Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema

*The Diabetic Retinopathy Clinical Research Network**
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Objective: Evaluate intravitreal 0.5 mg ranibizumab or 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for treatment of diabetic macular edema (DME).

Design: Multicenter, randomized clinical trial.

Participants: A total of 854 study eyes of 691 participants with visual acuity (approximate Snellen equivalent) of 20/32 to 20/320 and DME involving the fovea.

Methods: Eyes were randomized to sham injection + prompt laser (n=293), 0.5 mg ranibizumab + prompt laser (n=187), 0.5 mg ranibizumab + deferred (≥24 weeks) laser (n=188), or 4 mg triamcinolone + prompt laser (n=186). Retreatment followed an algorithm facilitated by a web-based, real-time data-entry system.

Main Outcome Measures: Best-corrected visual acuity and safety at 1 year.

Results: The 1-year mean change (±standard deviation) in the visual acuity letter score from baseline was significantly greater in the ranibizumab + prompt laser group (+9±11, $P<0.001$) and ranibizumab + deferred laser group (+9±12, $P<0.001$) but not in the triamcinolone + prompt laser group (+4±13, $P=0.31$) compared with the sham + prompt laser group (+3±13). Reduction in mean central subfield thickness in the triamcinolone + prompt laser group was similar to both ranibizumab groups and greater than in the sham + prompt laser group. In the subset of pseudophakic eyes at baseline (n=273), visual acuity improvement in the triamcinolone + prompt laser group appeared comparable to that in the ranibizumab groups. No systemic events attributable to study treatment were apparent. Three eyes (0.8%) had injection-related endophthalmitis in the ranibizumab groups, whereas elevated intraocular pressure and cataract surgery were more frequent in the triamcinolone + prompt laser group. Two-year visual acuity outcomes were similar to 1-year outcomes.

Conclusions: Intravitreal ranibizumab with prompt or deferred laser is more effective through at least 1 year compared with prompt laser alone for the treatment of DME involving the central macula. Ranibizumab as applied in this study, although uncommonly associated with endophthalmitis, should be considered for patients with DME and characteristics similar to those in this clinical trial. In pseudophakic eyes, intravitreal triamcinolone + prompt laser seems more effective than laser alone but frequently increases the risk of intraocular pressure elevation.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2010;117:1064–1077

Macular edema is a frequent manifestation of diabetic retinopathy and an important cause of impaired vision in individuals with diabetes.[1–3] Focal/grid photocoagulation, the current standard care for diabetic macular edema (DME), has been the mainstay of treatment since its benefit was demonstrated in the Early Treatment Diabetic Retinopathy Study (ETDRS) in 1985.[4] In a randomized, multicenter clinical trial, the Diabetic Retinopathy Clinical Research Network (DRCR.net) showed that focal/grid photocoagulation in eyes with center-involved DME and visual acuity ≤20/40 produces gradual visual acuity improvement of ≥2 lines in approximately one third of eyes after 2 years of follow-up, although approximately 20% of laser-treated eyes worsen by ≥2 lines.[5] Thus, other treatment modalities, including anti-vascular endothelial growth factor (VEGF) therapy and steroids, alone or in combination with laser, are under investigation.

The rationale for anti-VEGF therapy for DME is based on the observation that VEGF levels are increased in the retina and vitreous of eyes with diabetic retinopathy.[6] Vascular endothelial growth factor has been demonstrated to increase

vessel permeability in vivo possibly by increasing the phosphorylation of tight junction proteins.[7] Therefore, therapy that inhibits VEGF may represent a useful therapeutic modality that targets the underlying pathogenesis of DME. Pegaptanib (Macugen, Eyetech Pharmaceuticals, Palm Beach Gardens, FL) was the first anti-VEGF drug reported to have a favorable effect on macular edema,[8] although more recently, the anti-VEGF drugs ranibizumab (Lucentis, Genentech, South San Francisco, CA) and bevacizumab (Avastin, Genentech), among others, also have been evaluated for DME. Prior studies, which were small with short-term follow-up, have reported promising results.[9] Intravitreal triamcinolone also was evaluated previously as treatment for DME in a randomized trial conducted by the DRCR.net.[5] Although the data suggest that triamcinolone treatment was superior to the expected untreated course in the ETDRS, it was not superior to focal/grid photocoagulation.[5]

