

Two-Year Outcomes of the Ranibizumab for Edema of the mAcula in Diabetes (READ-2) Study

Quan Dong Nguyen, MD, MSc,¹ Syed Mahmood Shah, MBBS,^{1,2} Afsheen A. Khwaja, MD,¹ Roomasa Channa, MD,¹ Elham Hatef, MD,¹ Diana V. Do, MD,¹ David Boyer, MD,³ Jeffery S. Heier, MD,⁴ Prema Abraham, MD,⁵ Allen B. Thach, MD,⁶ Eugene S. Lit, MD,⁷ Bradley S. Foster, MD,⁸ Erik Kruger, MD,⁹ Pravin Dugel, MD,¹⁰ Thomas Chang, MD,¹¹ Arup Das, MD,¹² Thomas A. Ciulla, MD,¹³ John S. Pollack, MD,¹⁴ Jennifer I. Lim, MD,¹⁵ Dean Eliot, MD,¹⁶ Peter A. Campochiaro, MD,¹ for the READ-2 Study Group*

Objectives: To determine the long-term effects of ranibizumab (RBZ) in patients with diabetic macular edema (DME).

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

Participants: One hundred twenty-six patients with DME.

Methods: Subjects were randomized 1:1:1 to receive 0.5 mg RBZ at baseline and months 1, 3, and 5 (group 1), focal or grid laser photocoagulation at baseline and month 3 if needed (group 2), or a combination of 0.5 mg RBZ and focal or grid laser at baseline and month 3 (group 3). Starting at month 6, if retreatment criteria were met, all subjects could be treated with RBZ.

Main Outcome Measures: The mean change from baseline in best-corrected visual acuity (BCVA) at month 24.

Results: After the primary end point at month 6, most patients in all groups were treated only with RBZ, and the mean number of injections was 5.3, 4.4, and 2.9 during the 18-month follow-up period in groups 1, 2, and 3, respectively. For the 33 patients in group 1, 34 patients in group 2, and 34 patients in group 3 who remained in the study through 24 months, the mean improvement in BCVA was 7.4, 0.5, and 3.8 letters at the 6-month primary end point, compared with 7.7, 5.1, and 6.8 letters at month 24, and the percentage of patients who gained 3 lines or more of BCVA was 21, 0, and 6 at month 6, compared with 24, 18, and 26 at month 24. The percentage of patients with 20/40 or better Snellen equivalent at month 24 was 45% in group 1, 44% in group 2, and 35% in group 3. Mean foveal thickness (FTH), defined as center subfield thickness, at month 24 was 340 μ m, 286 μ m, and 258 μ m for groups 1, 2, and 3, respectively, and the percentage of patients with center subfield thickness of 250 μ m or less was 36%, 47%, and 68%, respectively.

Conclusions: Intraocular injections of RBZ provided benefit for patients with DME for at least 2 years, and when combined with focal or grid laser treatments, the amount of residual edema was reduced, as were the frequency of injections needed to control edema.

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*Group members listed online in Appendix 1 (available at <http://aaojournal.org>)

Diabetic retinopathy is the most common cause of severe and moderate vision loss in working-aged Americans.^{1,2} Advanced retinopathy complicated by retinal neovascularization and traction retinal detachment is responsible for most severe loss of vision in diabetics, but diabetic macular edema (DME) is the most prevalent cause of moderate vision loss.

Although the pathogenesis of diabetic retinopathy is not completely understood, it seems that hyperglycemia is the primary insult because poor glycemic control is associated with progression of retinopathy.³ Hyperglycemia causes

damage to retinal blood vessels, resulting in hemorrhages, microaneurysms, and capillary closure. Capillary closure causes retinal hypoxia, which long has been known to be associated with retinal neovascularization,⁴ but more recently has also been linked to DME.⁵ Hypoxic retina produces high levels of vascular endothelial growth factor (VEGF), which can stimulate retinal neovascularization,⁶ but also causes leakiness of retinal vessels when injected into the vitreous cavity of mice and causes macular edema when provided by sustained release in the vitreous of pri-

mates.^{7,8} This provided the rationale for testing VEGF antagonists in patients with DME.

