What Is New with Anti-VEGF Therapy for DME

A wealth of evidence supports anti-VEGF therapy in DME.

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The landscape for the treatment of diabetic macular edema (DME) is evolving. Over the past 24 months alone, the US Food and Drug Administration (FDA) granted approval for three new medications for treatment of DME: the intravitreal dexamethasone implant (Ozurdex, Allergan), the fluocinolone acetonide implant 0.19 mg (Iluvien, Alimera Sciences), and aflibercept (Eylea, Regeneron) for intravitreal injection. Retina specialists have welcomed these additional agents as weapons in their toolkit for a commonly occurring, potentially vision-threatening condition that is challenging to treat.

For most physicians, anti-VEGF agents have become the first-line choice for center-involved DME. A plethora of clinical trial data help support the use of these agents, including the recently released results of the DRCR.net Protocol T study,[1] which provides additional guidance on the selection of an appropriate first-line agent for particular patients.

BACKGROUND

DME is a major cause of vision loss among people with diabetes. The incidence of DME increases with the severity and duration of diabetes, occurring in about 3% to 20% of patients.[2] Although the pathophysiology of DME is not wholly understood, VEGF has been identified as a major contributor.[3-5] Moreover, levels of VEGF have been demonstrated to be elevated in the vitreous of patients with diabetic retinopathy (DR) and DME.[3] Both DR and DME are characterized by a loss of pericytes and endothelial cells in the retina, and by capillary basement membrane thickening. Eventual microaneurysm formation paired with a compromised blood-retina barrier lead to vascular leakage and macular edema.[6,7]

In addition, recent information suggests that acute and chronic inflammatory changes occur in the retina and choroid. Interactions between vascular damage and inflammation further accelerate retinal injury, leading to advanced stages of DR and blindness.[8] The multimechanism pathophysiologies of DR and DME suggest a role for combination therapies.

For many years, focal laser photocoagulation was the standard of care for the treatment of DME. The results of the landmark Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated a 50% reduction in moderate vision loss (> 3 lines) with laser compared with observation. Significant visual gains were not seen with laser photocoagulation,[9] however, resulting in a continued need for better and more effective therapies.

The entry of VEGF inhibition as a therapeutic modality for the treatment of DME has resulted in a paradigm shift. Now, therapy can yield significant visual acuity gains and anatomic improvement.[10] Moreover, treatment with anti-VEGF agents has been shown to potentially decrease the worsening of DR in patients with DME.[11]

ANTI-VEGF THERAPY

To date, four intravitreal anti-VEGF agents have been tested in prospective randomized clinical trials for the treatment of DME: pegaptanib (Macugen, Valeant), bevacizumab (Avastin, Genentech), ranibizumab (Lucentis, Genentech), and aflibercept. Both ranibizumab and aflibercept are FDA-approved for the treatment of DME. Bevacizumab is used off-label by a large number of retina specialists (54% of US retina specialists responding to a survey reported using bevacizumab as first-line therapy for phakic patients with 20/50 vision[12]). Pegaptanib is used to a much lesser extent for DME.

Bevacizumab

Bevacizumab is a fully humanized recombinant monoclonal antibody that binds all isoforms of VEGF-A.[13] Several

studies support the efficacy of bevacizumab compared with focal laser photocoagulation for DME treatment.[14-20] Notable among these is the BOLT trial, in which 80 patients with persistent DME after macular laser therapy were randomly assigned to receive either bevacizumab or continuing laser therapy. Patients in the bevacizumab treatment arm had a mean gain of 8.6 letters versus 2.5 letters for those in the macular laser therapy arm at 24 months ($P = .005$). Vision gain of at least 15 letters was seen in 32% of patients in the bevacizumab arm compared with 4% in the laser arm.[18]

Ranibizumab

Derived from the same murine antibody as bevacizumab, ranibizumab is a monoclonal antibody fragment.[21] Data from the DRCR.net Protocol I study, RESTORE, and RISE and RIDE trials demonstrated the efficacy of ranibizumab against DME. In our view, these study results leave no doubt about the efficacy of ranibizumab in treatment of DME.[10,22-26] All of these studies had a duration of 36 months; the greatest benefit in visual acuity gain was seen in the first year of each study, with more modest changes thereafter.