The combination of intravitreal treatment (either triamcinolone or an anti-VEGF drug) with focal/grid photocoagulation, theoretically, could be more effective than either treatment alone. The intravitreal treatment might rapidly reduce macular edema and lead to more rapid visual acuity improvement, whereas slower benefit accrues over time as a result of laser treatment. In addition, combined treatment could enhance the effect of focal/grid photocoagulation because the retina would be less edematous if laser treatment was administered some time after the intravitreal treatment reduced macular edema. Also, laser treatment theoretically could reduce the number of repeat intravitreal injections required to optimize the outcome of DME treatment. In a study of 86 eyes randomized to 4 mg intravitreal triamcinolone alone or followed by macular laser photocoagulation, Kang et al[10] reported that after 6 months visual acuity was better and more eyes had resolution of central edema with the combined treatment when compared with intravitreal triamcinolone without macular laser. Other studies have shown greater mean visual acuity improvements at 6 months using ranibizumab + laser, or ranibizumab alone, when compared with laser alone.[9]

To determine whether anti-VEGF therapy alone or in combination with focal/grid laser, or intravitreal triamcinolone combined with focal/grid laser, might result in improved outcomes compared with the standard treatment for DME of laser alone, the DRCR.net designed a clinical trial to evaluate 3 treatment modalities for DME in comparison with focal/grid photocoagulation: ranibizumab combined with prompt (within 1 week) focal/grid photocoagulation, intravitreal triamcinolone combined with prompt (within 1 week) focal/grid photocoagulation, and intravitreal ranibizumab with focal/grid photocoagulation deferred for at least 24 weeks. The study design also provided an opportunity to determine which regimen resulted in fewer treatments if safety and efficacy were comparable.

Materials and Methods

This phase 3 randomized, multicenter clinical trial was conducted by the DRCR.net at 52 clinical sites in the United States. The study adhered to the tenets of the Declaration of Helsinki. The protocol and informed consent forms were compliant with the Health Insurance Portability and Accountability Act and approved by multiple institutional review boards. Each study participant gave written informed consent before participation in the study. Study oversight was provided by an independent data and safety monitoring committee. The study was conducted under an Investigational New Drug Application from the Food and Drug Administration. The study is listed on www.clinicaltrials.gov under identifier NCT00445003 (website registration date 03-06-2007), and the protocol is available on the DRCR.net website (www.drcr.net, date accessed January 1, 2010). Key aspects of the protocol pertinent to this article are summarized next.

Study Population

Eligible patients were at least 18 years old with type 1 or 2 diabetes. The major eligibility criteria for a study eye included the following: (1) best-corrected Electronic-Early Treatment Diabetic Retinopathy Study (E-ETDRS Visual Acuity Test[11]) visual acuity letter score 78 to 24 (20/32–20/320), (2) definite retinal thickening due to DME on clinical examination involving the center of the macula assessed to be the main cause of visual loss, and (3) retinal thickness measured on time domain optical coherence tomography (OCT) $\geq$250 μm in the central subfield. Principal exclusion criteria included the following: (1) treatment for DME within the prior 4 months, (2) panretinal photocoagulation within the prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months, (3) major ocular surgery within the prior 4 months, (4) history of open-angle glaucoma or steroid-induced intraocular pressure (IOP) elevation that required IOP-lowering treatment, and (5) IOP $\geq$25 mmHg. Patients were excluded if their systolic blood pressure was $>$180 mmHg or diastolic blood pressure was $>$110 mmHg, or if a myocardial infarction, other cardiac event requiring hospitalization, cerebrovascular accident, transient ischemic attack, or treatment for acute congestive heart failure occurred within 4 months before randomization. A patient could have 2 study eyes in the trial only if both were eligible at the time of study entry.

