Primary End Point (Six Months) Results of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study

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Objectives: To compare ranibizumab with focal/grid laser or a combination of both in diabetic macular edema (DME).

Design: Prospective, randomized, interventional, multicenter clinical trial.

Participants: A total of 126 patients with DME.

Methods: Subjects were randomized 1:1:1 to receive 0.5 mg of ranibizumab at baseline and months 1, 3, and 5 (group 1, 42 patients), focal/grid laser photocoagulation at baseline and month 3 if needed (group 2, 42 patients), or a combination of 0.5 mg of ranibizumab and focal/grid laser at baseline and month 3 (group 3, 42 patients).

Main Outcome Measures: The primary end point was the change from baseline in best-corrected visual acuity (BCVA) at month 6.

Results: At month 6, the mean gain in BCVA was significantly greater in group 1 (+7.24 letters, P = 0.01, analysis of variance) compared with group 2 (−0.43 letters), and group 3 (+3.80 letters) was not statistically different from groups 1 or 2. For patients with data available at 6 months, improvement of 3 lines or more occurred in 8 of 37 (22%) in group 1 compared with 0 of 38 (0%) in group 2 (P = 0.002, Fisher exact test) and 3 of 40 (8%) in group 3. Excess foveal thickness was reduced by 50%, 33%, and 45% in groups 1, 2, and 3, respectively.

Conclusions: During a span of 6 months, ranibizumab injections by the current protocol had a significantly better visual outcome than focal/grid laser treatment in patients with DME.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

Diabetic retinopathy is the most prevalent cause of vision loss in working-age individuals in developed countries. Severe vision loss occurs because of tractional retinal detachments that complicate retinal neovascularization, but the most common cause of moderate vision loss is diabetic macular edema (DME). The pathogenesis of DME is not completely understood, but hypoxia is a contributing factor. Vascular endothelial growth factor (VEGF) is a hypoxia-regulated gene, and VEGF levels are increased in hypoxic or ischemic retina. Hyperglycemia also causes elevation of VEGF, and even before there is evidence of ischemia, VEGF is elevated in diabetic retinas. Injection of VEGF into mouse eyes causes breakdown of the inner blood–retinal barrier, and sustained release of VEGF in the eyes of monkeys causes macular edema. This combination of observations in patients and animal models led to the hypothesis that VEGF plays an important role in the pathogenesis of DME.

An orally active nonselective blocker of VEGF receptors was found to significantly reduce DME, which recurred when the drug was stopped, providing the first suggestion that VEGF antagonists might provide benefit in patients with DME. The development of selective antagonists of VEGF allowed for more definitive testing of the hypothesis. Ranibizumab is a Fab fragment of a humanized monoclonal antibody that binds all isoforms of VEGF-A with high affinity. In a small open-label study in patients with DME, it was found that 4 intraocular injections of 0.5 mg of ranibizumab over the span of 7 months resulted in a mean reduction in excess foveal thickening of 85% and an average improvement in visual acuity of greater than 2 lines. This strongly implicated VEGF in the development of DME and provided preliminary evidence that ranibizumab could provide benefit, suggesting that larger controlled clinical trials should be performed.

The Early Treatment of Diabetic Retinopathy Study (ETDRS) has shown that focal/grid laser photocoagulation can reduce the risk for moderate visual loss in eyes with DME. Focal/grid laser therapy is currently standard care and the gold standard with which new treatments are compared. We now report the results of a multicenter randomized trial in which a regimen of intraocular injections of
ranibizumab was compared with focal/grid laser photocoagulation over the course of 6 months. A potential impediment to the use of ranibizumab is the chronic nature of DME that could require long-term injections. A potential problem with focal/grid laser is that severe edema may make treatment more technically difficult and less effective, because the edematous retina is less transparent so that some laser energy is absorbed by the inner retina, which is undesirable. Also, the lack of transparency makes it difficult to assess when an appropriate end point is achieved. Injecting ranibizumab 1 week before focal/grid laser could reduce the amount of thickening and improve the transparency of the retina, thereby facilitating the laser treatment. Perhaps the more precise focal/grid laser could lead to long-term stability and eliminate the need for continued injections of ranibizumab. Therefore, combination treatment with ranibizumab and focal/grid laser was also tested.

