1 to year 2, and the statistically significant superiority of aflibercept over ranibizumab observed at the year 1 mark was no longer observed. Although mean VA improvement remained greatest with aflibercept (+18.1), gains with both bevacizumab (+13.3) and ranibizumab (+16.1) increased such that the only statistically significant difference at year 2 was aflibercept versus bevacizumab (P = .02).

Another focus from year 1 data was an analysis aiming to encapsulate the clinical impact of the different medications by considering the proportion of eyes with baseline VA of 20/50 or worse that gained 15 or more letters. In this analysis, aflibercept yielded 63% and 34% more eyes gaining 15 or more letters compared to bevacizumab and ranibizumab respectively.10 At year 2, these differences were less impressive, at 12% and 5%, respectively.9 In absolute terms, 58%, 52%, and 55% of patients treated with aflibercept, bevacizumab, and ranibizumab, respectively, achieved this mark at year 2 with no significant differences between the arms.

How should one reconcile year 2 with year 1 outcomes? Broadly, aflibercept appeared the overall winner at the year 1 primary endpoint. If that is a clinical reality, then why did the statistical significance and apparent clinical impact of aflibercept over ranibizumab seemingly diminish at year 2? Many factors may contribute. Was it regression to the mean? Or possibly, more frequent application of macular focal/grid laser to the bevacizumab (64%) and ranibizumab (52%) groups compared to the aflibercept group (41%; global: P < .001; aflibercept vs. ranibizumab: P = .04) contributed to improved outcomes in the former patients in year 2. Or, perhaps these medications have such similar efficacy on visual outcomes that differences are minimized when they are given intensively.

Alternatively, maybe we need to apply more comprehensive statistics to find consistency in the data. Given the numerically greater mean VA gains of aflibercept compared to the other two medications at every time point through 2 years for the full cohort as well as eyes with 20/50 or worse baseline VA, other analyses such as area under the curve studies may reveal significant differences between the drugs. However, such analyses have not been presented or reported to date.

Perhaps the results of this trial corroborate the U.S. Food and Drug Administration recommendation that two trials be conducted in order to adequately evaluate efficacy and safety of a given treatment.11 The VIEW sister trials are a classic example. In VIEW1, monthly 2 mg aflibercept achieved statistically significantly more letters than 0.5 mg ranibizumab; however, when data from both trials were combined, intertrial differences were nullified, and all four treatment arms appeared remarkably similar.12

Finally, it is possible that patients in the bevac-
bevacizumab and ranibizumab arms received alternative treatments. Following publication of year 1 results, all participants were unmasked to their treatment and, though discouraged, patients could have switched to a non-study anti-VEGF agent or used a non-VEGF agent such as a steroid. In fact, few patients switched anti-VEGF medications, with just one patient reportedly switching from bevacizumab to aflibercept. But notably, more patients did receive an “alternative treatment,” with three, 10, and one such patients in the aflibercept, bevacizumab, and ranibizumab arms, representing 1%, 5%, and less than 1% of their respective populations.

ANATOMIC OUTCOMES

All Protocol-T VA analyses employed standardized ETDRS BCVA. No retina physician I know uses this method to evaluate VA clinically. What exactly is an ETDRS BCVA level of 20/50 in Snellen? Although conversions between Snellen and ETDRS BCVA are reported, these are correlative, and the answer likely varies between patients and longitudinally. OCT, in comparison, is consistent in and out of standardized trial protocols and readily available to nearly every retina physician.

In contrast to converging VA outcomes between the arms, anatomically, bevacizumab’s inferiority persisted relative to both aflibercept and ranibizumab. This was most apparent among patients with mild VA impairment at baseline, in which bevacizumab remained strikingly inferior through year 2, with OCT improvements about 50% less than that achieved with either other agent (P < .001 aflibercept or ranibizumab vs. bevacizumab). Further indicating compromised efficacy, normal optical coherence tomography (OCT) central subfield thickness (CST) measurements, defined as less than 250 µm by time-domain OCT after conversion, were achieved in statistically significantly fewer patients with bevacizumab than either aflibercept or ranibizumab for both baseline VA populations.

Comparing OCT-based anatomic outcomes between aflibercept and ranibizumab, no significant differences were identified at year-2. Additionally, the relationship of baseline CST (< 400 µm vs. > 400 µm) on outcomes favoring aflibercept that was observed at year 1 disappeared at year 2, with no statistically significant difference in outcomes observed with any of the three agents relative to baseline DME thickness.