Synopsis of Study Design

After eligibility was determined and informed consent was obtained, study participants with 1 study eye were assigned randomly on the DRCR.net study website (using a permuted blocks design stratified by study eye visual acuity) with equal probability to 1 of 4 treatment groups: (1) sham injection plus prompt (within 3–10 days after injection) focal/grid photocoagulation (sham + prompt laser group), (2) 0.5 mg intravitreal ranibizumab plus prompt (within 3–10 days after injection) focal/grid photocoagulation (ranibizumab + prompt laser group), (3) 0.5 mg intravitreal ranibizumab with deferred ($\geq$24 weeks) focal/grid photocoagulation (ranibizumab + deferred laser group), and (4) 4 mg intravitreal triamcinolone plus prompt (within 3–10 days after injection) focal/grid photocoagulation (triamcinolone + prompt laser group). For study participants with 2 study eyes, the right eye was assigned randomly with equal probability to 1 of the 4 groups as indicated above. If the right eye was assigned to a treatment group other than the sham + prompt laser group, then the left eye was assigned to the sham + prompt laser group. If the right eye was assigned to the sham + prompt laser group, then the left eye was assigned randomly to 1 of the other 3 groups. Thus, there were more eyes in the sham + prompt laser group than in the other 3 groups.

Follow-up was planned for 3 years, with the primary outcome at 1 year. During the first year, follow-up visits occurred every 4 weeks ($\pm$1 week). Study participants in the 3 groups receiving laser were masked to treatment assignment through the primary

outcome visit, whereas the ranibizumab + deferred laser group was not masked. After the first year, visits occurred every 4 to 16 weeks depending on the treatment group, disease course, and treatment administered. After a study participant completed the primary outcome visual acuity examination at 1 year, the study participant was made aware of his or her treatment group assignment and sham injections were discontinued. Visual acuity examiners and OCT technicians were masked to treatment group assignment before and at the 1-year primary outcome visit.

Examination Procedures

At baseline and each follow-up visit, best-corrected visual acuity letter score was measured at 3 m by a certified examiner using an E-ETDRS Visual Acuity Test.[11] The OCT images were obtained at baseline and each follow-up visit by a certified operator using the Zeiss Stratus OCT (OCT3) machine (Carl Zeiss Meditec, Inc., Dublin, CA). Scans were 6 mm in length and included the 6-radial line fast macular scan pattern for quantitative measures and the cross-hair pattern (6–12 o'clock and 9–3 o'clock) for qualitative assessment of retinal morphology. All baseline OCT scans, annual follow-up scans with a standard deviation of the center point ≥10.0%, and scans from any visits in which the investigator suspected erroneous measurements because of the algorithm placement of the lines created by the OCT software that delineate the inner and outer aspects of the retina were sent to the Fundus Photograph Reading Center (University of Wisconsin, Madison) for grading. If the automated thickness measurements were judged by the Reading Center to be inaccurate on any submitted image, center point thickness was measured manually, and this value was used to impute a value for the central subfield based on a correlation of the 2 measures of 0.98 as published previously[12] (20% of 854 baseline scans were imputed and 1 scan was unable to be manually graded at baseline, and 2% of 10 849 follow-up scans were imputed and 22 [<1%] were unable to be manually graded during follow-up through 1 year). Manual grading of the baseline scans resulted in an imputed baseline central subfield value <250 μm for 60 eyes (7%), which does not necessarily mean that the true thickness measurement is <250 if measureable. Of note, 22 (37%) of the 60 scans with an imputed central subfield thickness <250 μm were from 1 clinical site and represented 85% of the 26 baseline scans from that site. All intent-to-treat results presented were similar when evaluated with exclusion of eyes from that clinical site (data not shown) and when evaluated with exclusion of eyes from any clinical site with a baseline central subfield thickness <250 μm. Baseline OCT images also were assessed by the Reading Center for cystoid abnormalities and subretinal fluid.