Materials and Methods

This is a phase II, randomized clinical trial conducted at 14 sites in the United States through an investigator-initiated Investigational New Drug granted by the Food and Drug Administration. The study adhered to the guidelines of the Declaration of Helsinki, and the protocol and consent form were approved by a local institutional review board for some sites and by the Western Institutional Review Board for others. Each subject provided written informed consent. The study was monitored by an independent data and safety monitoring committee. The study is registered at www.clinicaltrials.gov under the identifier NCT00407381.

Patient Eligibility and Exclusion Criteria

Patients (aged ≥18 years) with type 1 or 2 diabetes and DME were eligible if they had reduction in visual acuity between 20/40 and 20/320 and met the following criteria: (1) center subfield thickness measured by optical coherence tomography (OCT) ≥250 μm, (2) glycosylated hemoglobin ≥6% within 12 months before randomization, (3) no potential contributing causes to reduced visual acuity other than DME, (4) reasonable expectation that scatter laser photocoagulation would not be required for the next 6 months. Patients were excluded if they had received focal/grid laser treatment within 3 months, intraocular injection of steroid within 3 months, or intraocular injection of a VEGF antagonist within 3 months. Patients were excluded if they had received focal/grid laser treatment no more than every 3 months if the center subfield thickness was ≥250 μm. Patients were called the day after each injection and were asked if they had decreased vision, eye pain, unusual redness, or any new symptoms.

Study Protocol

Consenting patients were screened for the study with a medical history, physical examination, measurement of best-corrected visual acuity (BCVA) by an experienced examiner using the ETDRS protocol, a slit-lamp examination, measurement of intraocular pressure, dilated funduscopic examination, an OCT evaluation, a fluorescein angiogram, and laboratory tests on blood and urine. Eligible patients were randomized 1:1:1 to injections of 0.5 mg of ranibizumab alone (group 1), focal/grid laser alone (group 2), or combination treatment consisting of injection of 0.5 mg of ranibizumab and focal/grid laser (group 3). Patients in group 1 received an injection of ranibizumab at baseline and months 1, 3, and 5. Patients in group 2 received focal/grid laser photocoagulation at baseline and again at month 3 if center subfield thickness was ≥250 μm. At baseline and month 3, patients in group 3 received an intraocular injection of ranibizumab followed by focal/grid laser treatment 1 week later. Month 6 was the primary end point of the study. After month 6, patients were eligible to receive intraocular injections of ranibizumab no more than every 2 months or focal/grid laser treatment no more than every 3 months if the retreatment criterion of center subfield thickness of ≥250 μm was met. Safety evaluations, measurement of BCVA, eye examinations, and OCT scans were done at all study visits. Fluorescein angiography was performed at baseline and 3 and 6 months. Measurements of glycosylated hemoglobin were done at baseline and 3 and 6 months. Hematology and blood chemistry tests were performed at baseline and 6 months.

Administration of Study Drug

A lid speculum was inserted, and after topical anesthesia the injection site was cleaned with 5% povidone iodine. Additional topical anesthesia or subconjunctival injection of 2% lidocaine was given, and 0.5 mg of ranibizumab was injected through the pars plana into the vitreous cavity. The fundus was examined to ensure retinal perfusion after the injection, and patients were observed for 1 hour or until intraocular pressure returned to normal. Patients were called the day after each injection and were asked if they had decreased vision, eye pain, unusual redness, or any new symptoms.

