REAL-WORLD OUTCOMES OF ANTI-VEGF THERAPY FOR DIABETIC MACULAR EDEMA IN THE UNITED STATES

Visual outcomes for DME treatment in the real world are meaningfully worse than in randomized clinical trials.

BY THOMAS A. CIULLA, MD, MBA

Diabetic macular edema (DME, Figure 1) is a leading cause of blindness in the working-age population of most developed countries.[1] Anti-VEGF therapy is the first-line treatment for DME associated with decreased VA in the United States,[2] resulting in approximately 2 lines of visual improvement on average at 1 year. Specifically, in the VISTA and VIVID DME registration trials for aflibercept (Eylea, Regeneron), monthly loading followed by bimonthly aflibercept was associated with a mean gain in BCVA of 10.7 letters at 1 year.[3] In the ranibizumab (Lucentis, Genentech) DME registration trials, monthly ranibizumab was associated with mean BCVA gains of +12.5 (in RISE) and +10.9 (in RIDE) at 1 year.[4]

Few large prospective randomized clinical trials (RCTs) have compared the efficacy of the anti-VEGF agents for DME. The Diabetic Retinopathy Clinical Research Network (DRCR.net), sponsored in part by the National Institutes of Health, compared aflibercept, off-label bevacizumab (Avastin, Genentech), and ranibizumab for the treatment of DME in the Protocol T study. After 2 years, all three therapies, dosed according to a protocol-specific algorithm, demonstrated similar ETDRS letter improvement in VA from baseline (+12.8 letters for aflibercept, +10.0 letters for bevacizumab, and +12.3 letters for ranibizumab). Compared with this total study population, a subgroup of patients with moderate to severely diminished BCVA (20/50 to 20/320) at baseline experienced a greater number of letters gained (+18.3 letters for aflibercept, +13.3 letters for bevacizumab, and +16.1 letters for ranibizumab), and in this subgroup aflibercept was significantly more effective than bevacizumab.[5]

Several studies have investigated the translatability of the results of Protocol T and similar RCTs to the

AT A GLANCE

- Few large prospective randomized clinical trials (RCTs) have compared the efficacy of anti-VEGF agents for DME.
- Few large studies have investigated the translatability of DRCR.net Protocol T and similar RCTs to the real world, where outcomes for DME patients often diverge from data in RCTs because of exclusion criteria due to systemic or ocular disease.
- Compared with the selected populations of RCTs, real-world DME patients are prone to worse therapeutic outcomes because of more diverse patient presentations.
- Real-world DME patients with well-preserved VA are more prone to vision loss than patients with worse VA.
- Undertreatment of real-world DME may partially limit therapeutic outcomes.

