I charged Dr. Charles Wykoff with the monumental task of analyzing and dissecting the DRCR Protocol T study, the first and only comparative effectiveness study of intravitreal aflibercept, bevacizumab, and ranibizumab for the treatment of diabetic macular edema (DME). Since the data were published last month, it would be hard to find a retina specialist who does not know the top-line results revealing the superior efficacy of aflibercept for treating patients with DME who have a presenting vision worse than 20/40.

However, Dr. Wykoff delves deeper into the data, focusing on differences in anatomical outcomes and treatment burden between the various agents. Furthermore, there are safety nuances that he highlights. Lastly, reading this article leads one to consider the ethics of offering a patient an off-label, inexpensive treatment when a “superior” agent exists to treat DME in patients with moderately worse vision.

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 NEI. I believe it will be considered the most impactful study of the year when we look back at 2015. Dr. Wykoff’s insights and review of this complex topic will be highly valued by our community.

Comparing aflibercept, bevacizumab, and ranibizumab for DME: Analysis of DRCR Protocol T

by Charles C. Wykoff, MD, PhD

The super-sized society throughout the developed world has created obesity and diabetes epidemics of alarming proportions. Nearly one in 20 people on the planet has diabetes mellitus. The collective impact of diabetic retinopathy (DR) and subsequent visual impairment is tremendous and growing. More than 95% of people with diabetes develop DR if they live long enough, and over 10% of these will develop diabetic macular edema (DME), the most common cause of visual loss from DR.1,2

ETDRS-validated macula laser remained the bedrock of DME management for 2 decades.3 Pharmacologic management has since taken center stage, driven by the use of pharmaceuticals that block the activity of vascular endothelial growth factor A (VEGF) and corticosteroids. Validated through the phase 3 VISTA and VIVID4 and RISE and RIDE trials,5 aflibercept (Eylea; Regeneron, Tarrytown, NY) and ranibizumab (Lucentis; Genentech, South San Francisco, CA) are FDA-approved for the management of DME. Bevacizumab (Avastin, Genentech), the most commonly employed agent6 due to cost and access limitations, is used off-label and has been evaluated through smaller trials including BOLT.7

A plethora of data has confirmed the efficacy and safety of anti-VEGF therapy in the management of exudative retinal diseases, but few trials have directly compared the agents. The Diabetic Retinopathy Clinical Research Network’s Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab for DME (Protocol T), also known as DRCR-T, stands alone as the only trial to compare the three agents head to head. The trial’s 1-year results were published February 18, 2015.8
DRCR-T overview

DRCR-T randomized 660 patients with central-involved DME with Snellen equivalent visual acuity (VA) of 20/32 to 20/320 equally to aflibercept (2.0 mg), bevacizumab (1.25 mg), or ranibizumab (0.3 mg). Unlike CATT and IVAN, DRCR-T did not employ a non-inferiority design. DRCR-T enrolled predominantly treatment-naïve patients; anti-VEGF treatment in the study eye within 12 months was exclusionary, and only 11% to 14% of patients had prior anti-VEGF treatment. The primary outcome measure was the change in VA from baseline to 1 year adjusted for baseline VA. At baseline, mean age was 61 years, 47% of participants were female, mean HbA1c was 7.7, mean duration of diabetes mellitus was 17 years, and mean VA was 20/50.

Visual and anatomic outcomes

Top-line results revealed clinically meaningful VA improvement with all three medications: +13.3 letters with aflibercept, +11.2 with ranibizumab, and +9.7 with bevacizumab. These +2.1 and +3.6 mean letter differences favoring aflibercept were statistically significant (\(P = .03\) aflibercept vs ranibizumab; \(P < .001\) aflibercept vs bevacizumab; \(P = .12\) ranibizumab vs bevacizumab).

In a pre-specified subgroup analysis, the medication effect on VA gains was strongly influenced by baseline VA (\(P < .001\) for interaction of VA gain with baseline VA as a continuous variable). Specifically among the 51% of patients with initial mild visual impairment (VA of 20/32 to 20/40), mean VA improvements were similar and not significantly different between the study arms: ranibizumab +8.3, aflibercept +8.0, and bevacizumab +7.5. Among the 49% of patients with initial VA of 20/50 or worse, mean VA improvement was greatest with aflibercept (+18.9) compared to ranibizumab (+14.2) or bevacizumab (+11.8) (\(P = .0031\) aflibercept vs ranibizumab; \(P < .001\) aflibercept vs bevacizumab; \(P = .21\) ranibizumab vs bevacizumab).

Anatomically, aflibercept and ranibizumab were both significantly better retinal-drying agents than bevacizumab, yielding mean optical coherence tomography (OCT) central subfield thickness improvements of −169 µm, −147 µm, and −101 µm, respectively (\(P < .001\) for both aflibercept vs bevacizumab and ranibizumab vs bevacizumab; \(P = .036\) for aflibercept vs ranibizumab). Among both patients with initial mild visual impairment and those with 20/50 or worse VA, aflibercept and ranibizumab had similar anatomic efficacy with no statistically significant differences between the drugs, and both were significantly more effective anatomically than bevacizumab (\(P < .001\) for aflibercept and ranibizumab vs bevacizumab in both subgroups).