In a pilot trial, it was found that 5 intraocular injections of 0.5 mg ranibizumab (RBZ) over the span of 7 months resulted in a mean reduction in excess foveal thickness of 85% and an average improvement in best-corrected visual acuity (BCVA) of 12 letters.⁹ This led to a multicenter trial designated the Ranibizumab for Edema of the mAcula in Diabetes-2 (READ-2) Study, in which patients with DME were randomized to receive intraocular injections of RBZ, focal or grid laser, or a combination of RBZ and focal or grid laser. At the month 6 primary end point, patients treated with intraocular injections of 0.5 mg RBZ at baseline and months 1, 3, and 5 showed a mean improvement in BCVA that was significantly greater than that seen in patients treated with focal or grid laser (7.24 versus -0.43 letters), whereas patients treated with the combination had a mean improvement of 3.80 letters.¹⁰ After the primary end point, if retreatment criteria were met, patients in the RBZ group were treated with 0.5 mg RBZ, patients in the laser group could be treated with laser or RBZ, and patients in combination group could receive laser plus RBZ or RBZ alone. This article reports the 2-year outcomes for the READ-2 Study.

Patients and Methods

The READ-2 Study is a phase II, randomized clinical trial conducted at 14 sites in the United States through an investigator-initiated investigational new drug application granted by the Food and Drug Administration. The study adheres to the guidelines of the Declaration of Helsinki and the protocol and consent form are approved by a local investigational review board for some sites and by Western Investigational Review Board for others. Each subject provided written informed consent. The study is monitored by an independent data and safety monitoring committee, which is made up of 2 retina specialists with expertise in clinical trials who monitored adverse events and data at regular intervals. The study is registered at www.clinicaltrials.gov under the identifier NCT00407381.

Study Protocol

The protocol details, including eligibility criteria and procedures for intraocular injections, focal or grid laser, optical coherence tomography, and data collection and management, have been described previously.¹⁰ Briefly, patients with BCVA between 20/40 and 20/320 resulting from DME and center subfield thickness (FTH) measured by time-domain optical coherence tomography of 250 μ m or more were randomized 1:1:1 to injections of 0.5 mg RBZ alone (group 1), focal or grid laser alone (group 2), or combination treatment consisting of injection of 0.5 mg RBZ and focal or grid laser (group 3). Patients in group 1 received an injection of RBZ at baseline and months 1, 3, and 5. Patients in group 2 received focal or grid laser photocoagulation at baseline and again at month 3 if center subfield thickness was 250 μ m or more. At baseline and month 3, patients in group 3 received an intraocular injection of RBZ followed by focal or grid laser treatment 1 week later. Month 6 was the primary end point of the study.

After month 6, patients in group 1 were evaluated every 2 months and were eligible to receive an intraocular injection of 0.5 mg RBZ if the FTH was 250 μ m or more. Patients in group 2 were

evaluated every 2 months, and if center subfield thickness was 250 μ m or more, they could receive intraocular injections of 0.5 mg RBZ or focal or grid laser treatment, provided it had been at least 3 months since the last laser treatment. If the last laser was 2 months before and the patient and investigator opted for more laser treatments, it was deferred for 1 to 2 months. Patients in group 3 were evaluated every 3 months, and if center subfield thickness was 250 μ m or more, they could receive an intraocular injection of 0.5 mg RBZ followed by focal or grid laser treatment within 7 $\pm$ 2 days or RBZ alone. Safety evaluations, measurement of BCVA, eye examinations, and optical coherence tomography scans were performed at all study visits. Fluorescein angiography was performed at baseline and at 6, 12, and 24 months. Measurements of glycosylated hemoglobin were obtained at baseline and at 3, 6, 12, and 24 months. Hematology and blood chemistry tests were performed at baseline and at 6, 12, and 24 months.