In Protocol I, ranibizumab 0.5 mg was administered for four loading doses and then given on an as-needed (PRN) basis, with evaluations every 4 weeks thereafter. Patients received either prompt or deferred laser as an adjunct treatment. At 12 months, patients receiving ranibizumab plus deferred laser had a 9-letter improvement in visual acuity compared with a gain of 3 letters in the sham plus prompt laser group.[23] Results were similar in the ranibizumab plus prompt laser group.

Protocol I demonstrated the superiority of ranibizumab with prompt or deferred laser over laser alone. Moreover, this study demonstrated that PRN dosing could achieve visual and anatomic outcomes similar to those achieved with monthly dosing regimens. In this study, visual acuity gains following the first year of treatment were maintained with fewer treatments in subsequent years. Patients required an average of four injections in year 2, an average of two injections in year 3, and an average of one injection in year 4, highlighting the potential to safely and effectively use a modified retreatment protocol.[24,27]

In the RESTORE trial, patients received three loading doses of monthly ranibizumab 0.5 mg followed by PRN dosing with scheduled monthly visits. At 1 year the ranibizumab monotherapy group gained 6.1 letters compared with 0.8 letters in the laser monotherapy group.[22] Similarly, RISE and RIDE demonstrated robust gains of 12.5 and 10.9 letters, respectively, at month 24 for patients receiving ranibizumab 0.3 mg monthly.[10]

Comparing trials using PRN (RESTORE and Protocol I) and those using monthly treatment regimens, it appears at first glance that there were stark differences in visual outcomes. However, the differences likely reflect a "ceiling effect." Because the PRN trials on average included patients with higher levels of baseline visual acuity, patients had less opportunity for gain (ie, the ceiling effect). Overall, the PRN trials reassured us that monthly treatment was not necessary to enjoy visual benefits from anti-VEGF treatment.

Aflibercept

The efficacy of aflibercept is supported by the phase 3 trials VIVID and VISTA. In these parallel phase 3 studies, patients received aflibercept 2.0 mg every 4 weeks for five loading doses followed by continued treatment every 4 weeks (2q4) or every 8 weeks (2q8). At 12 months patients in both trials gained 10.7 letters in the 2q8 group compared with 0.2- to 1.2-letter gains seen in the laser control groups.[28] Again, the most robust gains in visual acuity were seen in the first 12 months of VIVID and VISTA, with more modest gains after the first 12 months.[28]

PROTOCOL T

Retina specialists are fortunate to have three anti-VEGF agents that have demonstrated efficacy based on well-controlled randomized trials. However, these agents are not structurally or pharmacologically identical. Surely, the greatest publicized and perceived difference in these agents has been cost. Allowable charges for Medicare vary from approximately $67 for 1.25 mg bevacizumab, to $1189 for 0.3 mg ranibizumab, to $1961 for 2.0 mg aflibercept. Payers and legislators have questioned whether the added cost for the latter two agents can be justified by demonstrable visual acuity or anatomic gains. Protocol T, much like its counterpart CATT in patients with age-related macular degeneration,[29] set out to investigate potential efficacy and safety differences among anti-VEGF agents in the treatment of central DME.

Data

The DRCR.net Protocol T trial was conducted at 89 clinical sites in the United States. In total, 660 adults with center-involved DME were randomized to 0.05 mL of 1.25 mg bevacizumab, 0.3 mg ranibizumab, or 2.0 mg aflibercept. The primary endpoint was change in visual acuity at 1 year, with planned follow-up through 24 months. Patients did not have to be naïve to treatment but could not have received anti-VEGF therapy within the previous year. A computer-assisted treatment algorithm was used to guide therapy. The algorithm was a modified PRN therapy based on visual acuity and optical coherence tomography (OCT) findings.

