A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Focal/Grid Photocoagulation for Diabetic Macular Edema

Diabetic Retinopathy Clinical Research Network

Objective: To evaluate the efficacy and safety of 1-mg and 4-mg doses of preservative-free intravitreal triamcinolone in comparison with focal/grid photocoagulation for the treatment of diabetic macular edema (DME).

Design: Multicenter, randomized clinical trial.

Participants: Eight hundred forty study eyes of 693 subjects with DME involving the fovea and with visual acuity of 20/40 to 20/320.

Methods: Eyes were randomized to focal/grid photocoagulation (n = 330), 1 mg intravitreal triamcinolone (n = 256), or 4 mg intravitreal triamcinolone (n = 254). Retreatment was given for persistent or new edema at 4-month intervals. The primary outcome was evaluated at 2 years.

Main Outcome Measures: Visual acuity measured with the Electronic Early Treatment Diabetic Retinopathy Study method (primary), optical coherence tomography-measured retinal thickness (secondary), and safety.

Results: At 4 months, mean visual acuity was better in the 4-mg triamcinolone group than in either the laser group ($P<0.001$) or the 1-mg triamcinolone group ($P = 0.001$). By 1 year, there were no significant differences among groups in mean visual acuity. At the 16-month visit and extending through the primary outcome visit at 2 years, mean visual acuity was better in the laser group than in the other 2 groups (at 2 years, $P = 0.02$ comparing the laser and 1-mg groups, $P = 0.002$ comparing the laser and 4-mg groups, and $P = 0.49$ comparing the 1-mg and 4-mg groups). Treatment group differences in the visual acuity outcome could not be attributed solely to cataract formation. Optical coherence tomography results generally paralleled the visual acuity results. Intraocular pressure increased from baseline by 10 mmHg or more at any visit in 4%, 16%, and 33% of eyes in the 3 treatment groups, respectively, and cataract surgery was performed in 13%, 23%, and 51% of eyes in the 3 treatment groups, respectively.

Conclusions: Over a 2-year period, focal/grid photocoagulation is more effective and has fewer side effects than 1-mg or 4-mg doses of preservative-free intravitreal triamcinolone for most patients with DME who have characteristics similar to the cohort in this clinical trial. The results of this study also support that focal/grid photocoagulation currently should be the benchmark against which other treatments are compared in clinical trials of DME.

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Macular edema is a frequent manifestation of diabetic retinopathy and an important cause of impaired vision in individuals with diabetes.[1–3] The Wisconsin Epidemiologic Study of Diabetic Retinopathy, a population-based study in southern Wisconsin, estimated that after 20 years of known diabetes, the prevalence of diabetic macular edema (DME) was approximately 28% in both type 1 and type 2 diabetes.[1]

The most widely accepted methods to reduce the risk of vision loss from DME are: (1) intensive glycemic control, as demonstrated by the Diabetes Control and Complications Trial[4] and the United Kingdom Prospective Diabetes Study[5]; (2) blood pressure control, as demonstrated by the United Kingdom Prospective Diabetes Study[6,7]; and (3) focal/grid photocoagulation, as demonstrated by the Early Treatment Diabetic Retinopathy Study (ETDRS).[8] The ETDRS reported that focal/grid photocoagulation of eyes with edema involving or threatening the fovea reduced the 3-year risk of losing 3 or more lines of visual acuity by 50%, from 30% in the control group to 15% in the laser group.

During the last decade, a number of additional treatments for DME have been proposed. Such treatments include vitrectomy,[9–16] pharmacologic therapy with oral protein kinase C-β inhibitors,[17] intravitreal injection of aptamers or antibodies targeted at vascular endothelial growth factor (VEGF),[18–20] and intravitreal injection of corticosteroids such as triamcinolone acetonide. In 2001 and 2002, the first reports were published of the use of intravitreal injection(s) of triamcinolone acetonide (hereafter referred to as intravitreal triamcinolone) for DME,[21,22] suggesting that intravitreal triamcinolone potentially was an effective treatment for

