A POSTMODERN VIEW OF ANTI-VEGF TREATMENT

Knowledge is power in treating patients with DME.

BY NANCY M. HOLEKAMP, MD

At one time, laser photocoagulation was the only option for treating patients with diabetic macular edema (DME), but retina specialists now have three anti-VEGF agents in their arsenal: ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron), and bevacizumab (Avastin, Genentech). These drugs are so effective at neutralizing biologic VEGF that they are simultaneously diagnostic and therapeutic; if they are effective in the treatment of DME in a given patient, then we know that the patient's DME is VEGF-mediated.

Large prospective clinical trials have consistently confirmed that many patients have VEGF-mediated DME.[1,2] In the RIDE and RISE trials, 39% of patients met the primary endpoint of 15 or more letters of visual acuity improvement at 2 years (Figure 1).[1] Similarly, in the VISTA and VIVID trials, 38% of patients met a secondary endpoint of 15 or more letters of visual acuity improvement at 100 weeks.[2] This article reviews recent findings related to the treatment of DME with intravitreal injections of anti-VEGF agents.

BASELINE VISION A DRIVING FACTOR

The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study found that baseline vision was a driving factor in determining a favorable response to anti-VEGF therapy.[3] Of the eyes with baseline visual acuity of 20/50 or worse ETDRS equivalent letters, between 50% and 67% improved 15 or more letters at the primary endpoint of 1 year, depending on the anti-VEGF agent used.[3] Note, however, that these favorable visual acuity results required frequent or monthly injections. According to 2-year data from Protocol T, all three anti-VEGF agents evaluated in the study were still effective in treating DME at 2 years, and some significant differences between the evaluated anti-VEGF agents seen at the 1-year point were no longer present at year 2.[4]

In RIDE and RISE, patients received monthly injections through 2 years.[1] In VISTA and VIVID, the statistics cited above refer to patients who also received monthly injections through 100 weeks.[2] The average number of anti-VEGF injections given in Protocol T was nine (aflibercept) or 10 (ranibizumab and bevacizumab) in the first year.[3] However, recent real-world analyses of anti-VEGF injection use indicates that patients with DME, on average, receive fewer than four injections in the first 12 months of treatment.[5]

Furthermore, treatment with fewer anti-VEGF injections for DME has been correlated with less visual acuity improvement compared with the results seen in these randomized clinical trials.[6] Anti-VEGF agents are not magic; they are pharmacologic agents with a vitreous half-life.

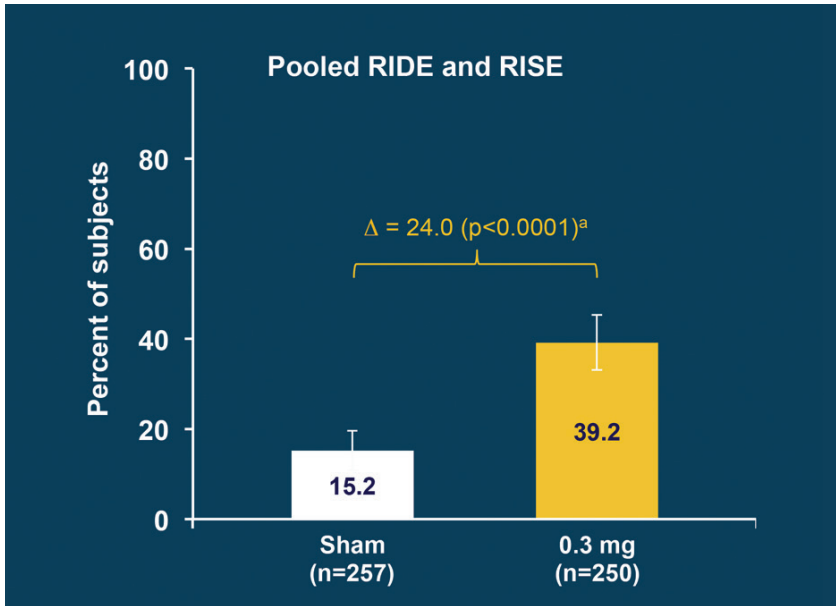

Figure 1. Patients gaining 15 or more ETDRS letters from baseline at year 2. Three-line gains in visual acuity were seen at 24 months in almost 40% of patients treated with ranibizumab.