Focal/Grid Laser Photocoagulation

The ETDRS protocol with some modifications (50-μm light gray spots) was used for focal/grid laser treatment. Focal treatment was administered to each leaking microaneurysm, and grid treatment was placed in areas of thickened retina and areas of nonperfusion within 300 and 3000 μm from the center of the fovea.

Data Collection and Management

The Retinal Imaging Research and Reading Center (RIRRC) at the Wilmer Eye Institute served as the coordinating, data management, and reading center. Personnel from the participating sites were certified by RIRRC to perform digital fluorescein angiography and OCT based on standardized protocols developed by the RIRRC. Visual acuity examiners were required to be certified by EMMES Corporation or by a multicenter Phase II/III clinical trial. Data were collected online using a customized version of StudyTrax (ScienceTrax Inc., Jacksonville, FL), and training was provided to each site for use of the online system. Files for fluorescein angiography and OCT were uploaded to the RIRRC web site. Coordinators at the RIRRC monitored the database weekly and alerted sites of missed visits or failure to upload files and followed up until these tasks were completed.

Optical Coherence Tomography

At each clinical site, OCT scans were performed by a certified technician with a StratusOCT (Carl Zeiss Meditec, Dublin, CA) using the fast macular scan protocol. This protocol consists of 6 line scans that are 6.0 mm long centered on fixation and spaced 30 degrees apart around the circumference of a circle. Each line consists of 128 A-scan measurements. With each A-scan, the OCT software measures the distance between the inner surface of the retina and the anterior border of retinal pigment epithelium-choriocapillaris. The center subfield thickness, the average of 21 measurements along the central 1 mm of each of the 6 scans (total of 126 measurements), was used as a measure of foveal thickness. Readers at the RIRRC examined the images for each OCT file to be sure that there were no artifacts such as misidentification of inner
or outer surface of the retina. When artifacts were present, corrected measurements were obtained using RetinaTomographer software (version 1.1, RIRRC, Baltimore, MD). Macular volume throughout the entire 6-mm zone is calculated using extrapolated values between the line scans. Excess foveal thickness was calculated by subtracting the measured foveal thickness value from 212 μm, the upper limit of the normal range of center subfield thickness determined from measurements on a large population of subjects.9 Excess macular volume was determined by subtracting the upper limit of the normal range of 6.47 ± 0.37 mm³ from the measured value.

Data Safety and Monitoring Committee

An independent Data Safety and Monitoring Committee made up of 2 retina specialists with expertise in clinical trials monitored adverse events and data at regular intervals.

Statistical Analyses

The primary outcome measure was the change in BCVA between baseline and month 6. Secondary vision-related outcome measures were the change in BCVA between baseline and month 3 and the percentage of patients with 3 or more lines or 2 or more lines improvement at month 6. Secondary anatomic outcomes were the change in foveal thickness between baseline and month 6 and the percentage of patients with elimination of 90% or 50% excess foveal thickness.

Change from baseline in ETDRS visual acuity and change from baseline in excess foveal thickness were compared across the 3 groups at months 3 and 6 using 1-way analysis of variance with Bonferroni post hoc analysis. Outcome comparison between different time points within a group was done using a single-sample t test. Secondary anatomic and functional outcomes were compared using a 2-sided Fisher exact test.

Results

Baseline Characteristics of the Study Groups

The baseline characteristics of the 126 patients who were randomized in the study are listed in Table 1. The 3 groups were balanced with respect to mean BCVA, excess foveal thickness, and glycated hemoglobin. At baseline, 78 of the 126 patients had hypercholesterolemia that required treatment, and this was balanced among the groups: 26 patients in group 1, 29 patients in group 2, and 23 patients in group 3. There were no significant differences in any baseline characteristics among the 3 groups.