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DME. As a result of these reports, this treatment gained widespread use, most commonly as a dose of 4 mg Kenalog (triamcinolone; Bristol-Myers Squibb, Princeton, NJ), despite the lack of data from a controlled study demonstrating efficacy that exceeds risks. A 2002 Preferences and Trends Survey conducted by the American Society of Retina Specialists showed that 52% of retina specialists surveyed that year (n = 337) had used an intravitreal injection of triamcinolone as a treatment for DME. In 2005, the Preferences and Trends Survey showed that 91% of retina specialists surveyed that year (n = 371) would treat a patient with intravitreal triamcinolone if cystic DME persisted despite at least 2 sessions of focal/grid photocoagulation. A multitude of case series presentations, case reports, and clinical experience suggested that intravitreal triamcinolone produced a short-term reduction in macular edema and concomitant improvement in visual acuity. However, in many case series previously reported, the effects seemed to be transient, requiring repeat injections to sustain a reduction in edema. Not unexpectedly, steroid-related complications such as cataract and glaucoma have been reported in these case series.[22–26]

The rationale for the use of corticosteroids to treat DME follows from the observation that the increase in retinal capillary permeability that results in edema may be caused by a breakdown of the blood–retina barrier mediated in part by VEGF, a 45-kD glycoprotein.[27–29] One proposed mechanism by which VEGF may induce retinal vascular permeability is through phosphorylation of the tight junctional protein occludin, resulting in the dissolution of the junctional complex.[30,31] Another mechanism entails Fas-mediated endothelial cell apoptosis.[32] The pathogenesis of retinal vascular permeability also has been attributed to inflammation, particularly through leukostasis within retinal capillaries. The attraction and adhesion of leukocytes to the vascular wall in the setting of diabetes may be the result of an increased expression of leukocyte adhesion molecules such as retinal endothelial cell intercellular adhesion molecule-1 and CD 18.[33–35] Therefore, attenuation of the effects of VEGF and a reduction in inflammation may reduce the macular edema associated with diabetic retinopathy. Because corticosteroids have been demonstrated to inhibit the expression of both VEGF and the VEGF gene[36,37] and to have antiinflammatory properties, a strong rationale exists for their use in the treatment of DME.

In light of the short-term results from early reports of intravitreal triamcinolone for DME and increasingly widespread clinical use despite a lack of long-term clinical trial data, the Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a randomized clinical trial to evaluate the efficacy and safety of 2 doses of preservative-free intravitreal triamcinolone, 1 mg and 4 mg, in comparison with standard focal/grid photocoagulation. A preservative-free preparation was used in an attempt to avoid the occurrence of postinjection ocular inflammation that has been reported with Kenalog, presumably attributable to the excipients in Kenalog, endotoxins, or a particle dispersion phenomenon.[38,39]

Patients and Methods

This phase III randomized, multicenter clinical trial was conducted by the DRCR.net at 88 clinical sites in the United States. The study adhered to the tenets of the Declaration of Helsinki. The protocol and Health Insurance Portability and Accountability Act-compliant informed consent forms were approved by multiple institutional review boards. Each subject gave written informed consent to participate in the study. Study oversight was provided by an independent data and safety monitoring committee. The study is listed on www.clinicaltrials.gov, under identifier NCT00367133 (web site registration date, August 3, 2006), and the protocol is available on the DRCR.net web site (www.drcr.net; date accessed, June 5, 2008). Key aspects of the protocol pertinent to this manuscript are summarized below.