Treatment burden

During the first 6 months of DRCR-T, participants received injections every 4 weeks unless an eye reached protocol-defined stability (not improved or worsened by at least five letters for at least two injections) and OCT central subfield thickness was less than 250 µm with VA 20/20 or better. After 6 months, injection was deferred when stability was reached even if the OCT demonstrated DME, and macular laser was applied if DME persisted according to protocol-specified criteria. While the mean number of injections was similar between the three agents, ranging from 9.2 to 9.7, aflibercept treatment resulted in fewer median injections (nine vs 10 and 10; \(P = .045\)) and fewer macular laser treatments (37% vs 46% and 56%; \(P < .001\)) compared to ranibizumab, and bevacizumab, respectively.

Safety

Differences in systemic exposure to anti-VEGF activity between the medications based on the presence or absence of an Fc domain is a potentially clinically relevant issue. In DRCR-T, there were no differences among the three medications in rates of serious adverse events, deaths, or hospitalizations. Furthermore, no significant differences were observed in rates of major cardiovascular events including stroke, myocardial infarction, and any APTC event. However, a post hoc analysis noted a higher frequency of combined cardiac and vascular disorders excluding hypertension among ranibizumab patients (17%) compared to aflibercept (9%) and bevacizumab (9%) patients (\(P = .024\)). The clinical relevance of this post hoc grouping is unclear and may be due to chance; indeed, the statistical significance of this difference was absent after including hypertension and adjusting for confounders (\(P = .081\)).

Limitations

While well-powered and well-designed, DRCR-T has limitations as do all clinical trials. First, the bevacizumab employed was provided in individual glass vials, as was performed in CATT. The process
of compounding and storing bevacizumab in plastic syringes may result in high variability in its integrity and potency.\textsuperscript{14} We do not know if compounded bevacizumab stored and delivered in plastic syringes, the norm for retina practices around the world, is functionally distinct from the bevacizumab used in DRCR-T.

Second, this is 1-year data. DME is a chronic disease. Despite similar VA outcomes in patients with baseline mild VA impairment among all three drugs, the anatomic inferiority of bevacizumab compared to the other two medications was striking. The effect of persistent retinal fluid on long-term visual outcomes in this population is unknown and demands further study, especially because 75% of DME patients may present with 20/40 or better VA.\textsuperscript{15} In both RISE and RIDE\textsuperscript{16} and VISTA and VIVID,\textsuperscript{17} delaying access to anti-VEGF treatment for control patients ultimately resulted in worse VA gains, presumably related to the effect of chronic undertreatment of central DME. The second year of DRCR-T is ongoing, and longer-term outcomes with as complete a data set as possible are needed.

Third, this is a single trial. In its guidelines on structuring a trial program intended to demonstrate clinical efficacy and achieve FDA approval of a pharmaceutical agent, the FDA states, “It has been the FDA’s position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.”\textsuperscript{18} Variability is inherent to biological systems. The VIEW 1 and VIEW 2 trials of neovascular age-related macular degeneration (AMD) are good examples.\textsuperscript{19} At the 1-year end point of VIEW 1, monthly aflibercept (2.0 mg) achieved 2.8 mean letters of VA gain versus monthly ranibizumab (0.5 mg), a statistically significant finding ($P=.005$). In VIEW 2, monthly ranibizumab (0.5 mg) achieved 1.8 mean letters of VA gain versus monthly aflibercept (2.0 mg). The authors reconciled these differences thus: “Numerical differences between treatment groups in one study at any given time point were not reproduced in the other study, suggesting that they reflected random variability even in groups of this size.”\textsuperscript{19} Similarly, identical dosing of monthly aflibercept gained 12.5 versus 10.5 mean letters at the 1-year end point in VISTA and VIVID, respectively.\textsuperscript{4}

Fourth, the approval of 0.3 mg ranibizumab is unique to the United States. Canada, Europe, and all other countries in which ranibizumab has been approved for DME management employ 0.5 mg. In moles, 0.3 mg ranibizumab represents 64% less medication than 2.0 mg aflibercept. RISE and RIDE identified no significant differences between ranibizumab doses,\textsuperscript{3} and the 0.3 mg dose may have been FDA-approved because fewer numerical cases of stroke (1.2% vs 3.2%) and death (2.8% vs 4.4%) were observed at the 2-year end point with 0.3 mg vs 0.5 mg respectively, although these differences were not analyzed statistically because the trials were not powered to evaluate differences in safety events. We do not know whether the 0.5 mg dose would have performed differently in DRCR-T.

Fifth, DRCR-T did not consider whether switching from one anti-VEGF medication to another or employing intravitreal corticosteroids\textsuperscript{20,21} could have improved outcomes, especially in eyes with persistent DME.

A real-world perspective

Independent of trial data, we practice retina in a world where cost matters, a lot. I often have the following discussion with my DME patients: “There is a medication that costs about $60 a treatment, another that costs about $1,100, and a third that costs about $1,900. Guess which one your insurance company may agree to pay for it, but making this request frequently puts the physician at risk for termination from insurance carriers for being designated a “high-cost provider.” Our patients deserve better. They deserve access to the optimal treatments for potentially blinding diseases such as DME.
Conclusion

DME is a global public health challenge. Treatment options have expanded tremendously from ETDRS laser to now include four FDA-approved pharmaceuticals in addition to off-label options. DRCR-T 1-year results afford a unique opportunity to directly compare the three anti-VEGF pharmaceuticals. The short summary is two-fold. First, visually: Aflibercept performed the best, primarily in patients with worse initial vision. Second, anatomically: Bevacizumab was significantly worse at retinal deturgescence compared to either aflibercept or ranibizumab in all subgroups. As always in research, much remains to be understood, and more data are needed in this complex disease.

REFERENCES


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