Missing Values and Early Terminations

Data were available for 115 of 126 patients at the 6-month primary end point. Nine patients exited the study before the primary end point for the reasons listed in Table 2. The treatment randomization, time point of the patients’ last visit, and BCVA at baseline and last visit are also shown. One patient in group 3 died of a cerebral vascular accident 6 weeks after study entry and injection of ranibizumab. Three patients were lost to follow-up, and 3 patients withdrew consent. One patient received scatter laser photocoagulation by an ophthalmologist not participating in the study and by protocol had to exit the study. One patient in group 2 had a substantial decrease in BCVA at the 3-month visit, which was reported to be due to a combination of marked worsening of DME and vitreous hemorrhage. The treating physician thought it was in the patient’s best interest to exit the study and receive alternative treatment. Four patients (1 patient in group 1, 2 patients in group 2, and 1 patient in group 3) withdrew from the study before receiving any treatment. Two patients (both in group 1) missed the window for the 6-month visit. All patients who did not have 6-month visit data, but had any posttreatment data at a time point before month 6, had the last observation carried forward for analysis of the primary outcome.

Primary Outcome Measure: Mean Change from Baseline in Best-Corrected Visual Acuity

In group 2, the laser only group, 36 patients had a center subfield thickness >250 μm at 3 months; 32 patients received additional focal/grid laser and 4 patients were judged to have maximum laser in the macula and were not treated. At month 6, the mean gain in BCVA was 7.24 letters in group 1, which was significantly better than the outcome in group 2, in which there was a mean loss of 0.43 letters (Fig 1; P = 0.0001, analysis of variance with Bonferroni post hoc analysis). There was no statistically significant difference between group 1 and group 3, in which there was a mean gain of 3.8 letters (P = 0.08). Thus, with regard to the primary outcome of mean change in BCVA at 6 months, the current regimen of injecting 0.5 mg of ranibizumab for 2 months and then 2 additional injections 2 months apart was superior to focal/grid laser treatment.

Secondary Vision-Related Outcome Measures

The mean change in BCVA between baseline and 3 months in group 1 was 3.98 letters, significantly better than the mean loss of 1.48 letters in group 2 (P = 0.01, analysis of variance with Bonferroni post hoc analysis), but not significantly different from the 1.93 letters gain (P = 0.22) in group 3 (Fig 1). Of the 37 patients in group 1 for whom data were available at 6 months, 8 (22%) had an improvement of 3 or more lines of BCVA and 17 (46%) had an improvement of 2 or more lines (Fig 2A). None of the 38 patients with only focal/grid laser therapy in group 3 improved by 3 or more lines and 2 patients (5%) improved by 2 more lines, both significantly less than in the ranibizumab group. Three of 40 patients (8%) in group 2 who had combined treatment improved by 3 or more lines, and 12 patients (30%) improved by 2 or more lines.

<table>
<thead>
<tr>
<th>Group 1: Ranibizumab (n = 42)</th>
<th>Group 2: Laser (n = 42)</th>
<th>Group 3: Ranibizumab (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% women)</td>
<td>69</td>
<td>55</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>76</td>
<td>64</td>
</tr>
<tr>
<td>Age (mean yrs)</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Mean BCVA (ETDRS letters read)</td>
<td>24.85</td>
<td>28.35</td>
</tr>
<tr>
<td>Mean BCVA (Snellen equivalent)</td>
<td>20/80</td>
<td>20/80+3</td>
</tr>
<tr>
<td>Mean excess foveal thickness (μm)</td>
<td>198.75</td>
<td>227.67</td>
</tr>
<tr>
<td>Hemoglobin A1C (mean mg/dl)</td>
<td>7.39</td>
<td>7.77</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.
Group 3 Day 7 Patient received scatter photocoagulation and by protocol had to be exited from the study.

Group 3 Day 7 Died of stroke 6 wks after enrollment and treatment.

Group 2 Baseline Patient refused laser treatment and withdrew consent.

Group 2 Baseline Lost to follow-up with multiple failed attempts to contact patient.

Group 1 Baseline Lost to follow-up with multiple failed attempts to contact patient.