Study Population

Eligible subjects were at least 18 years of age with type 1 or type 2 diabetes. The major eligibility criteria for a study eye included the following: (1) best-corrected electronic ETDRS visual acuity letter score between 73 (approximately 20/40) and 24 (approximately 20/320), (2) definite retinal thickening resulting from DME on clinical examination involving the center of the macula assessed to be the main cause of visual loss, (3) retinal thickness measured on optical coherence tomography (OCT) of 250 μm or more in the central subfield (average of 2 measurements), and (4) no expectation for scatter photocoagulation within the next 4 months. Principal exclusion criteria included (1) prior treatment with intravitreal corticosteroids (at any time), peribulbar steroid injection within the prior 6 months, photocoagulation for DME within the prior 15 weeks, panretinal scatter photocoagulation within the prior 4 months, or pars plana vitrectomy (at any time); (2) a history of open-angle glaucoma or steroid-induced intraocular pressure elevation that required intraocular pressure-lowering treatment; and (3) intraocular pressure of 25 mmHg or more. A subject 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 at the clinical center and informed consent was obtained, subjects with 1 study eye were assigned randomly on the DRCR.net web site (using a permuted blocks design stratified by visual acuity and prior photocoagulation for DME in the study eye) with equal probability to 1 of 3 treatment groups: (1) focal/grid photocoagulation (referred to as the laser group), (2) 1 mg intravitreal triamcinolone (referred to as the 1-mg triamcinolone group), or (3) 4 mg intravitreal triamcinolone (referred to as the 4-mg triamcinolone group). Eyes assigned to either dose of triamcinolone were not to receive focal/grid photocoagulation during follow-up unless specific failure criteria, outlined below, were reached. Photocoagulation was selected for the control group rather than a sham injection to compare triamcinolone treatment directly with the only ocular treatment proven to have long-term benefit for DME. For subjects with 2 study eyes, the right eye was assigned randomly to 1 of the 3 groups as indicated above and the left eye received the alternate treatment (focal/grid photocoagulation or randomly assigned to the 1-mg or 4-mg dose of triamcinolone). Thus, there were more eyes in the laser group than either the 1-mg triamcinolone group or the 4-mg triamcinolone group. Subjects were masked to triamcinolone dose but were not masked to focal/grid photocoagulation versus intravitreal triamcinolone assignment. Although visual acuity testers, OCT technicians, and fundus photographers were not formally masked to treatment group, these individuals generally were not aware of the treatment group assignments.

The time point of the primary study outcome was 2 years, with a secondary outcome at 3 years. Follow-up visits occurred every 4 months. Testing at each visit included measurement of best-corrected visual acuity and retinal thickness on OCT. At each visit, the study eye(s) was evaluated for retreatment according to the guidelines presented below.

Examination Procedures

At baseline and at each follow-up visit, best-corrected visual acuity letter score was measured at 3 m by a certified tester using an electronic procedure based on the ETDRS method.[40] A standardized refraction was performed at 4, 12, 24, and 36 months. At other visits, a refraction was performed when there was a decrease in visual acuity of 15 letters or more, unless there was an obvious cause for the reduction other than macular edema, such as vitreous hemorrhage.

After pupil dilation, OCT images were obtained at baseline (2 scans were performed and the average of the 2 central subfield thickness measurements was used for eligibility determination and as the baseline for analysis) and at each follow-up visit by a certified operator using the Zeiss Stratus OCT machine (Carl Zeiss Meditech, 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 to 12 o'clock and 9 to 3 o'clock for qualitative assessment of retinal morphologic features). The OCT scans were sent to the University of Wisconsin Fundus Photograph Reading Center for grading. If the automated thickness measurements were judged by the reading center to be inaccurate, 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[41]; imputation was used for 18% of scans). OCT images also were assessed for cystoid abnormalities and subretinal fluid.

Additional testing at baseline and at each follow-up visit included the following: (1) slit-lamp examination, (2) fundus examination after pupil dilation, and (3) measurement of intraocular pressure with a Goldmann tonometer. Standard ETDRS 7-field color stereoscopic fundus photographs were obtained at baseline and annually by a certified photographer and were graded at the reading center.[42] Glycosylated hemoglobin was measured at baseline and then annually. Any untoward medical occurrence, regardless of whether the event was considered treatment related, was considered an adverse event and was recorded. Adverse events were reported through the 2-year visit, or if the visit was missed, through 2 years from randomization.