Additional testing at baseline and each follow-up visit included slit-lamp examination, measurement of IOP, and fundus examination after pupil dilation. Standard ETDRS 7-field color stereoscopic fundus photographs were obtained at baseline and 12 months by a certified photographer and graded at the reading center for level of diabetic retinopathy.[13] Hemoglobin A1c was measured at baseline. Any untoward medical occurrence, regardless of whether the event was considered treatment related, was considered as an adverse event and recorded. Treatment of adverse events and proliferative diabetic retinopathy was at the discretion of the investigator.

Treatment Protocol

Overview. The treatment protocol (summarized in Appendix 1, available at http://aaojournal.org) included a baseline treatment followed by intravitreal study drug or sham injection retreatments every 4 weeks through the 12-week study visit. From the 16-week study visit and thereafter, a retreatment algorithm for study drug injections and sham injections (Appendices 2 and 3, available at http://aaojournal.org) was designed to require retreatments unless a study visit was deemed a 'success' (defined below and in Table 1, available at http://aaojournal.org) at which point retreatment was at investigator discretion. From the 24-week study visit and thereafter retreatment was at investigator discretion if the study visit was deemed 'no improvement' (defined in Table 1, available at http://aaojournal.org). If retreatment with a study drug or sham injection was not given, 'alternative treatment' (defined in Table 1, available at http://aaojournal.org) was permitted only if a study eye met criteria for 'failure' or 'futility' (defined in Table 1, available at http://aaojournal.org). When retreatment with a study drug or sham injection was indicated, eyes assigned to one of the ranibizumab groups could receive ranibizumab as often as every 4 weeks; eyes assigned to intravitreal triamcinolone could receive triamcinolone as often as every 16 weeks with sham injections as often as every 4 weeks in between triamcinolone injections; eyes assigned to sham + prompt laser could receive sham injections as often as every 4 weeks. A retreatment algorithm for focal/grid laser (Appendix 4, available at http://aaojournal.org) was designed to require retreatment if there was 'edema involving the center of the macula' or 'edema threatening the center of the macula' (defined in Table 1, available at http://aaojournal.org) and if 'complete laser' had not been given (defined in Table 1, available at http://aaojournal.org), provided that it had been at least 13 weeks since the last focal/grid laser application.

Retreatment Algorithm System. Compliance with the details of the treatment protocol, which depended mainly on visual acuity and OCT measurements over time, was facilitated by a web-based, real-time data-entry system. At each follow-up visit, the system provided real-time feedback to the treating physician regarding whether treatment was required or at investigator discretion. If treatment was to be given, the system also provided feedback as to whether the treatment should be an intravitreal study drug or sham injection, whether focal/grid photocoagulation should be applied, and what the next follow-up interval should be.

Statistical Methods

Data are reported that were collected by the clinical sites from March 2007 to February 8, 2010. This includes at least 1-year follow-up for the entire study population and up to 2-year follow-up for participants enrolled early in the trial. Mean change in visual acuity from baseline to 1 year adjusted for baseline visual acuity was the primary outcome measure. The primary analysis consisted of 3 pairwise comparisons of the mean change in the sham + prompt laser group compared with each of the other 3 groups.

Sample size was estimated to be 842 eyes (~701 study participants assuming 20% of study participants would have 2 study eyes) on the basis of an expected population difference in the letter score of 6.0 and standard deviation of the visual acuity letter score of 18, a correlation between baseline and 1-year scores of 0.48, a type 1 error rate of 0.016 (adjusted for multiple comparisons and alpha spending for interim data reviews), and a power of approximately 90%.