Change in visual acuity from baseline in patients with diabetic macular edema treated with ranibizumab, focal/grid laser, or a combination of both (RBZ+laser). The mean (±standard error of the mean) change from baseline in number of letters read at 4 m at 6 and 3 months was significantly greater for ranibizumab alone versus focal/grid laser alone. The combination group was not significantly different from the other 2 groups at either time point. *P = 0.01; †P = 0.0003 by 1-way analysis of variance and Bonferroni post hoc analysis. ETDRS = Early Treatment Diabetic Retinopathy Study; RBZ = ranibizumab.

Secondary Anatomic Outcome Measures

Patients in group 1 showed a reduction in mean excess foveal thickness from 210.0 μm at baseline to 103.7 μm, approximately a 50% reduction in macular edema (Fig 3). The improvement in foveal thickness correlated well with improvement in mean visual acuity. Patients in group 2 had a mean excess foveal thickness of 227.6 μm at baseline that improved to 144.8 μm at 6 months, approximately a 36% reduction, which as noted above was not accompanied by improvement in mean visual acuity. Patients in group 3 had a mean excess foveal thickness of 262.5 μm at baseline that improved to 145.3 μm at 6 months, a 45% reduction in macular edema. The mean excess foveal thickness at 6 months was 103.7 μm in group 1, 144.8 μm in group 2, and 145.3 μm in group 3. For those patients for whom data were available at 6 months, the percentage of patients who had elimination of 90% or greater of excess foveal thickness was 24% in group 1, which was greater than the 8% for groups 2 and 3 (Fig 4A). The percentage of patients who had elimination of 50% or greater of excess foveal thickness was not significantly different among the groups: 54%, 48%, and 32% for groups 1, 2, and 3, respectively (Fig 4B).

Adverse Events

There was 1 serious adverse event; a patient in group 3 died of a cerebral vascular accident 6 weeks after his first injection of ranibizumab. The patient was at high risk for cerebral vascular accident because of preexistent cardiovascular disease, and the event was judged to be unrelated to ranibizumab because of the long period between its occurrence and the prior injection. Mean systolic/diastolic readings at baseline, month 3, and month 6 were 134.19/77.64, 131.56/74.15, and 134.75/75.31, respectively, in group 1 compared with 138.33/80.69, 135.95/79.58, and 139.97/77.56, respectively, in group 2 and 136.93/76.00, 139.49/78.82, and 136.93/76.00, respectively, in group 3. The small differences among groups and at different time points within groups were not statistically significant. Ocular adverse events included vitreous hemorrhages in 8 patients (1 patient in group 1, 4 patients in group 2, and 3 patients in group 3). One patient in group 2 had substantial worsening of macular edema and mild vitreous hemorrhage at the 3-month visit, and the investigator thought it was in the patient’s best interest to exit the study and receive alternative treatment (Table 2). The other patients were thought to have mild vitreous hemorrhages that according to funduscopic examinations were noted to have cleared by the 6-month visit. This information and comparison of BCVA measurements before the event with those at
the 6-month visit suggest that vitreous hemorrhage had no impact on the primary outcome variable for these patients (Table 3).

**Discussion**

We previously showed that VEGF plays an important role in the pathogenesis of DME and provided preliminary evidence suggesting that intravitreal injections of ranibizumab provides benefit in patients with DME. Ten patients with DME who received injections of 0.5 mg of ranibizumab at baseline and months 1, 2, 4, and 6 showed a mean improvement in visual acuity of 12.3 letters read and a reduction in mean excess foveal thickness from 503 μm to 257 μm, constituting an elimination of 85% of edema. Although those results are encouraging, small uncontrolled trials must be viewed with caution and serve primarily to stimulate and help design controlled clinical trials. In particular, it is important to know how new treatments compare with treatments that constitute standard care, which for DME is focal/grid laser photocoagulation. We now report the results

Figure 2. Percentage of patients with improvement in visual acuity between baseline and 6 months of ≥3 lines or ≥2 lines. A, Eight of 37 patients (22%) treated with ranibizumab for whom data were available at 6 months improved ≥3 lines, which was significantly greater than 0% of patients treated with laser alone (P = 0.002, Fisher exact test). B, The percentage of patients with ≥2 lines of improvement was also significantly greater in the ranibizumab group (46%, P = 0.00004) or the combination group (30%, P = 0.007) compared with the focal/grid group (5%). VA = visual acuity.