Initial Treatment Protocol

The intravitreal triamcinolone injection technique followed a standardized protocol. The study drug was a preservative-free preparation (1 mg or 4 mg) of triamcinolone acetonide injectable suspension (manufactured by Allergan, Inc., Irvine, CA; 4 mg brand name TRIVARIS) in a prefilled syringe. The study was conducted under an Investigational New Drug application from the Food and Drug Administration because this specific triamcinolone preparation was considered an investigational drug. Initially, siliconized syringes with a staked needle design were used. However in October 2007, after silicone oil droplets were observed in the vitreous of some eyes after injection, siliconized syringes with a Luer-cone design were used. This alteration, by increasing the residual space between the needle and the syringe, was made to reduce the amount of silicone oil injected with the triamcinolone, which was confirmed by in vitro testing performed by Allergan. Because all subjects in the triamcinolone groups already had received at least 1 injection with the original syringe before the change was made, it could not be evaluated whether or not the change in design reduced the amount of silicone oil injected. The corticosteroid preparation consisted of micronized triamcinolone acetonide suspended in a hydrogel vehicle with minimal dispersive properties. Topical antibiotics were not used before the day of injection. On the day of the injection, topical gatifloxacin (Zymar; Allergan, Inc., Irvine, CA) was placed on the ocular surface at least 3 times over a 15-minute period or more before the injection. Using topical anesthesia followed by a povidone iodine preparation, triamcinolone was injected into the vitreous cavity through the pars plana 3.0 to 4.0 mm posterior to the limbus. After injection, subjects were instructed to use gatifloxacin 4 times daily for 3 days. Safety evaluations were performed 4 days and 4 weeks after each injection. A protocol amendment on July 20, 2007 eliminated the 4-day safety evaluation based on a lack of adverse events detected at the 4-day visits and an advisory from the Food and Drug Administration that postinjection visits were discretionary.

The focal/grid photocoagulation technique was modified from the original ETDRS protocol as described previously and used in prior DRCR.net protocols.[43] Laser photocoagulation burns were less intense (light gray instead of gray) and were limited to a smaller spot size (50 μm instead of 50 to 200 μm) than in the original ETDRS protocol.[44] The focal/grid photocoagulation treatment almost always was completed in a single sitting and involved direct (focal) treatment to all leaking microaneurysms and grid treatment to areas of retinal thickening and, if identified on an optional fluorescein angiogram, nonperfusion between 500 and 3000 μm from the center of the macula.

Retreatment Protocol

At each 4-month visit, the investigator assessed whether persistent or recurrent DME was present that warranted retreatment. Retreatment, when indicated, was performed within 4 weeks after the follow-up visit (usually on the same day as the follow-up visit) and no sooner than 3.5 months from the time of the last treatment. In general, an eye was retreated unless at least one of the following deferral criteria was present, in which case retreatment was determined according to investigator judgment: (1) little or no edema involving the center of the macula and OCT central subfield of 225 μm or less; (2) visual acuity letter score of 79 or more (20/25 or better); (3) substantial improvement in macular edema since the last treatment (e.g., 50% or more decrease in OCT central subfield thickening); (4) clinically significant adverse effect from prior treatment; (5) additional treatment apparently futile (defined as a less than 5-letter improvement in the visual acuity letter score or the lack of reduction in OCT central subfield thickening of at least 50 μm representing at least a 20% reduction in retinal thickening over an 8-month period or more during which 2 treatments [either focal/grid photocoagulation or intravitreal triamcinolone depending on randomization group] were received); and (6) for the laser group, complete focal/grid photocoagulation had already been given, with no areas identified for which additional treatment was indicated. An eye with a decrease from baseline in the best-corrected visual acuity letter score of 15 or more because of macular edema at 2 consecutive 4-month visits could receive an alternate treatment method at investigator discretion (e.g., focal/grid photocoagulation for eyes assigned to a triamcinolone group or 4 mg intravitreal triamcinolone for eyes assigned to focal/grid photocoagulation).

Statistical Methods

Visual acuity was the primary outcome measure. Two analyses were preplanned: (1) a comparison of the mean change in visual acuity among groups and (2) for regulatory purposes, a comparison of the proportion of eyes in each group with a decrease in the visual acuity letter score of 15 or more. The protocol initially included 2 time points for assessing the outcome, 1 year and 3 years, with the latter being required for regulatory purposes. The protocol subsequently was amended to have the primary analysis at 2 years and a secondary analysis at 3 years after the Food and Drug Administration indicated that 2-year follow-up may be considered sufficient for DME treatments. This report includes data collected through the 2-year visit.

Sample size was estimated to be 813 eyes (approximately 689 subjects assuming 18% of subjects had 2 study eyes) based on an expected population percentage of eyes with a 15-letter or more worsening of acuity of 20% in the laser group, 20% in the 1-mg triamcinolone group, and 10% in the 4-mg triamcinolone group; type 1 error rate of 0.049 (adjusted for α spending for interim data reviews); and power of approximately 90%. For the outcome of the change in visual acuity letter score from baseline, with a sample size of 813 eyes and assuming a common standard deviation (SD) for the outcome visual acuity letter scores of 18 and correlation between the baseline and outcome visual acuity letter scores of 0.4, statistical power was estimated to be 87% for detecting a difference in the visual acuity letter score means between groups if the population difference was 5 or more.