The primary analysis included all randomized eyes and followed the intent-to-treat principle. Data were included in the 1-year analysis when an examination was performed between 308 and 420 days from randomization. When more than 1 visit occurred in this window, data from the visit closest to the 1-year target date were used. For eyes without 1-year data, the last-observation-carried forward method was used to impute data for the primary analysis. Similar results (data not shown) were produced when analyses (1) used Rubin's method[14] to impute for missing data; (2) included only eyes with a completed 1-year

examination and used the last visual acuity before additional treatment for those who received a treatment other than the randomly assigned treatment before the 1-year examination (per-protocol analysis); (3) included adjustment for the following potential confounders in addition to baseline visual acuity: age, gender, race/ethnicity, baseline hemoglobin A1c, baseline OCT central subfield thickness, and prior panretinal scatter photocoagulation and prior DME treatment at baseline; (4) were performed with outlying values truncated to 3 standard deviations from the mean; and (5) used van der Waerden's normal score transformation on the visual acuity scores. For analyses other than the primary analysis, only data from completed visits were used with no imputation for missing data. For some results, medians and interquartile ranges have been reported instead of, or in addition to, means and standard deviations to describe the distribution of the data. Analyses of the number of study treatments received before the 1- and 2-year visits included only the eyes of participants completing the 1- and 2-year visits.

Three pairwise comparisons were made for all analyses, except the ranibizumab groups were pooled for analysis of progression of diabetic retinopathy and all safety analyses. For all continuous outcomes, treatment group comparisons were made using analysis of covariance models with generalized estimating equations to account for correlated data from study participants with 2 study eyes. For binary outcomes, proportions similarly were compared between treatment groups using logistic regression models with generalized estimating equations. All analyses included adjustment for baseline visual acuity. In addition, models in which the central subfield thickness was the outcome included baseline central subfield thickness as a covariate, and models with retinal volume as the outcome included both baseline central subfield thickness and retinal volume as covariates. Similar analyses were performed on 2-year results. All *P* values are 2-sided. SAS version 9.1 (SAS Inc, Cary, NC) was used for all analyses.

Results

Between March of 2007 and December of 2008, 691 study participants (mean age 63±10 years; 44% women) were enrolled, 163 (24%) with 2 study eyes. The mean baseline visual acuity letter score in study eyes was 63±12 (~20/63±2.4 lines), and the mean OCT central subfield retinal thickness was 405±134 μm. The 854 study eyes were assigned to either sham + prompt laser (n=293), ranibizumab + prompt laser (n=187), ranibizumab + deferred laser (n=188), or triamcinolone + prompt laser (n=186). The baseline characteristics of the 4 groups were similar (Table 2, available at http://aaojournal.org).

Follow-Up

The follow-up status for all study participants (eyes) is shown in Figure 1 (available at http://aaojournal.org). Thirteen study participants (2%) died before the 1-year primary outcome visit and 15 participants died subsequently of causes apparently unrelated to study treatment. For the remaining study participants, the 1-year primary outcome visit was completed for 94% to 96% of eyes in the 4 treatment groups. Those who completed the 1-year primary outcome visit completed 94% of the non-annual visits before 1 year. Baseline visual acuity was similar in the 55 study eyes of the 44 study participants who did not complete the 1-year primary outcome visit compared with the 799 eyes of the 647 study participants who completed the 1-year primary outcome visit (data not shown). The 2-year visit was completed for 484 eyes (57%), with 267 (31%) still pending, as of February 8, 2010.

Treatments

Sham Injections and Intravitreal Study Drug Injections. For each study participant, there were 13 possible sham or study drug injections during the first year of follow-up. The median (25th, 75th percentile) number of sham injections before the 1-year primary outcome visit was 11 (8, 13) in the sham + prompt laser group (of note, this excludes 56 eyes among 163 participants with 2 study eyes that were unmasked at baseline because the study participant's other eye was in the ranibizumab + deferred laser group, precluding sham injections for the study eye assigned to sham + prompt laser). The median number of study drug injections before the 1-year primary outcome visit was 8 (6, 10) ranibizumab injections (of 13 maximally possible injections) in the ranibizumab + prompt laser group, 9 (6, 11) ranibizumab injections (of 13 maximally possible injections) in the ranibizumab + deferred laser group, and 5 (3, 7) sham injections (of 9 maximally possible sham injections) and 3 (2, 4) triamcinolone injections (of 4 maximally possible triamcinolone injections) for a total of 13 maximally possible sham plus triamcinolone injections in the triamcinolone + prompt laser group (Fig 2, available at http://aaojournal.org).