Results

Patient Disposition

The baseline characteristics were well balanced among the 3 study groups.¹⁰ Twenty-eight patients left the study before the month 24 end point: 10 in group 1, 8 in group 2, and 10 in group 3. The reasons for discontinuations and missed visits are shown in Table 1 (available at <http://aaojournal.org>). Any patient who did not have a month 24 visit, but had a study visit at month 20 or beyond, had their last observation carried forward and included in the month 24 analysis. The number of patients included in the month 24 analysis was 33, 34, and 34 in groups 1, 2, and 3, respectively.

Visual Outcomes at 24 Months

Considering only those patients for whom data were available at month 24, the mean improvement in BCVA at month 6 was 7.4, 0.5, and 3.8 letters, compared with 7.7, 5.1, and 6.8 letters at month 24 in groups 1, 2, and 3, respectively. Figure 1 shows the mean BCVA for all patients who were still in the study at the illustrated

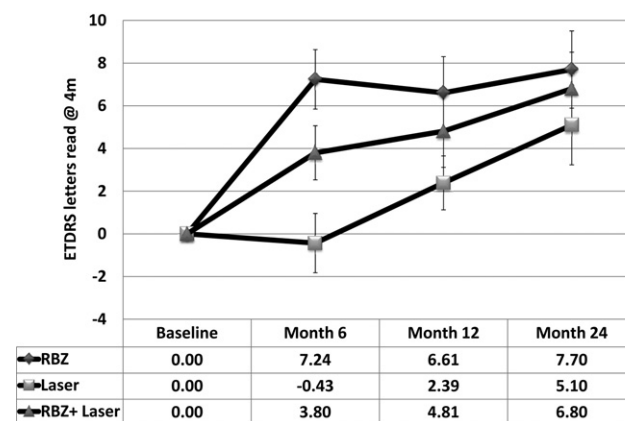


Figure 1. Graph showing the mean change from baseline in best-corrected visual acuity at several time points. Each point shows the mean ($\pm$ standard error of the mean) change from baseline in best-corrected visual acuity measured in letters read at 4 m on an Early Treatment Diabetic Retinopathy (ETDRS) chart for group 1, ranibizumab (RBZ) injection alone; group 2, focal laser; and group 3, RBZ plus laser. For each time point, data were included for all patients who remained in the trial at that time point.

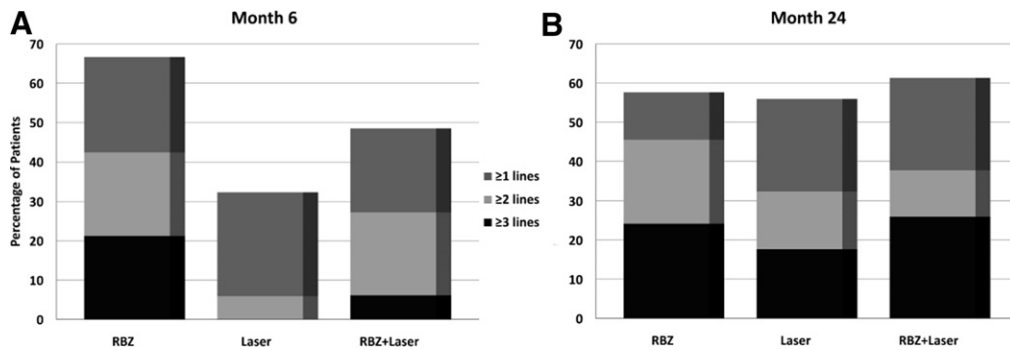


Figure 2. Bar graphs showing the percentage of patients with improvement in best-corrected visual acuity of 1 line or more at (A) 6 and (B) 24 months. Stacked bars show the percentage of group 1, ranibizumab (RBZ); group 2, laser; or group 3, RBZ plus laser; and patients who gained 1 or more lines, 2 or more lines, or 3 or more lines of vision between baseline and 6 or 24 months. Data are included only for patients who remained in the study through 24 months.