The primary analysis included all randomized eyes and followed the intent-to-treat principle. Data were included in the 2-year analysis when an examination was performed between 609 and 852 days (20 and 28 months) from randomization. When more than 1 visit occurred in this window, data from the visit closest to the 2-year target date were used. For eyes without 2-year data, the last observation carried forward method was used to impute data for the primary analysis. Similar results were produced when analyses (1) used Rubin's method[45] to impute for missing data, (2) included only eyes with a completed 2-year examination, (3) were performed with truncation of outlier values to be 3 SDs from the mean, and (4) were performed using ranks of the visual acuity scores (instead of the actual scores) transformed to have normal distributions using van der Waerden scores (data not shown). 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 SDs to describe the distribution of the data.

Three pairwise comparisons were made for all analyses. For all continuous outcomes, the treatment group comparisons were made using repeated-measures analysis of covariance models accounting for correlated data from subjects with 2 study eyes. For binary outcomes, proportions similarly were compared between treatment groups using repeated-measures generalized estimating equations logistic regression models. All analyses included adjustment for baseline visual acuity and prior macular photocoagulation (the 2 variables being used to stratify randomization). 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. For the primary analysis, a step-down Hochberg adjustment was used to account for the multiple statistical comparisons.[46] A treatment by time interaction for visual acuity was tested in a longitudinal model to evaluate whether treatment group differences varied from 4 months to 2 years. All *P* values were 2-sided. SAS software version 9.1 (SAS Institute, Cary, NC) was used for all analyses. All analyses included data available as of May 27, 2008.

Results

Between July 2004 and May 2006, 693 subjects (mean age±SD, 63±9 years; 49% women) were enrolled, 147 (21%) with 2 study eyes. The 840 study eyes with DME were assigned randomly to either focal/grid photocoagulation (n = 330), 1 mg triamcinolone (n = 256), or 4 mg triamcinolone (n = 254). At baseline, the mean±SD visual acuity letter score in study eyes was 59±11 (approximately 20/63) and the mean±SD OCT central subfield retinal thickness was 424±130 μm. The baseline characteristics of the 3 groups were similar (Table 1). Additional baseline characteristics of the cohort have been reported.[47]

Follow-up

The 2-year follow-up status for all study participants (eyes) is shown in Figure 1 (available at http://aaojournal.org). Thirty-three subjects (with 20, 12, and 12 study eyes in the laser, 1-mg triamcinolone and 4-mg triamcinolone groups, respectively) died before the 2-year visit of causes unrelated to study treatment. For the living subjects, the 2-year visit was completed for 272 (88%) of the 310 eyes in the laser group, 220 (90%) of 244 in the 1-mg triamcinolone group, and 205 (85%) of 242 in the 4-mg triamcinolone group. Baseline visual acuity was similar in the 115 subjects (143 study eyes) with incomplete 2-year follow-up compared with the 578 subjects (697 eyes) who completed a 2-year visit.

Treatments

All eyes received the randomization-assigned treatment regimen at baseline, except for 2 eyes in the laser group and 1 eye in the 1-mg triamcinolone group that were dropped from the study before receiving study treatment and 1 eye in the laser group that received a 4-mg triamcinolone injection. Among those completing the 2-year visit, the mean number of treatments with the assigned treatment regimen before the 2-year visit was 2.9 in the laser group, 3.5 in the 1-mg triamcinolone group, and 3.1 in the 4-mg triamcinolone group, with 2.1, 2.3, and 2.1, respectively, being given before the 1-year visit (Table 2, available at http://aaojournal.org).

Before the 2-year visit, treatment for DME other than the randomly assigned treatment was received by 43 (13%) eyes in the laser group, 46 (18%) eyes in the 1-mg triamcinolone group, and 34 eyes (13%) in the 4-mg triamcinolone group. Eighteen eyes (5%) in the laser group received 4 mg intravitreal triamcinolone, 25 eyes (10%) in the 1-mg triamcinolone group received focal/grid photocoagulation, and 20 eyes (8%) in the 4-mg triamcinolone group received focal/grid photocoagulation because of persistent edema and reduced visual acuity. A vitrectomy was performed because of macular traction thought to be exacerbating the DME in 18 (5%), 14 (5%), and 10 (4%) eyes in the 3 groups, respectively, and an intravitreal injection of an anti-VEGF drug was given to 6 (2%), 5 (2%), and 5 (2%) eyes in the 3 groups, respectively.