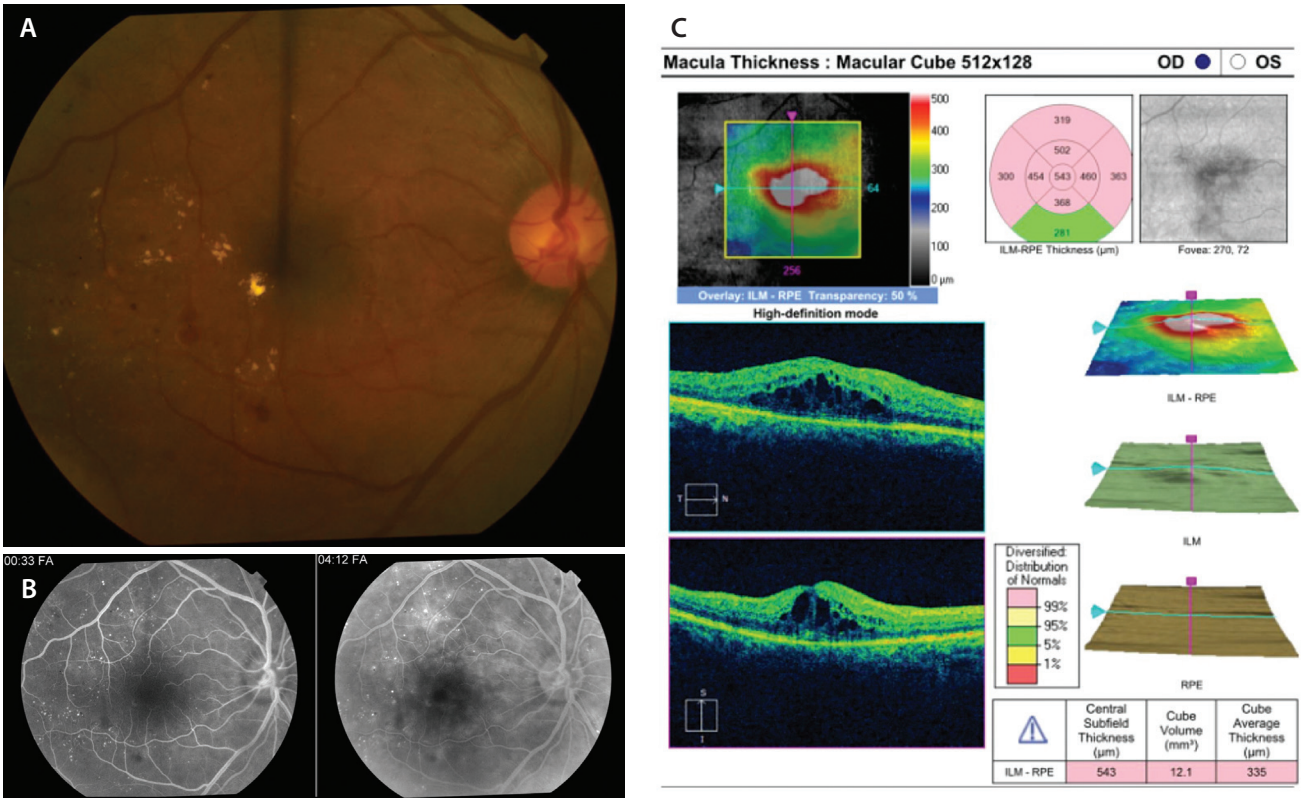

Figure 1. DME in a right eye. A color fundus photo depicts microaneurysms, hemorrhages, and circinate rings of hard exudates temporal to the fovea, typical of chronic DME (A). Middle and late frames of a fluorescein angiogram reveal leaking diabetic microaneurysms (B). OCT reveals central macular edema (C).

real world, in which DME patients diverge from RCT eligibility criteria due to concomitant systemic or ocular disease. These studies suggest that patients in the real world, on average, receive fewer injections and have worse visual outcomes compared with patients in RCTs.[6-11]

REAL-WORLD DME EXPERIENCE WITH ANTI-VEGF THERAPY AMONG US RETINA SPECIALISTS

In a recent study, my colleagues and I assessed real-world DME experience with anti-VEGF therapy in a large database of aggregated, longitudinal electronic medical records (EMRs) from a geographically and demographically diverse sample of US retina specialists, the Vestrum Health Retina Database.[11] The eyes of DME patients who underwent at least 3 monthly anti-VEGF injections within 4 months of the first injection between January 2011 and March 2017 were eligible if follow-up data were available up to March 2018.

The eyes were divided into three groups based on choice of initial intravitreal anti-VEGF agent (aflibercept, bevacizumab, or ranibizumab). These eyes were then subdivided into three cohorts, depending on length of follow-up (6, 12, or 24 months), with each cohort mutually exclusive. In this analysis, 15,608 DME patient eyes were included. The mean overall patient age, similar across the cohorts, was 62.9 years. The initial anti-VEGF agent was aflibercept in 21.3% of eyes, bevacizumab in 51.3%, and ranibizumab in 27.4%. The results are summarized in Figures 2 and 3.

REAL-WORLD OUTCOMES WITH ANTI-VEGF THERAPY ARE MEANINGFULLY WORSE THAN IN RCTS

Mining EMR data has numerous limitations, including the retrospective nature and the utilization of aggregated data, as well as nonstandardized VA assessment from multiple sites. Nevertheless, the resulting data can yield important longitudinal insights to better understand patient outcomes in clinical practice. Overall, our study demonstrated that VA outcomes in DME patients treated with anti-VEGF agents in the real world are inferior to those in RCTs by approximately 1 line of VA at 1 year.

