

New Paradigms for Treatment of Center-involved Diabetic Macular Edema

An update on anti-VEGF therapy and laser for DME.

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Diabetic macular edema (DME) is a major cause of vision loss in people with diabetes.¹ Focal/grid laser photocoagulation has been the standard-of-care treatment for DME since its positive effect was shown in the landmark Early Treatment Diabetic Retinopathy Study a quarter century ago.² More recently, a randomized controlled trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net)³ found that focal/grid laser was more effective and had fewer side effects than intravitreal injection of triamcinolone acetonide (delivered as a monotherapy) over a 2-year period in patients with DME. The study authors suggested that focal/grid laser should remain the benchmark against which other treatments for DME are compared in clinical trials.

In that DRCR.net study, focal/grid laser produced gains of two lines or more in visual acuity in one-third of eyes with center-involved DME over 2 years of follow-up. However, approximately one-fifth of laser-treated eyes in the study lost two or more lines over the same period.³ Thus, the search for alternative, more efficacious therapies for DME continues.

The DRCR.net conducted a randomized controlled trial to assess whether intravitreal injection of the vascular endothelial growth factor (VEGF) inhibitor ranibizumab (Lucentis, Genentech), combined with either prompt or deferred laser, or intravitreal triamcinolone acetonide combined with prompt laser, might result in improved visual acuity outcomes in comparison with the gold standard of focal/grid photocoagulation for DME.⁴ This article reviews the results of that trial, DRCR.net Protocol I.

FOUR GROUPS

This phase 3 multicenter trial included patients 18 years of age or older with type 1 or type 2 diabetes. Participants had best corrected visual acuity (BCVA) of Snellen-equivalent 20/32 to 20/320 (ETDRS letter score 78 to 24), center-involved retinal thickening due to

DME on clinical examination, and center subfield retinal thickness of 250 μ m or greater on time domain optical coherence tomography (OCT).

A total of 854 eyes of 691 participants were enrolled and randomly assigned to one of four treatment groups: sham injection plus prompt focal/grid photocoagulation, 0.5 mg intravitreal ranibizumab plus prompt laser, 0.5 mg intravitreal ranibizumab plus deferred laser, or 4 mg intravitreal triamcinolone plus prompt laser. "Prompt laser" meant that initial laser treatment occurred within 1 week of the initial intravitreal injection. "Deferred laser" group individuals were not eligible for laser until at least 6 months (24 weeks) had elapsed, and then only if there was persistent edema and only if that edema was no longer sequentially improving with serial injections. The primary outcome measure was BCVA at 1 year.

RETREATMENT

The retreatment algorithm used in the study was designed to avoid mandatory monthly treatment while also avoiding vision loss. The rationale was to provide a series of mandatory initial injections and then treat on an as-needed (PRN) basis until the eye achieved success or had stabilized. Once treatment was deferred, individuals continued to be monitored carefully, and treatment was resumed if there was any sign of relapse or recurrence.

In the first year, investigators used a 4-2-7 treatment rule. Every participant was seen monthly throughout the first year. The "4" stood for mandatory injection during the first four visits. Beginning at the fifth encounter, at week 16, treatment could be deferred, but only if the eye met the success criteria, meaning the visual acuity was the equivalent of 20/20 or the OCT had normalized. If these were not met, two mandatory additional injections were given; this was the "2" in the 4-2-7 rule. The "7" stood for the seven remaining monthly (ie, 4-weekly) visits to the end of month 12, at which monthly injections

could be given if edema persisted and if, with each successive injection, the eye continued to improve. Continued improvement meant that, relative to the last visit, visual acuity improved by 5 or more letters or thickness on OCT decreased by at least 10%.

There was a possibility of a maximum 13 injections during the first year. In the second year, 13 additional injections could be given if edema persisted and the eye was still improving with monthly injections. Beginning at week 60, however, the follow-up interval could be elongated to 8 weeks if treatment was deferred at that visit, either because the eye had met success or had stabilized, and if at the last two prior visits treatment had been deferred. Beginning at week 68, if the eye then satisfied the same criteria, the follow-up interval could be elongated to 16 weeks. That regimen was continued, and some participants have now been followed for more than 3 years, with a plan to continue follow-up for a total of 5 years from study entry.

RESULTS

At baseline, the mean visual acuity of the 854 randomized eyes was approximately 20/50, and median retinal thickness on OCT in the four groups ranged from approximately 370 μ m to approximately 400 μ m. Follow-up in the study was excellent, with 94% completing the 1 year primary endpoint.

Using the treatment algorithm described above, during the first 6 months of the study, the median number of injections in each of the ranibizumab groups was six. Throughout the first year, the median number was eight in the ranibizumab plus prompt laser group and nine in the ranibizumab plus deferred laser group. That means that, in months 7 through 12, the median numbers of additional injections were two and three in those groups, respectively. In the second year, the median number of injections in those groups was again two and three, respectively, spread over 12 months rather than 6 months.

As noted above, beginning at 16 weeks of follow-up, if success criteria were met, treatment could be deferred. Only approximately 25% of eyes in the ranibizumab groups achieved success at the week 16 visit. Among these patients, during the remainder of the first year, approximately 90% relapsed and needed additional treatment.