Figure 3. Mean change in excess foveal thickness between baseline and 6 months. Normal 1-mm center subfield thickness (212 μm) was subtracted from measured center subfield thickness to give the excess foveal thickness for each patient at each time point. The bars show the mean (±standard error of the mean) excess foveal thickness at baseline and 3 and 6 months for patients treated with ranibizumab alone (A), focal/grid laser alone (B), and a combination of ranibizumab and focal/grid laser (C). When compared with baseline, all 3 groups had statistically significant reduction in excess foveal thickness at month 6 (P = 0.0000002, P = 0.003, and P = 0.0000002 for groups 1, 2, and 3, respectively). EFTH = excess foveal thickness; FTH = foveal thickness; RBZ = ranibizumab.
of a multicenter, randomized study comparing a similar regimen of intraocular ranibizumab with focal/grid laser photocoagulation. The results show that patients given an intraocular injection of 0.5 mg of ranibizumab at baseline and months 1, 3, and 5 showed a significantly better visual outcome at 6 months (mean improvement of 7.24 letters) compared with patients treated with focal/grid laser at baseline and again at month 3 if there was persistent edema (loss of 0.43 letters). This confirms that intraocular injections of ranibizumab provide benefit in patients with DME, which, over a time frame of 6 months is greater than that provided by focal/grid laser therapy.

Secondary outcome measures also suggested superiority of ranibizumab over focal/grid laser. Of 37 patients treated with ranibizumab for whom data were available at 6 months, 8 (22%) had an improvement of 3 or more lines of BCVA and 17 (46%) had an improvement of 2 or more lines. This is significantly better than the focal/grid laser group, in which no patients improved by 3 or more lines ($P = 0.007$, Fisher exact) and 2 patients (5%) improved by 2 or more lines ($P = 0.002$, Fisher exact). The mean reduction in excess foveal thickness was 50% in the ranibizumab group and 33% in the focal/grid laser group. Thus, focal/grid laser treatment had some impact in that it caused a modest reduction in edema, but that reduction was not accompanied by improvement in visual acuity.

A recent study compared focal/grid laser treatment with intraocular injections of 1 or 4 mg of preservative-free triamcinolone acetonide with repeat treatments every 4 months for persistent or recurrent DME. At 4 months, mean improvement in visual acuity was significantly better in the 2 triamcinolone groups compared with the focal/grid laser group, but at the 2-year primary end point the focal/grid laser group showed a mean improvement of $17$, which was significantly better than the triamcinolone groups (4 mg group, $22$; 1 mg group $22$). Therefore, we cannot rule out the possibility that with longer follow-up, the difference between our ranibizumab injection group and the focal/grid laser group would disappear or even reverse. This should be determined by ongoing studies with longer primary end points.

A second objective of our study was to determine if injections of ranibizumab 1 week before focal/grid laser photocoagulation enhanced the effects of focal/grid treatment. The combined treatment group showed a mean improvement of 3.8 letters compared with the 0.43 reduction

![Figure 4](image-url). The percentage of patients with elimination of ≥90% or ≥50% excess foveal thickness at 6 months. A, More patients treated with ranibizumab alone (24%) had elimination of ≥90% of excess foveal thickness than patients treated with focal/grid laser alone (8%) or a combination of ranibizumab and focal/grid laser (8%). B, There was no significant difference among the groups in the percentage of patients with elimination of ≥50% of excess foveal thickness. EFTH = excess foveal thickness.