time points; the values at the 6- and 12-month time points are quite similar to the values listed above, indicating similarity between the patients who remained in the study through month 24 and the entire study population. Using a random effects model, which considers the correlation among the measurements from the same patient over time and does not eliminate any data or replace missing data, the difference from baseline in BCVA in group 1 was 7.9, 7.0, and 8.2 letters at months 6, 12, and 24, and each of these differences was statistically significant ($P < 0.0001$). The difference from baseline in BCVA in group 2 was 0.1, 2.6, and 4.6 letters at months 6, 12, and 24, respectively, and only the difference at month 24 was statistically significant ($P = 0.007$). The difference from baseline in BCVA in group 3 was 3.6 letters ($P = 0.020$), 4.4 letters ($P = 0.005$), and 6.5 letters ($P < 0.0001$) at months 6, 12, and 24. The mean differences between baseline and month 24 in BCVA were not significantly different among the 3 groups.

For the remainder of this report, except for the random effects model analysis for FTH, only the data for patients who had values at month 24 are considered for all early time points so that comparisons between early and late outcomes can be made in the exact same patient population. The percentage of patients who gained 3 lines or more of BCVA between baseline and year 2 was 24, 18, and 26 compared with 21, 0, and 6 between baseline and month 6 in groups 1, 2, and 3, respectively (Fig 2). The percentage of patients with a Snellen equivalent BCVA of 20/40 or better was 45, 44, and 35 at month 24 in groups 1, 2, and 3, respectively, compared with 39, 24, and 29, respectively, at month 6 (Fig 3).

Because in group 1 the mean BCVA changed by only 0.3 letters between months 6 and 24, one might conclude that patients remained stable during the 18 months of follow up after the primary end point. This was true for 36% of patients who had a month 24 BCVA that was within 4 letters higher than or lower than their month 6 BCVA, but 64% of patients had a substantial change. Approximately 36% of patients improved by at least 5 letters (≥ 15 letters, 6%; ≥ 10 letters, 9%), and 27% of patients worsened by at least 5 letters (≥ 15 letters, 3%; ≥ 10 letters, 15%). In group 2, the mean BCVA improved by 4.6 letters between months 6 and 24, and as one would expect, a substantial number of patients, 47%, showed improvement of at least 5 letters (≥ 15 letters, 21%; ≥ 10 letters, 29%), whereas 32% of patients were within 4 letters of their month 6 value and 21% worsened by 5 letters or more (≥ 15 letters, 6%; ≥ 10 letters, 9%). In group 3, the mean BCVA improved by 3.0 letters between months 6 and 24; 47% improved by 5 letters or more (≥ 15 letters, 6%; ≥ 10 letters, 24%), 18% worsened by 5 letters or more (≥ 15 letters, 6%; ≥ 10 letters, 9%), and 35% showed no change (± 4 letters).

Anatomic Outcomes and Anti-Vascular Endothelial Growth Factor Injections

Considering only patients for whom month 24 data were available, the mean FTH in group 1 decreased substantially from 420.1 μm at baseline to 318.1 μm at month 6, but then increased at months 12 and 24 (Fig 4A). In contrast, there was a steady decline in the mean FTH over 24 months in groups 2 and 3, and in these 2