All three anti-VEGF agents produced visual acuity gains at 12 months. For all patients, improvement was greatest with aflibercept (13 letters) versus ranibizumab (11 letters)

TABLE. CHANGE IN VISUAL ACUITY FROM BASELINE AMONG TREATMENT GROUPS IN THE PROTOCOL T STUDY

	Aflibercept	Ranibizumab[a]	Bevacizumab[a]
Overall	+13.3 letters	+11.2 letters (P = .03)	+9.7 letters (P < .001)
Initial visual acuity 20/32 to 20/40 (78-69 letter score)	+8.0 letters	+8.3 letters (P > .5)	+7.5 letters (P > .5)
Initial visual acuity 20/50 or worse (letter score < 69)	+18.9 letters	+14.2 letters (P = .003)	+11.8 letters (P < .001)

[a] P values represent interaction versus aflibercept.

or bevacizumab (10 letters). The 2 to 3 letter benefit seen with aflibercept over both ranibizumab and bevacizumab was statistically significant, although the primary driver for this difference was baseline visual acuity.

A prespecified data analysis divided patients into those with baseline visual acuity of 20/40 or better versus those with 20/50 or worse (Table). For patients with baseline visual acuity of 20/40 or better, no significant difference was seen among all three drugs: gains of 7.5 letters with bevacizumab, 8.3 letters with ranibizumab, and 8.0 letters with aflibercept. For patients with 20/50 or worse visual acuity, aflibercept had a larger advantage, with gains of 18.9 letters for aflibercept, 14.2 letters for ranibizumab, and 11.8 letters for bevacizumab (P < .001 for aflibercept vs bevacizumab, P = .003 for aflibercept vs ranibizumab, and P = .21 for ranibizumab vs bevacizumab).

Moreover, the superiority of aflibercept in patients with worse baseline visual acuity translated into a clinically useful advantage, with significantly more patients achieving gains of greater than 3 lines (67% with aflibercept, 50% with ranibizumab, and 41% with bevacizumab). A similar effect to visual outcomes was seen with baseline OCT central thickness: the worse the disease (baseline OCT > 400 µm), the greater the benefit for patients treated with aflibercept.

The anatomic benefit at 1 year (reduction in central retinal thickness) was numerically superior for aflibercept over ranibizumab, but the difference was not statistically significant. However, both aflibercept and ranibizumab reduced central retinal thickness to a greater extent than bevacizumab regardless of baseline vision. These differences were statistically significant.

Analysis

The relative benefit of aflibercept was not driven by more injections or other treatments. In fact, the median number of injections was one fewer in the aflibercept group (9) than in the ranibizumab or bevacizumab groups (10; P = .045 for overall comparison). Laser was also performed less often with aflibercept (37% of patients) than with ranibizumab (46%) or bevacizumab (56%; P < .001 for overall comparison).

What is the reason for the apparent superiority of aflibercept, particularly in patients with baseline visual acuity worse than 20/40? One possibility is the relative differences in effective dosages (molar equivalent) of the individual anti-VEGF agents. This might lead one to wonder whether higher dose ranibizumab might have fared better. However, no such benefit was seen in RISE and RIDE comparing the 0.5 mg and 0.3 mg doses, or in the READ 3 study with the use of 2.0 mg ranibizumab.[26] A recently published smaller trial, however, has suggested a benefit with higher-dose ranibizumab in the treatment of refractory DME in some cases.[30]

The intraocular and systemic safety of intravitreal anti-VEGF agents has been well documented. Protocol T did not reveal any increased rates of intraocular inflammation or endophthalmitis among the treatment groups or in comparison with previous trials. Moreover, systemic adverse events, deaths, hospitalizations, and major cardiovascular events were similar in the three treatment groups and consistent with earlier studies. A post hoc analysis did find a small but significant increase in reported cardiac and/or vascular events in the ranibizumab group. The authors concluded that, given the inconsistency of this result with prior trials, this finding may have been a chance event. Overall, given the relatively small number of patients in this study, no definitive conclusions can be drawn about potentially rare safety differences among the drugs.

CONCLUSION

The results of Protocol T have been long awaited and are a welcome addition to the body of literature that supports the use of all three anti-VEGF agents in the treatment of center-involved DME. Aflibercept's superior performance in patients with 20/50 or worse visual acuity is notable. In considering the applicability of this study to our day-to-day practice, one must factor in that these results reflect population outcome averages with much underlying individual variability.

Moreover, questions linger, such as the applicability of this data in the setting of step therapy and anti-VEGF switching. Certainly, cost will continue to play a role in

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the implementation of these results. We look forward to the continued evolution of DME treatment, including the year 2 results of Protocol T. ■

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