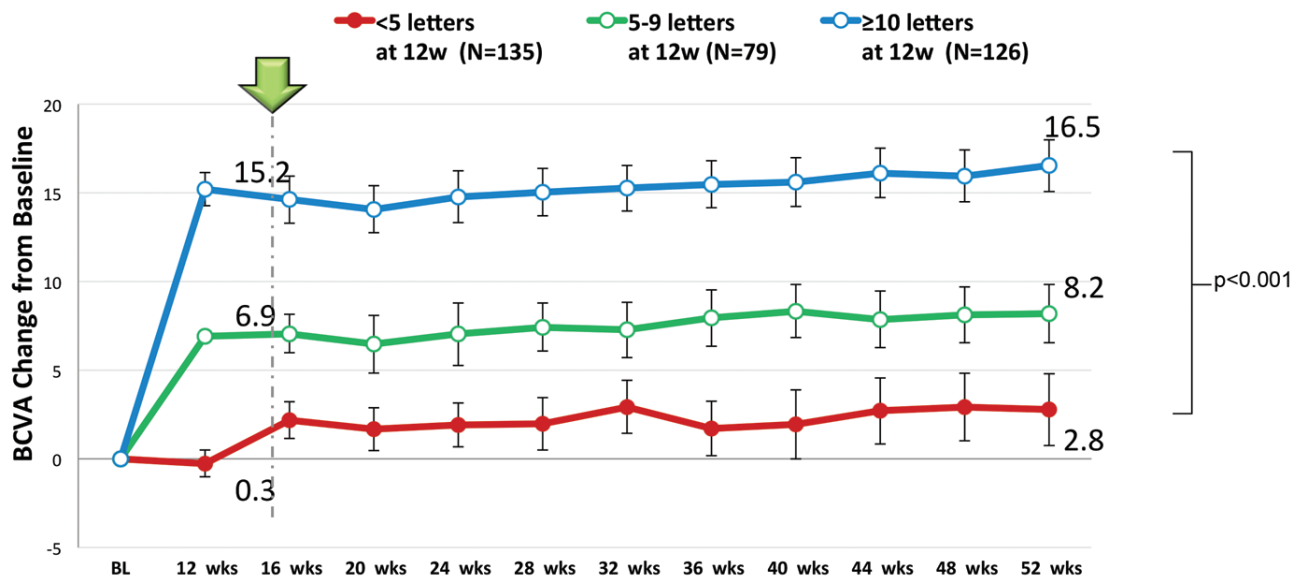

Figure 2. On average, stratification observed after three injections persisted for the first year.

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Nevertheless, we can find assurance in data from numerous prospective clinical trials that anti-VEGF agents, given frequently and regularly, are effective for treatment of DME. Furthermore, the safety profiles of these agents have been rigorously studied, and they have been deemed safe for patients with diabetes mellitus.[1-3] Thus, all three anti-VEGF agents are generally considered first-line therapies for treating center-involved DME.

The majority of the analyses of these clinical trials (RIDE and RISE, VISTA and VIVID, and Protocol T) have focused on the patients who improved with anti-VEGF treatment.

AT A GLANCE

- Anti-VEGF drugs must be dosed frequently and regularly in order to produce the intended biologic effect.
- Anti-VEGF agents are both diagnostic and therapeutic; if they are effective in a given patient, this means the patient's DME is VEGF-mediated.
- According to the EARLY Analysis, visual acuity stratification observed after three anti-VEGF injections in DRCR.net Protocol I predicted visual acuity outcomes at one year despite continued anti-VEGF treatment.