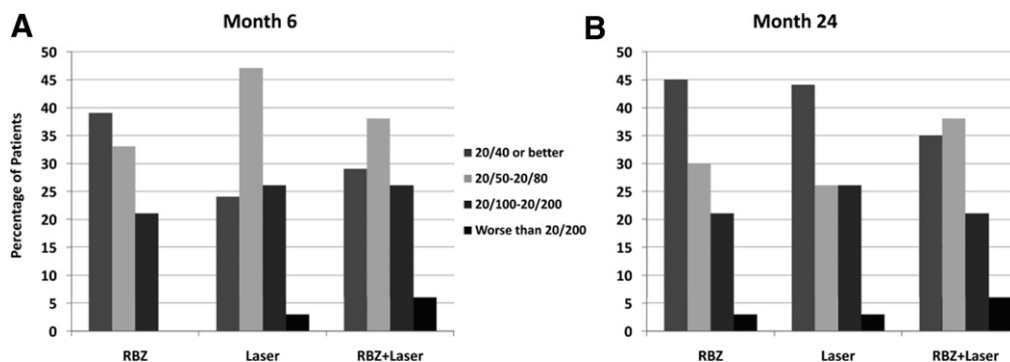


Figure 3. Bar graphs showing best-corrected visual acuity in Snellen equivalent at (A) 6 months and (B) 24 months. The bars show the percentage of patients within the listed vision ranges for group 1, ranibizumab (RBZ); group 2, laser; and group 3, RBZ plus laser at 6 and 24 months. Data are included only for patients who remained in the study through 24 months.

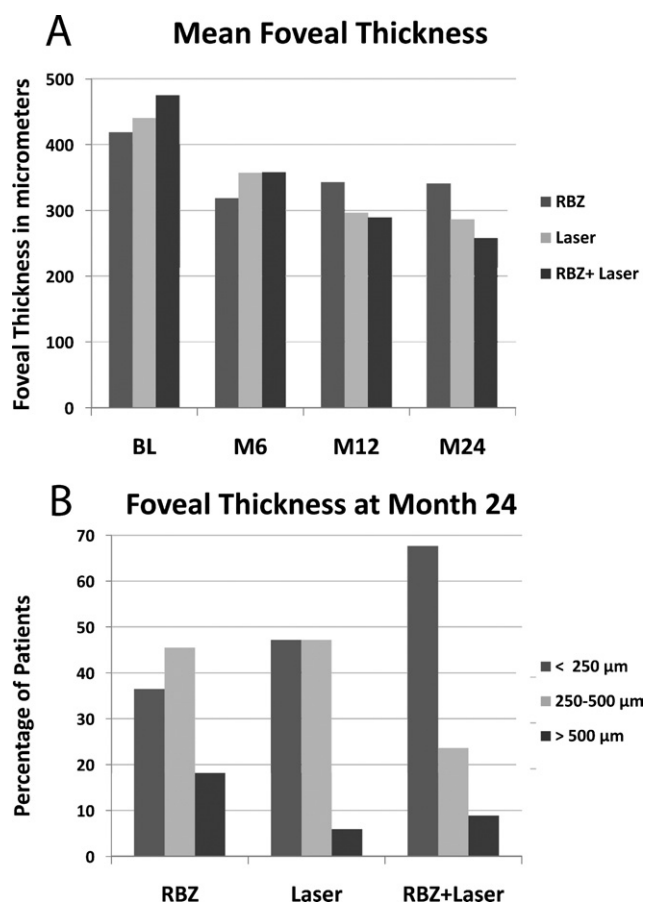


Figure 4. Bar graphs showing assessments of macular edema. **A**, Changes in center subfield thickness (foveal thickness [FTH]) over time. The bars show the mean FTH at baseline (BL), month 6 (M6), month 12 (M12), and month 24 (M24) in group 1, ranibizumab (RBZ); group 2, laser; and group 3, RBZ plus laser. **B**, The percentage of patients with FTH of less than 250 μm , FTH between 250 and 500 μm , or FTH of more than 500 μm in group 1, RBZ; group 2, laser; and group 3, RBZ plus laser. Data are included only for patients who remained in the study through 24 months.

