Update on Laser Plus Intravitreal Ranibizumab for Diabetic Macular Edema

Two-year results of a clinical trial show continued efficacy.

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Diabetic macular edema (DME) is a major cause of visual loss in people with diabetic eye disease.[1] Standard treatment for DME since the time of the Early Treatment Diabetic Retinopathy Study has been focal/grid laser photocoagulation.[2] As recently as 2008, a randomized prospective clinical trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net) found that focal/grid laser was more effective than intravitreal injection of triamcinolone acetonide in the treatment of DME and was associated with fewer complications.[3] The investigators at that time urged that focal/grid laser remain the gold standard for evaluating other treatments for DME in clinical trials.

However, emerging data suggest that pharmacotherapy may soon take a more primary role as a treatment option for DME. Specifically, in another DRCR.net trial,[4] the vascular endothelial growth factor (VEGF) inhibitor ranibizumab (Lucentis, Genentech), combined with either prompt or deferred laser, showed superior anatomic and functional outcomes through at least 1 year of follow-up compared with laser alone in the treatment of DME with central macular involvement.

Recently, expanded 2-year data from this DRCR.net trial have been presented.[5] This paper summarizes key points from the 2-year data presentation.

1-YEAR DATA, PROTOCOL CHANGES

In this multicenter, randomized clinical trial,[4] treatment regimens were compared in individuals with center-involved DME. A total of 854 eyes of 691 individuals with visual acuity ranging from 20/32 to 20/320 were randomly assigned to intravitreal injection of 0.5 mg ranibizumab plus prompt laser, ranibizumab plus laser deferred at least 24 weeks, 4 mg triamcinolone acetonide plus prompt laser, or sham injection plus prompt laser. Retreatments were given according to an algorithm aided by an online registry.

At the 1-year primary endpoint, ranibizumab with either prompt or deferred laser provided superior anatomic and visual outcomes in patients with DME compared with laser alone. In eyes that were pseudophakic at baseline, triamcinolone acetonide appeared to be more effective than laser alone, but it increased the risk of intraocular pressure elevation; this was a subgroup analysis of a smaller set of eyes leading to less confidence in the results for which the entire group (both phakic and pseudophakic eyes) assigned to triamcinolone acetonide was not shown to be superior to laser alone, and, because eyes that were pseudophakic at baseline were not randomized separately, it is possible that other confounding variables which were not balanced at baseline by randomization contributed to the subgroup analysis findings.

After these 1-year data with some 2-year data supporting the 1-year results were published, some changes were made to the study protocol. In order to gain a more longitudinal perspective on this chronic disease, the study follow-up was extended to 5 years from the point of randomization. Also, all study participants, most of whom were approaching or had completed the 2-year follow-up, including those initially randomized to laser alone or triamcinolone acetonide plus laser, were allowed to receive ranibizumab if edema developed or worsened. In addition, the original triamcinolone acetonide plus laser group could continue to receive triamcinolone acetonide instead of ranibizumab at the investigator's discretion.

At the time these protocol changes were implemented,

not all patients had completed the 2-year outcome visit. Therefore, the data summarized below include only the 75% of patients (n=642; ranibizumab plus prompt laser, n=136; ranibizumab plus deferred laser, n=139; triamcinolone acetonide plus deferred laser, n=141) who had completed 2-year follow-up at the time of the protocol change.

RESULTS

During the first 6 months of the study, several ranibizumab injections were mandated by the protocol; patients received 4 mandatory injections at the first 4 monthly visits. Beginning at the 16-week visit, treatment could be deferred if success criteria were met. For the remaining visits in year 1, monthly injections could be given based on retreatment criteria.

In the first 6 months, in the patients who completed 2 years of follow-up, the median number of injections in both ranibizumab groups was 6, and the median number in the triamcinolone acetonide group was 2. In the second half of year 1, a median of 3 injections was given in both ranibizumab groups, and a median of 1 in the triamcinolone acetonide group. Between the year 1 and year 2 visits, the ranibizumab plus prompt laser groups received a median of 2 injections, the ranibizumab plus deferred laser group a median of 3, and the triamcinolone acetonide group a median of 1, based on protocol retreatment criteria.