But what about the patients who did not improve? Roughly 60% of patients in RIDE and RISE did not meet the primary endpoint of the study after receiving monthly ranibizumab for 2 years, and more than 60% of patients in VISTA and VIVID did not meet a key secondary endpoint even though they received monthly aflibercept through week 100.[1,2] Despite the positive results of Protocol T for patients with poor vision at baseline, between 33% and 50% did not improve by 15 or more letters at 1 year, even after receiving nine to 10 anti-VEGF injections.[3] Thus, VEGF is clearly not the whole story in DME, and there is an opportunity to do more for patients who have the condition.

PREDICTING LONG-TERM RESPONSE AFTER THREE INJECTIONS

The Early Anti-VEGF Response and Long-term Efficacy (EARLY) Analysis of the DRCR.net Protocol I study is unique and thought-provoking because it examines the patients with DME who did not respond well to anti-VEGF therapy. The EARLY Analysis was an independent, post hoc analysis of the ranibizumab arms of Protocol I. Its purpose was to examine anti-VEGF treatment response at week 12 and to determine if it correlated with long-term BCVA outcomes in DME.[7] The results are surprising.

The EARLY Analysis divided patients into three groups based on their response at week 12 after three monthly anti-VEGF injections: those who gained less than 5 letters, those who gained 5 to 9 letters, and those who gained 10 or more letters. The analysis found that 39.7% of patients

improved by less than 5 letters. In fact, the mean visual acuity improvement in this group, which represented the largest group of patients from the entire cohort of monthly ranibizumab-treated patients, was -0.3 letters. The other groups were smaller: 23.2% of patients gained 5 to 9 letters, and 37.1% of patients gained 10 or more letters. Only 17.6% of patients gained 15 or more letters by week 12 (Figure 2).

A devil's advocate would point out that these visual acuity outcomes at 12 weeks were the result of only three monthly anti-VEGF injections, but one real-world analysis in an integrated health care system revealed that 75% of DME patients receive three or fewer anti-VEGF injections in their entire first year of treatment.[6] In Protocol I, patients continued to receive anti-VEGF treatment according to a prespecified DRCR.net algorithm and would receive, on average, eight or nine injections during their first year of treatment.[8] The most fascinating aspect of the EARLY Analysis is that the visual acuity results at week 12 predicted the long-term visual acuity response at 1 year and even at 3 years.[7]

This surprising result is best described by the term *swimming in their lanes*. If patients had a poor initial visual acuity response to anti-VEGF therapy (ie, <5-letter visual acuity gain), then they were unlikely to fare much better by 1 year. The mean visual acuity improvement for these patients at 1 year was within 5 letters of both baseline and the week 12 visual acuity results. In fact, visual acuity improvement at 12 weeks was a mean -0.3 letters, and by week 52 it was a mean 2.8 letters.

Similar results were observed in the group of patients gaining 5 to 9 letters by week 12, with mean visual acuity improvement of 6.9 letters at week 12 and mean visual acuity improvement of 8.2 letters at week 52. For the group of patients gaining 10 or more letters at week 12, the mean improvement at week 12 was 15.2 letters. By week 52 the mean visual acuity improvement was 16.5 letters. Thus, each group swims in its own lane. On average, the visual acuity stratification observed after the first three anti-VEGF injections persists for the first year despite continued anti-VEGF treatment.

CONCLUSION

Based on the information reviewed in this article, it is natural to wonder whether, by being astute clinicians and monitoring our DME patients closely, we can tell who will respond favorably to anti-VEGF injections over time. The answer is yes, we absolutely can—and a significant proportion of our patients will respond favorably. On the other hand, as astute clinicians who monitor our patients closely, can we identify which patients will not respond favorably to anti-VEGF injections? Again, the answer is yes. In fact, we can identify these patients early, allowing us to consider adding or switching to other therapies that may benefit this particular subset of patients. ■

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