groups, the reductions in mean FTH at months 12 and 24 were significantly greater than those in group 1 by the random effects model (month 12, $P = 0.028$ and $P = 0.002$; month 24, $P = 0.027$ and $P < 0.0001$). The mean number of RBZ injections over 2 years in group 1 was 9.3 of a maximum possible of 13. In 36% of group 1 subjects, the month 24 FTH was 250 μm or less, in 45% it was between 250 and 500 μm , and in 18% it was 500 μm or more (Fig 4B). The mean number of RBZ injections given during the 18-month follow up period in all of group 1 was 5.3 of a maximum of 9, while in those with a final FTH of 250 μm or less it was 2.4, in those with FTH between 250 and 500 μm it was 6.5, and in those with FTH $> 500 \mu\text{m}$ it was 8.2. At month 24 in group 2, FTH was 250 μm or less in 47%, between 250 and 500 μm in 47%, and 500 μm or more in 6%. The mean number of RBZ injections given during the 18-month follow-up period in all of group 2 was 4.4 of a maximum of 9, and in those with a final FTH of 250 μm or less it was 2.3, in those with FTH between 250 and 500 μm it was 6.4, and in those with FTH $> 500 \mu\text{m}$ it was 5.5, whereas the mean number of supplemental macular laser treatments was 0.3, 0.2, and 0. At month 24 in group 3, FTH was 250 μm or less in 68%, between 250 and 500 μm in 23%, and 500 μm or more in 9%. The mean number of RBZ injections in all

of group 3 was 2.9 of a maximum of 6, and in those with a final FTH of 250 μm or less it was 2.2, in those with FTH between 250 and 500 μm it was 4.0, and in those with FTH $> 500 \mu\text{m}$ it was 6.0, whereas the mean number of supplemental focal laser treatments was 0.6, 0.8, and 2.3.

Correlation of Visual and Anatomic Outcomes

Patients were divided into 3 categories based on their month 24 BCVA: good, 20/40 or better; moderate, 20/50 to 20/80; and poor, 20/100 or worse. Patients were also divided into 3 categories based on retinal edema: resolved, FTH of 250 μm or less and no treatments needed during year 2; controlled, FTH of 250 μm or less with treatments given during year 2; and uncontrolled, FTH of 250 μm or more. This resulted in 9 possible categories based on both outcomes. The distribution among these 9 subgroups was similar in groups 1, 2, and 3 (Table 2A, available at <http://aaojournal.org>), and the numbers are too small to draw any definite conclusions; however, more patients in group 2 and particularly in group 3 had moderate or poor vision despite resolved or controlled edema. An optimal outcome is good vision with resolved edema. This was seen in 5 patients in group 1 (3 of 5 had focal laser treatment before entering the study; Table 2B, available at <http://aaojournal.org>), in 9 patients in group 2 (Table 2C, available at <http://aaojournal.org>), and in 7 patients in group 3 (Table 2D, available at <http://aaojournal.org>). There was little change in glycosylated hemoglobin between baseline and month 24 in most patients and no correlation between magnitude of change and visual outcome. Only 3 patients, all in group 2, had a change of 3 percentage points or more in glycosylated hemoglobin; 2 had good vision with resolved edema and 1 had poor vision with controlled edema. There was also no correlation between duration of DME and visual outcome.

Discussion

Four intraocular injections of RBZ over 6 months in patients with DME resulted in a mean improvement in BCVA of 7.24 letters, which was significantly better than the mean reduction of 0.43 letters seen in patients treated with focal or grid laser.¹⁰ After the primary end point, patients in both groups were seen every 2 months, and if they had persistent or recurrent DME defined as FTH of 250 μm or more, they could receive an intraocular injection of 0.5 mg RBZ; patients in group 2 could receive RBZ alone or laser, and patients in group 3 could receive RBZ alone or RBZ combined with laser. In group 1, the mean improvement in BCVA at month 24 was 7.7 letters, compared with 7.4 letters in the same patients at month 6. Patients originally assigned to the laser group were treated predominantly with RBZ for persistent or recurrent DME between 6 and 24 months, and at month 24, they showed an improvement in BCVA of 5.1 letters, which was significantly better than the improvement of 0.5 letters seen in the same patients at month 6. A third group of patients given 2 combination treatments of RBZ and focal laser in the first 6 months were seen every 3 months between 6 and 24 months and were treated predominantly with RBZ alone for persistent or recurrent macular edema. At month 24, they showed an improvement in BCVA of 6.8 letters, compared with an improvement in BCVA of 3.8 letters in the same patients at month 6. These data indicate that RBZ treatment of recur-