Retreatments Relative to 'Success' and 'Failure' Criteria. At the 16-week study visit, 47 (25%) of the 187 eyes in the ranibizumab + prompt laser group and 41 (22%) of the 188 eyes in the ranibizumab + deferred laser group met 'success' criteria (visual acuity letter score ≥84 [~≥20/20] or OCT central subfield <250 μm) and did not receive an injection. A total of 17 eyes (9%) in the ranibizumab + prompt laser group and 15 eyes (8%) in the ranibizumab + deferred laser group met 'success' criteria at 16 weeks and did not receive an additional injection before the 1-year primary outcome visit. At the 1-year primary outcome visit, 89 (32%) of the eyes in the sham + prompt laser group, 109 (64%) of the eyes in the ranibizumab + prompt laser group, 92 (52%) of the eyes in the ranibizumab + deferred laser group, and 98 (56%) of the eyes in the triamcinolone + prompt laser group met the 'success' criteria, including 23 (8%), 23 (13%), 23 (13%), and 19 (11%), respectively, with a visual acuity letter score ≥84 (~≥20/20). 'Failure' criteria were met in 10 (4%), 3 (2%), 1 (1%), and 3 (2%) of the eyes in these 4 groups, respectively, during the first year of follow-up. Sham or study drug injections were not required for eyes meeting 'success' or 'failure' criteria.

Retreatments through Year 2. For the 218 study participants (58%) with 2 years of follow-up in the ranibizumab groups, there was a maximum of 25 possible ranibizumab injections. The median (25th, 75th percentile) number of ranibizumab injections between the 1-year visit, inclusive, and before the 2-year visit were 2 (0, 4) and 3 (1, 7) in the ranibizumab + prompt laser group and the ranibizumab + deferred laser group, respectively, for a total of 11 (7, 14) and 13 (8, 17) injections from baseline to the 2-year visit. Only 32% of participants in the ranibizumab + prompt laser group and 21% of participants in the ranibizumab + deferred laser group had no ranibizumab injections between the 1- and 2-year visits. The 103 study participants (55%) with 2 years of follow-up in the triamcinolone + prompt laser group received 1 (0, 2) triamcinolone injection between the 1-year visit, inclusive, and before the 2-year visit for a total of 4 (3, 5) from baseline to the 2-year visit of a total of 8 maximum possible injections.

Focal/Grid Laser Treatments. The distribution of laser treatments before the 1- and 2-year visits are shown in Table 3 (available at http://aaojournal.org). The median (25th, 75th percentile) number of focal/grid photocoagulation treatments before the 1-year primary outcome visit was 3 (2, 3) in the sham + prompt laser group, 2 (1, 3) in the ranibizumab + prompt laser group, and 2 (1, 3) in the triamcinolone + prompt laser group. In

Table 5. Change in Visual Acuity (Last Observation Carried Forward) from Baseline to 1 Year (Primary Outcome)*