If chronic fluid is damaging to retinal function and thereby vision, why were VA outcomes not more inferior among bevacizumab treated eyes during the course of 2 years? Multiple published analyses of the three most common exudative retinal diseases have indicated that a longer duration of retinal fluid and repeated recurrence of retinal fluid can result in suboptimal VA outcomes. In wet AMD, earlier treatment leads to better outcomes, aggressive treatment of residual retinal fluid optimizes visual outcomes from an exudative disease perspective, and repeated recurrence of fluid may limit ultimate mean visual gains. In venous occlusive disease, macular edema left un-treated for 6 months appears to incur a lasting visual penalty. Finally, substantial delay of anti-VEGF treatment for center-involved DME causing VA loss may blunt ultimate VA potential.

Despite these previous observations, Protocol-T year-2 OCT data suggests that residual DME may not be detrimental to visual outcomes in the context of ongoing anti-VEGF treatment. Alternatively, simply more time may be needed to identify the impact of persistent central DME in this chronic disease.

SAFETY

Through 2 years, more Anti-Platelet Trialists’ Collaboration events were recorded among patients treated with ranibizumab (12%) compared to bevacizumab (8%) or aflibercept (5%), with a global P value of .047. When potential baseline confounders were considered, however, significance was lost (P = .09). Similarly, when prior events were considered, there was no statistically significant difference in the incidence of myocardial infarctions and strokes between the agents, although numerically, ranibizumab had the largest proportion. Available meta analyses and large-cohort studies are conflicted regarding the potential systemic impact of intravitreally administered anti-VEGF agents and suggest that high-risk patients with higher levels of drug exposure may correlate with increased risk. More data are needed.

CHALLENGES AND REALITIES

Substantial opportunity remains for improving the patient-centric burden of DME care. Claims-based analyses imply most DME patients do not receive the intensity of care delivered during Protocol-T. Although the median number of intravitreal injections decreased from between nine and 10 in year 1 to between five and six in year 2, a median of 10 clinical visits were required during year 2 — identical to that required during year 1. In total, all patients, regardless of randomized arm, received approximately 20 clinical visits during the course of 2 years.

Even with the intensive care delivered across 2 years of Protocol-T, a majority of eyes demonstrated persistent DME and met criteria for macular laser. The frequent designation of “stability,” or futility,
criteria during Protocol-T echoes the incomplete effectiveness of anti-VEGF monotherapy in many eyes. Cumulatively, 25% to 29% of possible intravitreal injections were deferred during the entire 2 years because VA did not change by at least 5 letters and OCT did not change by more than 10% across consecutive visits, despite possible persistent DME. For such eyes with refractory DME, an integrated approach incorporating therapeutic agents, such as the dexamethasone23 and flucinolone inserts,24 deserves consideration.

Are we still justified in using bevacizumab first line for DME patients, as do the majority of U.S. retina specialists? The 2015 PAT survey reported the large majority of retina specialists would not choose bevacizumab first line for their own eye.25 Multiple explanations may contribute to this dichotomy between reality and preference. Foster, the bevacizumab used in all of the DRCR.net protocols as well as CATT25 was provided in individual glass vials. Storage of biologic medications such as bevacizumab in plastic results in potentially high variability of medication integrity and potency.26 Given the scope of DME care, ideally we would have clinical comparative data between bevacizumab stored in plastic, the norm for retina practices, versus glass, the norm for clinical trials, before mandating its use first line. Second, compounding-associated risks, although tiny, do exist.27 Third, comparative efficacy data from a multitude of trials involving both DME and neovascular AMD indicate that bevacizumab is an inferior drying agent. However, science is often not the driver of clinical practice. Cost, access to care, and access to providers are very real issues. Because of the current dramatic cost differences of aflibercept and ranibizumab compared to bevacizumab, when dollar values are assigned to visual outcomes, bevacizumab is easily the most cost-effective.28

Reassuringly from a practical perspective, all three anti-VEGF medications proved effective at achieving substantial and clinically meaningful visual benefit, with visual gains maintained or increased from year 1 to year 2 in all three arms of the complete Protocol-T dataset.9 Therefore, I believe that, yes, if needed, we as clinicians are justified in using any of the three anti-VEGF medications first line, so long as we keep the patient’s best interests and clinical progress always in focus and change course when indicated.

REFERENCES


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