rent or persistent DME only as frequently as every 2 months for a period of 18 months resulted in maintenance of the excellent visual benefit that had been obtained after 6 months of a fixed regimen of RBZ injections and was associated with significant improvement in patients treated previously only with focal/grid laser photocoagulation. Nearly half of the patients in groups 1 and 2 (44%–45%) and one third (35%) of the patients in group 3 had an excellent visual outcome, defined as Snellen equivalent BCVA of 20/40 or better, at month 24 after prolonged treatment with RBZ. Thus, the long-term benefits of treatment of DME with RBZ are excellent.

The visual outcomes at month 24 were not significantly different in groups 2 and 3 from those in group 1, whereas anatomic outcomes were better with fewer injections of RBZ required during year 2. This suggests that the additional focal/grid laser treatment in groups 2 and 3 helped to reduce persistent or recurrent macular edema and helped to reduce the number of required RBZ injections without a major disadvantage in visual outcome at 2 years when RBZ injections were given as needed only as frequently as every 2 months.

Although it is clear that a regimen in which patients with DME are evaluated every 2 months and are treated with 0.5 mg RBZ if FTH is 250 μ m or more provides long-term benefit, our data also indicated that there is substantial heterogeneity among patients with DME and that the same regimen may not be ideal for all patients. In group 1, 8 patients (24%) had resolved edema, 5 with good vision and 3 with moderate vision, whereas 4 patients (12%) had controlled edema with good (3 patients) or moderate (1 patient) vision (Table 2B, available at <http://aaojournal.org>). Thus, a regimen of RBZ injections only as frequently as every 2 months was sufficient to control edema for 36% of group 1 patients. In group 2 (Table 2C, available at <http://aaojournal.org>), 13 patients (38%) had resolved edema (9, 2, and 2 with good, moderate, and poor vision) and 3 patients (9%) had controlled edema (one in each vision category), and thus the current regimen combined with more aggressive focal/grid laser treatment was sufficient to control edema in 44% of patients. In group 3 (Table 2D, available at <http://aaojournal.org>), 17 patients (50%) had resolved edema (7, 5, and 5 patients with good, moderate, and poor vision, respectively) and 6 patients (18%) had controlled edema (2 and 4 with good and moderate vision, respectively), and thus the current regimen was sufficient to control edema for 68% of patients. These data suggest that a substantial number of patients, particularly in group 1, may not have achieved their best possible visual acuity and they may benefit from more frequent injections or higher doses of RBZ. It is likely that the worsening that occurred in one third of the group 1 patients between 6 and 24 months is the result of inadequate control of edema during the follow up phase. Furthermore, because most of the patients with severe edema at month 24 received close to the maximum number of injections, it is likely that these patients have particularly high levels of VEGF that require a greater amount of neutralizing activity than we achieved with injections of 0.5 mg RBZ every 2 months. Another conclusion from these data is that more aggressive focal/grid laser

treatment tends to reduce the percentage of patients that require RBZ injections more frequently than every 2 months to control edema, but it is not yet known if there is some sacrifice regarding ultimate visual outcome; none of the group 1 patients with resolved or controlled edema had poor visual acuity, whereas this was the case in 19% and 22% of group 2 and 3 patients, respectively. It is not clear if these are true differences and if they are, whether they are the result of the laser, but additional studies are needed to explore the impact of aggressive focal or grid laser treatment on ultimate visual outcome.