Specifically, in the 12-month cohort, of 1,379 eyes initially treated with aflibercept, the mean 12-month improvement was +5.5 letters (95% CI, +4.5 to +6.6 letters, $P < .001$ after 7.5 injections on average). Outcomes were similar for bevacizumab (3,109 eyes, +5.5 letters, 95% CI +4.7 to +6.3 letters, $P < .001$, 7.9 injections) and ranibizumab (1,352 eyes, +4.0 letters, 95% CI +2.9 to +5.2 letters, $P < .001$, 7.7 injections). These outcomes were comparable to those from a recent EMR analysis of data from a large health system, in which the mean change in corrected VA from baseline was +4.7 letters in DME patients.[10] Cross-trial comparisons have limitations, and, as might be expected, compared with RCTs, real-world

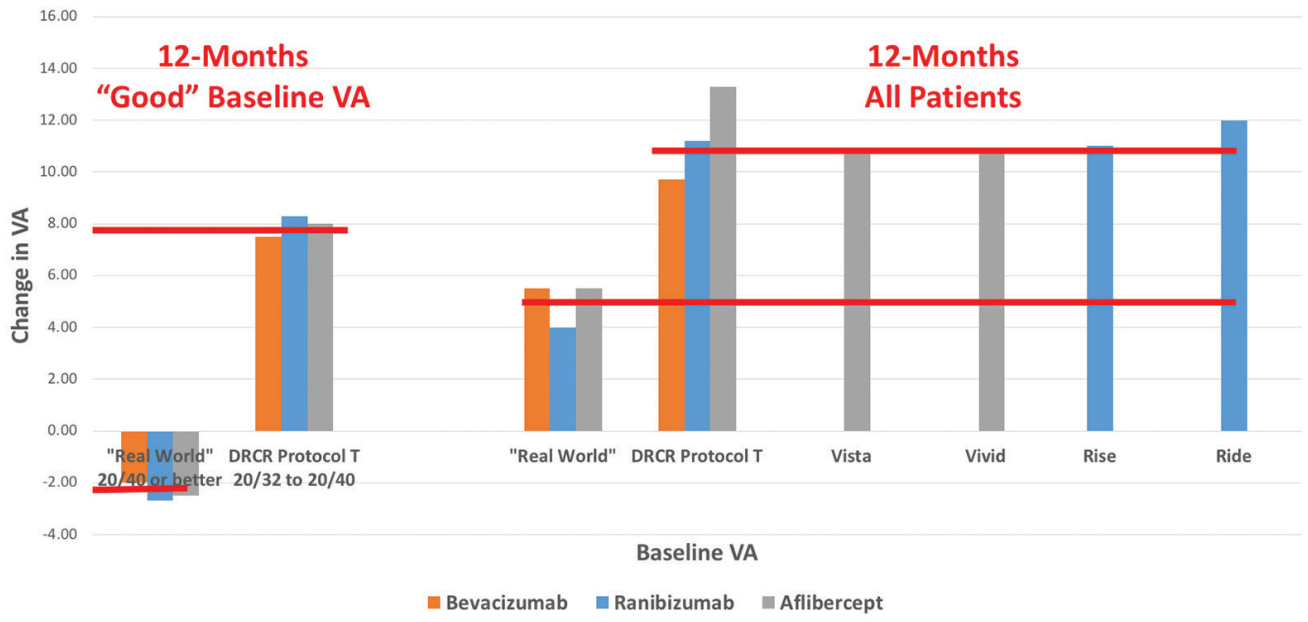

Figure 2. The change in VA from baseline for 12-month cohort is depicted. The change in VA from baseline was not meaningfully different between anti-VEGF agents. Real-world DME treatment outcomes in the United States compare poorly with results of RCTs. Although cross-trial comparisons have severe limitations, real-world DME patients gain approximately 5 letters at 12 months, in contrast to patients in RCTs who gain approximately 11 letters at 12 months. This difference in outcomes represents approximately 5 letters, or 1 line of VA. Also, real-world DME patients with baseline VA of 20/40 or better generally lost vision: approximately 2 letters by 12 months. In contrast, DRCR.net Protocol T patients with baseline VA of 20/32 to 20/40 gained approximately 8 letters. This difference in outcomes represents approximately 10 letters, or 2 lines of VA.