The investigators also tried to examine predictive effects in patients who completed 2 years' follow-up with respect to need for additional treatments; that is, if a patient had a success early on (visual acuity of 20/20 Snellen equivalent or Stratus (Carl Zeiss Meditec, Dublin, CA) optical coherence tomography (OCT) central subfield <250 µm), how likely is it that he or she will no longer need injections? The percentage of eyes that met success criteria at week 16 and then received another injection by the 1-year visit was high in all groups: 87% in the ranibizumab plus prompt laser group, 84% in the ranibizumab plus deferred laser group, and 85% in the triamcinolone acetonide group. However, for those who met success criteria at 1 year and then received another injection by the 2-year visit, the numbers were lower but certainly not zero: 56% in the ranibizumab plus prompt laser group, 59% in the ranibizumab plus deferred laser group, and 56% in the triamcinolone acetonide group. This means that more than 40% of eyes in each of these groups did not require any additional injections between the year 1 and year 2 visits.

The other possible treatment in the trial was focal/grid laser. The maximum possible number of laser treatments that could be given before the 2-year visit was 8 in the ranibizumab plus prompt laser group, 6 in the ranibizumab plus deferred laser group, and 8 in the triamcinolone acetonide plus deferred laser group. It is notable that in the ranibizumab plus deferred laser group, a median of 0 laser treatments was given in year 1. A median of 2 laser treatments were given in the other 2 groups in year 1. Between the year 1 and year 2 visits, more laser treatments were given in all groups: in 40% of eyes in the ranibizumab plus prompt laser group, 29% in the ranibizumab plus deferred laser group and 52% in the triamcinolone acetonide group.

Regarding visual acuity, at 1 year the 2 IVR groups gained a mean of 8 (immediate laser) and 9 (deferred laser) letters from baseline, whereas the laser-only and IVTA groups each gained 3 letters. At 2 years, the mean gains from baseline in the ranibizumab groups were 7 (immediate laser) and 9 (deferred laser) letters, the laser-only group gained 3 letters, and the triamcinolone acetonide group dropped off slightly from the 1 year result to a mean gain of 2 letters from baseline.

Visual acuity results were analyzed in several ways. A greater percentage of eyes in the 2 ranibizumab groups gained 2 lines (10 letters) or more of visual acuity from baseline at 1 year—approximately half the eyes in each group—compared with approximately 30% in the focal/grid laser only group. At 2 years, these percentages were substantially maintained in the ranibizumab groups and were still superior to the focal/grid laser group ($P = .01$).

A smaller percentage of eyes in the ranibizumab groups lost 2 or more lines of visual acuity from baseline at years 1 and 2 than the other 2 groups ($P = .005$). The most worsening was seen in the triamcinolone acetonide group, and at least some of this worsening was thought to be related to the development of media opacity and subsequent cataract surgery.

Subgroup analysis showed that, in patients with 20/50 or better visual acuity at baseline, eyes receiving ranibizumab experienced a greater mean gain in visual acuity than eyes in the other 2 groups. Eyes in this subgroup receiving triamcinolone acetonide on average lost letters from baseline at 2 years, while those in the 2 ranibizumab groups gained approximately 4 letters. Patients with baseline visual acuity worse than 20/50, who had greater potential for visual gain, gained letters in all groups, especially the ranibizumab plus deferred laser group.

In the subgroup of eyes that were pseudophakic at baseline, at 2 years those in the ranibizumab plus deferred laser group had the greatest gain in letters of visual acuity from baseline, and next below that was the triamcinolone acetonide group, followed by the ranibizumab plus prompt laser and then the laser-only groups.

For the whole study population at 2 years, the mean change in retinal thickening from baseline was similar in 3 of the groups, at -138 µm in the laser-only group, -141 µm in the ranibizumab plus immediate laser group, and -150 µm in the ranibizumab plus deferred laser group. Exhibiting less thinning was the triamcinolone acetonide group at -107 µm.

Regarding safety, no systemic adverse events related to the study treatments were seen. There were a higher number of intravitreal injections in the ranibizumab groups than in the other groups, and there were more endophthalmitis events in those groups (2 in each group) than in the other groups (1 in the laser-only, 0 in the triamcinolone acetonide group). Cataract surgery, as would be expected, was markedly more frequent in the triamcinolone acetonide group, with 84% proceeding to cataract surgery by the 2-year visit, as opposed to 16% in the ranibizumab groups.

CONCLUSION

These expanded 2-year results with IVR for the treatment of center-involved DME are similar to results previously published, and they help to reinforce previous conclusions regarding visual acuity, anatomic response, and safety results.

Multiple clinical trials have now reported evidence of the effectiveness of anti-VEGF therapy in patients with visual impairment due to DME. We look forward to the presentation of further evidence of the efficacy of this pharmacologic intervention and a change in practice paradigms, from laser to anti-VEGF as primary therapy for DME, which in many locales has already begun. ■

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Tim Donald, ELS, is a consulting editor for Retina Today.

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