In the ranibizumab plus deferred laser group, laser could not be considered until week 24, and then only if edema persisted and the eye was no longer improving with each injection. With those criteria, approximately 28% of eyes in this group underwent laser treatment in year 1. During year 2, an additional 14% received laser. Therefore, through 24 months in the ranibizumab plus deferred laser group, nearly 60% of eyes never received laser. All patients in the ranibizumab plus prompt laser group underwent initial

laser treatment following their first study injection of ranibizumab. In year 1, approximately 70% of eyes in this group received at least one additional laser. In year 2, nearly half in this group received laser again.

In the primary outcome of BCVA at month 12, the change in letter score was significantly greater in the two ranibizumab groups (nine letters improvement in each, $P<.001$ for each), but not in the triamcinolone group (4 letters improvement, $P=.31$), compared with the sham plus prompt laser group (three letters improvement).

In the approximately 75% of patients who completed 2-year follow-up (prior to the implementation of a protocol change that permitted eyes originally assigned to sham injections or triamcinolone to receive ranibizumab), the ranibizumab groups show a sustained benefit of treatment (with, as noted, only two or three additional injections during the second 12 months of the study). The mean improvements in BCVA letter score from baseline to month 24 were three in the sham plus laser group, seven in the ranibizumab plus prompt laser group, 10 in the ranibizumab plus deferred laser group, and two in the triamcinolone plus prompt laser group.

A greater percentage of eyes in the ranibizumab groups achieved a substantial improvement in BCVA of two or more lines (10 or more letters) at 1 year: Fifty percent in the deferred laser group and 47% in the prompt laser group, compared with 30% in the laser alone group. Gains of three lines or more at 1 year were also more common in the ranibizumab groups than the other groups. Loss of two or more lines of BCVA was less common for the ranibizumab groups than for laser alone.

The anatomic findings on OCT confirmed the visual acuity results; the ranibizumab groups had the most rapid decreases in thickness and relatively flat curves through 2 years. At 2 years there was still a significant difference of about 30 μ m between the ranibizumab groups and laser alone.

In subgroup analysis, among individuals who were pseudophakic at study entry—about one-third of participants—improvement in BCVA in the triamcinolone plus laser arm appeared comparable to the two ranibizumab arms through month 12. Reduction in central retinal thickness on OCT in the triamcinolone group through month 12 was similar to the reduction seen in the ranibizumab groups. It has been suggested that BCVA gains in the triamcinolone plus prompt laser group may have been masked by the development of cataract among the participants who remained phakic throughout the study.

SAFETY

No systemic adverse events related to the study treatment were apparent. Three eyes (0.8%) in the ranibizum-

ab groups experienced injection-related endophthalmitis. No evidence of progressive tractional retinal detachment was seen, despite a high percentage of patients with a history of proliferative diabetic retinopathy receiving anti-VEGF treatment.

Almost 60% of eyes in the triamcinolone group underwent cataract surgery over 2 years of follow-up, compared with a 14% incidence of cataract surgery in the ranibizumab groups. In addition, 28% of individuals in the triamcinolone group required intraocular pressure-lowering medications during 2 years of follow-up, compared with roughly 4% in the ranibizumab groups and 5% in the laser.

CONCLUSION

This phase 3 study clearly demonstrated that intravitreal ranibizumab with either prompt or deferred laser provided superior anatomic and functional outcomes in individuals with DME through 2 years compared with the previous gold standard of laser alone.

It is crucial to recognize that the regimens employed in this study require seeing patients with DME frequently and recognizing that, even once treatment is deferred, more often than not patients will relapse and require additional care. It is by being diligent that we can provide the tremendous levels of efficacy and safety achieved in this study.

The combination of triamcinolone plus laser was not superior in efficacy to laser alone and did not approach the efficacy and safety of ranibizumab. An exception to this was seen in eyes that were pseudophakic at study entry; this was a subgroup analysis, so we must be conservative in drawing any substantial conclusions from this finding. ■

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To evaluate response to treatment in DME, retinal thickness measurement with OCT is crucial to evaluate structural changes—decreases in intraretinal or subretinal fluid as markers for reduction of vascular leakage. Visual acuity is also fundamental to evaluate the response to treatment because it determines whether or not we repeat treatments. It does not make much sense to keep injecting a patient whose visual acuity is not improving. Visual acuity also gives clues to the photoreceptor status, which determines the patient's potential for recovery.

For patients with DME who do not respond or respond poorly to anti-VEGF therapy, combination treatments may offer an additional benefit. Applying laser immediately after the first or second injection in the initial stages of anti-VEGF treatment may reduce the number of injections needed and/or improve response. Adding steroid injection or an extended release steroid implant may improve the disease course in patients who do not respond or respond poorly to anti-VEGF monotherapy.

It is crucial to identify responders and nonresponders to therapy for DME. If we can develop mechanisms to recognize early those patients who are not responding to therapy and devise alternative treatment approaches for them, we can be sure we are getting the right treatments to the right patients at the right time. ■

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