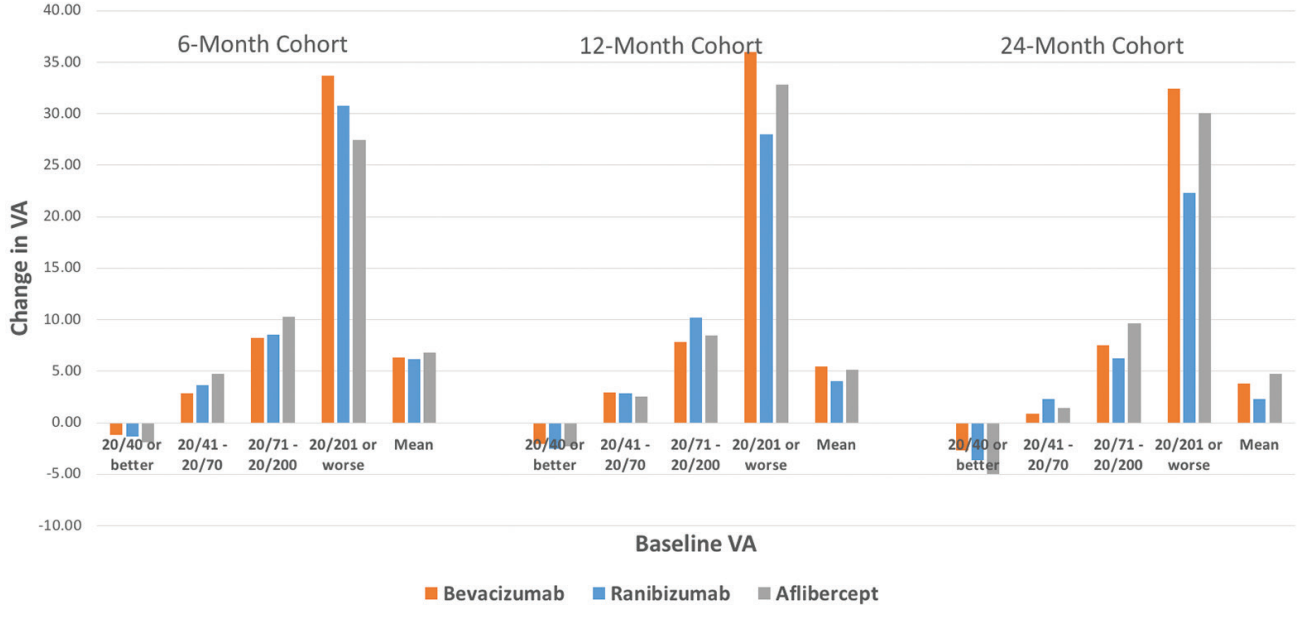

Figure 3. The change in VA between baseline and respective final follow-up dates for the 6-, 12- and 24-month cohorts is depicted, stratified by baseline VA. Eyes with initially good VA (20/40 or better) lost vision on average, while eyes with the worst VA (20/201 or worse) gained the most vision. No significant difference in VA outcomes was observed between follow-up groups, suggesting that poor VA at last follow-up was not a significant factor in loss to follow-up.

studies are prone to worse therapeutic outcomes, given the more diverse patient presentations, likely including advanced disease states not consistently eligible with RCT inclusion criteria. A specific limitation of our study was classification of DME patient eyes based on initial anti-VEGF agent, without accounting for switching between agents, which mutes the potential to detect differences between agents.