### Table 3. Ocular Adverse Events

<table>
<thead>
<tr>
<th>Group</th>
<th>Event</th>
<th>Pre-Event (ETDRS VA)</th>
<th>AE Visit (ETDRS VA)</th>
<th>Follow-up Visit (ETDRS VA)</th>
<th>Month 6 ETDRS VA</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Vitreous hemorrhage</td>
<td>Baseline (27)</td>
<td>Day 7 (43)</td>
<td>Month 1 (44)</td>
<td>51</td>
<td>Resolved</td>
</tr>
<tr>
<td>Group 2</td>
<td>Vitreous hemorrhage</td>
<td>Baseline (30)</td>
<td>Month 3 (21)</td>
<td>Month 6 (35)</td>
<td>35</td>
<td>Resolved</td>
</tr>
<tr>
<td>Group 2</td>
<td>Vitreous hemorrhage</td>
<td>Baseline (40)</td>
<td>Month 2+7 days</td>
<td>Month 3 (39)</td>
<td>35</td>
<td>Resolved</td>
</tr>
<tr>
<td>Group 2</td>
<td>Vitreous hemorrhage and</td>
<td>Baseline (16)</td>
<td>Month 3 (0)</td>
<td>Discontinued</td>
<td>Discontinued</td>
<td>NA</td>
</tr>
<tr>
<td>Group 2</td>
<td>worsening of DME</td>
<td></td>
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<tr>
<td>Group 2</td>
<td>Vitreous hemorrhage</td>
<td>Baseline (2)</td>
<td>Month 3 (4)</td>
<td>Month 6 (0)</td>
<td>0</td>
<td>Resolved</td>
</tr>
<tr>
<td>Group 2</td>
<td>Vitreous hemorrhage</td>
<td>Month 3 (4)</td>
<td>Month 4+7 days (2)</td>
<td>Month 6 (0)</td>
<td>27</td>
<td>Resolved</td>
</tr>
<tr>
<td>Group 3</td>
<td>Vitreous hemorrhage</td>
<td>Day 7 (27)</td>
<td>Month 3 (35)</td>
<td>Month 6 (37)</td>
<td>37</td>
<td>Resolved</td>
</tr>
<tr>
<td>Group 3</td>
<td>Vitreous hemorrhage</td>
<td>Month 3 (30)</td>
<td>Month 4+3 wks (24)</td>
<td>Month 6 (29)</td>
<td>29</td>
<td>Resolved</td>
</tr>
<tr>
<td>Group 3</td>
<td>Vitreous hemorrhage</td>
<td>Month 3 (32)</td>
<td>Month 6 (28)</td>
<td>Month 9 (29)</td>
<td>28</td>
<td>Resolved</td>
</tr>
</tbody>
</table>

AE = adverse event; DME = diabetic macular edema; ETDRS VA = visual acuity obtained with protocol from the Early Treatment Diabetic Retinopathy Study; NA = not available.
in the laser alone group. This difference was not statistically significant, and it appears that our sample size was insufficient to determine whether combined treatment is superior to focal/grid therapy or to ranibizumab injections alone.

In conclusion, the results of the current study confirm our previous study, but comparison of the 2 studies raises an important issue. In the first study, patients received injections of 0.5 mg of ranibizumab every month × 3 followed by every other month × 2 with a primary end point at 7 months, and patients showed elimination of 85% of edema. In the current study, the regimen was less aggressive in that patients received injections of 0.5 mg of ranibizumab × 2 followed by every other month × 2 with a primary end point at 6 months, and only 50% of edema was resolved. An ideal anatomic outcome is to eliminate ≥90% of edema, and this was achieved in 24% of patients on the current regimen, whereas 54% had resolution of ≥50% of edema. Thus, it appears that a significant number of patients were undertreated with the regimen of ranibizumab injections used in this study. Our results support the more aggressive regimen of monthly injections of ranibizumab for 2 years that is being used in the RISE and RIDE phase III trials sponsored by Genentech (San Francisco, CA). The more aggressive regimen, the 2-year primary end point, and the larger sample size will give a better indication of the maximal benefits achievable with ranibizumab in patients with DME.