Although many retina specialists are interested in the question of whether RBZ injections alone provide a better long-term outcome than focal/grid laser treatment alone, the authors believe that it is unlikely to be optimal to use either alone in most patients. It is clear that the benefit from laser treatment occurs very slowly and that over the span of 6 months, injections of RBZ provide greater visual improvement and reduction in macular edema than focal or grid laser treatment alone. The only reason to withhold RBZ treatment would be if its use did not provide long-term visual benefit or if the increase in cost or reduced convenience resulting from more frequent visits and injections was not balanced by visual benefit. The current study indicates that visual benefits from RBZ at 2 years are at least as good as those at 6 months, even with a regimen that is not sufficient to control edema completely in most patients. It seems that intermittent control of edema is sufficient to maintain good vision in some patients, because 33%, 28%, and 27% of patients in groups 1, 2, and 3, respectively, had a BCVA of 20/40 or better despite the presence of edema at the month 24 visit. Thus, these data suggest that a good approach for the treatment of DME is initial aggressive treatment with RBZ followed by a period in which RBZ is given as needed along with focal/grid laser treatment to try to reduce the need for frequent RBZ injections. This approach is supported by a larger and more complex study published by the Diabetic Retinopathy Clinical Research Network published after the present manuscript was submitted.¹¹ The role of steroids is yet to be determined, but there is likely a role for sustained delivery formulations¹² to reduce the need for frequent injections of RBZ, for overly aggressive focal/grid laser treatment, or both.

In conclusion, intraocular injections of RBZ provide long-term benefit in patients with DME. The authors believe that Ranibizumab Injection in Safety Efficacy (RISE) and Ranibizumab in Diabetic Macular Edema (RIDE) trials will confirm these benefits and are likely to show that benefits are even greater with more frequent injections that provide better control of edema. It is likely that in the future, suppression of VEGF will play an important role in the treatment of DME with additional treatments such as focal/grid laser treatment and sustained delivery formulations of steroids, as well as other as-yet unproven treatments added to achieve control of edema, maximum preservation of vision, and the least frequent intraocular injection schedule; however, the exact regimen will need to be tailored to individual patients because of the wide range of severity seen in patients with DME. Although a great deal of work remains to identify appropriate regimens for subgroups of

DME patients, it is worth acknowledging the substantial progress that has been made in treatment of DME and the important role played in that achievement by VEGF antagonists.

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¹ Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland.

² Department of Ophthalmology, University of Rochester School of Medicine, Rochester, New York.

³ Retina-Vitreous Associates Medical Group, Beverly Hills, California.

⁴ Ophthalmic Consultants of Boston, Boston, Massachusetts.

⁵ Black Hills Regional Eye Institute, Rapid City, South Dakota.

⁶ Retinal Consultants of Nevada, Las Vegas, Nevada.

⁷ East Bay Retina Consultants, Inc., Boston, Massachusetts.

⁸ New England Retina Consultants, Springfield, Massachusetts.

⁹ Eye Care Specialists, PC, Kingston, Pennsylvania.

¹⁰ Retina Consultants of Arizona, Phoenix, Arizona.

¹¹ Retina Institute of California, Pasadena, California.

¹² University of New Mexico School of Medicine, Albuquerque, New Mexico.

¹³ Midwest Eye Institute, Indianapolis, Indiana.

¹⁴ Illinois Retina Associates, SC, Joliet, Illinois.

¹⁵ Illinois Eye and Ear Infirmary, Chicago, Illinois.

¹⁶ Doheny Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles, California.

The list of READ-2 investigators and study personnel is located at <http://aaojournal.org>.

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Correspondence:

Peter A. Campochiaro, MD, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Maumenee 719, Baltimore, MD 21287-9277. E-mail: pcampo@jhmi.edu.