REAL-WORLD DME PATIENTS WITH WELL-PRESERVED VA ARE MORE PRONE TO VISION LOSS

In our study, real-world DME patient eyes with well-preserved baseline VA (better than 20/40) on average lost vision at 1 year. Cross-trial comparisons have limitations, but these visual outcomes differed by nearly 2 lines from the outcomes in eyes with similarly well-preserved VA in the DRCR.net Protocol T study. Specifically, in the 12-month cohort, when stratified by baseline VA (20/201 or worse, 20/71 to 20/200, 20/41 to 20/70, and 20/40 or better), the final numbers of mean letters gained or lost in these strata, respectively, were +28.0, +10.2, +2.8, and -2.5 in the aflibercept group, +36.0, +7.8, +2.9, and -2.0 in the bevacizumab group, and +30.5, +7.9, +1.6, and -2.7 in the ranibizumab group.

Naturally, a ceiling effect can limit improvement in eyes with better baseline BCVA; conversely, these eyes also have a relatively higher chance of experiencing vision loss. The visual outcomes of DME patient eyes with excellent baseline VA is being further evaluated by the DRCR.net in Protocol V.

UNDERTREATMENT MAY PARTIALLY LIMIT OUTCOMES

Previous real-world studies have demonstrated that DME patients are meaningfully undertreated, receiving as few as two to six treatments in the first year, with consistently poor visual outcomes.[6-10] Our data suggest that undertreatment potentially played only a partial role in accounting for the limited VA outcomes in this DME population. Because many US retina specialists include a series of initial monthly injections as part of an induction regimen, our inclusion criteria required at least three monthly anti-VEGF injections in the first 4 months from diagnosis.[11]

In our study, the mean number of injections at 12 months was 7.5, 7.9, and 7.7 for those started on aflibercept, bevacizumab, and ranibizumab, respectively. In the DRCR.net Protocol T trial, the mean number of injections at 12 months for those same drugs was 9.2, 9.7, and 9.4, respectively. Whereas RISE and RIDE employed monthly ranibizumab treatment[4] and VISTA and VIVID employed bimonthly aflibercept treatment after 5 monthly treatments,[3] the DRCR.net Protocol T employed a protocol-specific algorithm.* The slight decrease in injection frequency in this real-world analysis compared with DRCR.net Protocol T suggests that physicians are not frequently using fixed dosing regimens, but rather are employing as-needed or treat-and-extend regimens.

Consequently, undertreatment in real-world DME patients may not completely account for limited outcomes. In the real world, DME patient's eyes can have well-preserved baseline VA, leading to a ceiling effect that limits improvement in VA. Real-world DME patient eyes can also have extremely poor baseline VA due to advanced DME with ischemia or atrophy, which could limit visual recovery. Population characteristics such as more advanced ocular disease and/or uncontrolled systemic comorbidities are found in the real-world patient population but excluded in RCTs.

DEVELOPING A SOLUTION

Our study and other real-world DME studies highlight the importance of proper patient counseling regarding the need for frequent treatment visits. This is especially important for patients with well-preserved baseline VA, as these patients may not fully comprehend their increased risk of vision loss. Given the limited outcomes of anti-VEGF therapy highlighted by real-world DME studies, along with the burdensome need for repeated intravitreal injections to sustain efficacy, long-acting formulations of anti-VEGF drugs and therapies that address other pathways in diabetic retinopathy are being developed. In the future, sustained delivery systems, new classes of therapies, and combinations of therapies may meaningfully enhance outcomes for DME patients. ■

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* Eyes received monthly treatment unless BCVA was 20/20 or better, the central subfield thickness (CSFT) was less than the eligibility threshold, and there was no improvement or worsening after two monthly injections. Improvement was defined as an increase in BCVA of ≥ 5 letters or decrease in CSFT of ≥ 10%. Worsening was defined as a decrease in BCVA of ≥ 5 letters or an increase in in CSFT of ≥ 10%. Starting at week 24, treatment was withheld if there was no improvement or worsening after two injections, and treatment was reinitiated if BCVA or CSFT worsened.[5]