	Sham + Prompt Laser *N=293*	Ranibizumab + Prompt Laser *N=187*	Ranibizumab + Deferred Laser *N=188*	Triamcinolone + Prompt Laser *N=186*
Change in visual acuity (letters)				
Mean ± SD	+3±13	+9±11	+9±12	+4±13
Median (25th, 75th percentile)	+5 (−2, +10)	+10 (+3, +16)	+9 (+5, +15)	+5 (−3, +12)
Difference in mean change from sham + prompt laser (95% CI) [*P* value]†		+5.8 (+3.2 to +8.5) [*P*<0.001]	+6.0 (+3.4 to +8.6) [*P*<0.001]	+1.1 (−1.5 to +3.7) [*P*=0.31]
Distribution of change, No. (%)				
≥15 letter improvement	43 (15%)	57 (30%)	52 (28%)	39 (21%)
14–10 letter improvement	38 (13%)	38 (20%)	36 (19%)	22 (12%)
9–5 letter improvement	67 (23%)	34 (18%)	54 (29%)	32 (17%)
Same ±4 letters	86 (29%)	38 (20%)	35 (19%)	54 (29%)
5–9 letters worse	20 (7%)	14 (7%)	5 (3%)	12 (6%)
10–14 letters worse	16 (5%)	3 (2%)	2 (1%)	12 (6%)
≥15 letters worse	23 (8%)	3 (2%)	4 (2%)	15 (8%)
Difference in proportion with ≥10 letter improvement from sham + prompt laser (95% CI)‡		+23% (+13% to +34%)	+19% (+9% to +29%)	+6% (−4% to +16%)
Relative risk (95% CI) [*P* value]§ for comparison with sham + prompt laser	1.0	1.84 (1.40 to 2.42) [*P*<0.001]	1.68 (1.27 to 2.21) [*P*<0.001]	1.21 (0.88 to 1.66) [*P*=0.16]
Difference in proportion with ≥10 letter worsening from sham + prompt laser (95% CI)‡		−10% (−16% to −5%)	−10% (−16% to −4%)	+1% (−7% to +9%)
Relative risk (95% CI) [*P* value]‡ for comparison with sham + prompt laser	1.0	0.24 (0.09 to 0.65) [*P*<0.001]	0.24 (0.08 to 0.68) [*P*=0.001]	1.08 (0.62 to 1.87) [*P*=0.75]
Difference in proportion with ≥15 letter improvement from sham + prompt laser (95% CI)‡		+16% (+6% to +26%)	+13% (+4% to +22%)	+6% (−2% to +15%)
Relative risk (95% CI) [*P* value]§ for comparison with sham + prompt laser	1.0	2.09 (1.35 to 3.22) [*P*<0.001]	1.89 (1.25 to 2.87) [*P*<0.001]	1.43 (0.90 to 2.29) [*P*=0.07]
Difference in proportion with ≥15 letter worsening from sham + prompt laser (95% CI)‡		−6% (−11% to −2%)	−6% (−10% to −1%)	0 (−6% to +6%)
Relative risk (95% CI) [*P* value]§ for comparison with sham + prompt laser	1.0	0.21 (0.05 to 0.87) [*P*=0.009]	0.28 (0.08 to 0.97) [*P*=0.01]	1.02 (0.47 to 2.20) [*P*=0.95]

CI = confidence interval; SD = standard deviation.
*Visits occurring between 308 and 420 days (between 44 and 60 wks) from randomization were included as 1-yr visits. When > 1 visit occurred in this window, data from the visit closest to the 1-yr target date were used. For other eyes without any 1-yr data (19 eyes in the sham + prompt laser group, 16 eyes in the ranibizumab + prompt laser group, 10 eyes in the ranibizumab + deferred laser group, and 10 eyes in the triamcinolone + prompt laser group), the last observation carried forward method was used to impute data for the primary analysis.
†Analysis of covariance adjusted for baseline visual acuity and correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.
‡Adjusted for correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.
§Logistic regression adjusted for correlation between 2 study eyes. Confidence intervals are adjusted for multiple comparisons.

the ranibizumab + prompt laser group, after baseline and before the 1-year primary outcome visit, 53 (31%) study eyes received no additional focal/grid laser treatments, 54 (32%) received only 1 additional focal/grid laser treatment, 46 (27%) received only 2 additional focal/grid laser treatments, and 18 (11%) received 3 additional focal/grid laser treatments. Focal/grid laser treatment was not permitted in the ranibizumab + deferred laser group until the 24-week study visit; from the 24-week study visit and before the 1-year primary outcome visit, 128 (72%) of these study eyes received no focal/grid laser treatment, 35 (20%) received only 1 focal/grid laser treatment, and 15 (8%) received 2 focal/grid laser treatments. Forty-seven percent of the sham + prompt laser group, 57% of the ranibizumab + prompt laser group, 72% of the ranibizumab + deferred laser group, and 46% of the triamcinolone + prompt laser group received no focal/grid laser treatments between the 1- and 2-year visits.

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