References


Footnotes and Financial Disclosures

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Appendix 1. Investigators and Coordinators of the READ-2 Study

A. Clinical Sites

1. Black Hills Regional Eye Institute
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   Coordinator: Buffi Green, Kristi Libermont, Honor Evers

2. East Bay Retina Consultants
   Principal Investigator: Eugene S. Lit, MD
   Investigators: Daniel A. Brinton, MD, Scott S. Lee, MD
   Coordinator: Scotty Renslow

3. Eye Care Specialists
   Principal Investigator: Erik F. Kruger, MD
   Coordinator: Patty Yuhas, COA

4. Illinois Retina Associates
   Principal Investigator: Jonathan S. Pollack, MD
   Investigators: Joseph M. Civantos, MD
   Coordinator: Barbara J. Ciscato

5. Johns Hopkins University/Wilmer Eye Institute
   Principal Investigator: Diana V. Do, MD
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6. Midwest Eye Institute
   Principal Investigator: Thomas Ciulla, MD
   Coordinator: Neelam Thukral

7. New England Retina Consultants
   Principal Investigator: Bradley Foster, MD
   Coordinator: Sharon Parker

8. Ophthalmic Consultants of Boston
   Principal Investigator: Jeffrey S. Heier, MD
   Investigators: Janet J. Chieh, MD, Tina S. Cleary, MD, Gregory L. Fenton, MD, David S. Liao, MD, Jackie K. Nguyen, MD, Trexler M. Topping, MD, Torsten W. Wiegand, MD, Paul A. Yates, MD
   Coordinator: Lindsey Williams, Paul E. Daniel, Jr.

9. Retina Consultants of Arizona
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   Investigators: Jack Sipperley, MD, Donald W. Park, MD, Judy Liu, MD, Derek Y. Kunimoto, MD, Edward J. Quinlan, MD, Arthur Mollen, DO, Jaime R. Gaitan, MD
   Coordinator: Sarah G. Mobley, CCRC

10. Retina Consultants of Nevada - Las Vegas
    Principal Investigator: Allen Thach, MD
    Investigators: Roger Simon, MD, R. Jeffrey Parker, MD, Rodney D. Hollifield, MD, Roy H. Loo, MD, Meher Yepremyan, MD, Irene Voo, MD, Jason C. Wickens, MD
    Coordinators: Janet Seybert, Cassondra Major, Mia Davis, Christy Browder, Melissa Rediker

11. Retina Institute of California
    Principal Investigator: Thomas S. Chang, MD
    Investigators: Adam Martinis, MD
    Coordinator: Alexandra N. Tran

12. Retina-Vitreous Associates Medical Group
    Principal Investigator: David Boyer, MD
    Investigators: Roger L. Novack, MD, PhD, Thomas G. Chu, MD, PhD, Firas M. Rahhal, MD, Janet Jill Hopkins, MD, FRCSC, Homayoun Tabandeh, MD, MS, FRCP, FRCs, FRCOphth, Richard H. Roe, MD, MHS
    Coordinator: Saba Mukarram, Tammy Gaspanyan, Janet Kurokouchi

13. University of New Mexico
    Principal Investigator: Arup Das, MD, PhD
    Investigators: Mark Schluter, MD
    Coordinator: Sheila Nemeth, COMT

14. University of Southern California/Doheny Eye Institute
    Principal Investigator: Jennifer Lim, MD (year 1); Dean Eliot, MD (year 2)
    Coordinator: Margaret Padilla

B. Steering Committee
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   Jeffrey S. Heier, MD
   Jennifer Lim, MD
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C. Data Safety and Monitoring Committee
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