Effect of Treatment on Visual Acuity

The differences in treatment effect among the 3 groups varied over time ($P<0.001$ for interaction between time and treatment group). At 4 months, mean visual acuity was better in the 4-mg triamcinolone group than in the laser group (mean difference adjusted for baseline visual acuity and prior macular photocoagulation, 3.8; 95% confidence interval, 1.8–5.8; $P<0.001$) and the 1-mg triamcinolone group (mean difference adjusted for baseline visual acuity and prior macular photocoagulation, 3.6; 95% confidence interval, 1.4–5.8; $P = 0.001$). By 1 year, there were no significant

Table 1. Baseline Subject Characteristics According to Treatment Group

	Laser (n = 330 eyes)	1 mg (n = 256 eyes)	4 mg (n = 254 eyes)
Women, no. (%)	166 (50%)	120 (47%)	125 (49%)
Age (yrs) Median (25th, 75th percentile)	63 (57, 69)	63 (58, 70)	63 (57, 69)
Race, no. (%)			
White	243 (74%)	186 (73%)	183 (72%)
Black	31 (9%)	22 (9%)	26 (10%)
Hispanic or Latino	39 (12%)	34 (13%)	33 (13%)
Asian	7 (2%)	8 (3%)	5 (2%)
American Indian/Alaskan Native	2 (1%)	2 (1%)	2 (1%)
Native Hawaiian/other Pacific Islander	1 (<1%)	0	1 (<1%)
More than 1 race	1 (<1%)	1 (<1%)	0
Unknown/not reported	6 (2%)	3 (1%)	4 (2%)
Diabetes type, no. (%)			
Type 1	14 (4%)	12 (5%)	12 (5%)
Type 2	316 (96%)	244 (95%)	242 (95%)
Duration of diabetes (yrs) Median (25th, 75th percentile)	15 (9, 21)	15 (9 ,21)	16 (10 ,22)
HbA1c* Median (25th, 75th percentile)	7.5 (6.6, 8.5)	7.5 (6.8 ,8.4)	7.6 (6.8 ,8.8)
Prior photocoagulation for diabetic macular edema, no. (%)	198 (60%)	154 (60%)	158 (62%)
Prior panretinal scatter photocoagulation, no. (%)	53 (16%)	40 (16%)	42 (17%)
Intraocular pressure (mmHg) Median (25th, 75th percentile)	16 (13, 18)	16 (13, 18)	16 (14, 18)
History of ocular hypertension, no. (%)	3 (1%)	8 (3%)	4 (2%)
Lens status phakic (clinical examination), no. (%)	262 (79%)	203 (79%)	197 (78%)
E-ETDRS visual acuity (letter score) Median (25th, 75th percentile)	62 (53, 67)	62 (54, 67)	62 (52, 67)
Randomization strata, (letter score and approximate Snellen equivalent), no. (%)			
73–60 (20/32-2–20/63)	189 (57%)	149 (58%)	149 (59%)
59–36 (<20/63-1–20/200)	129 (39%)	94 (37%)	92 (36%)
35–24 (20/200–20/320-1)	12 (4%)	13 (5%)	13 (5%)
Central subfield thickness (μm) on OCT[†‡§] Median (25th, 75th percentile)	398 (329, 505)	405 (327, 514)	396 (323, 484)
Retinal volume (mm^3) on OCT[†‡] Median (25th, 75th percentile)	9.2 (7.9, 10.6)	8.9 (7.8, 10.5)	8.9 (7.9, 10.0)
OCT cystoid abnormality (questionable or definite), no. (%)[†]	315 (96%)	243 (96%)	246 (98%)
OCT subretinal fluid present (questionable or definite), no. (%)[†‖]	94 (29%)	64 (25%)	61 (24%)
Retinopathy severity (ETDRS severity scale), no. (%)[†]			
Microaneurysms only (level 20)	1 (<1%)	1 (<1%)	0
Mild to moderately severe nonproliferative (levels 35, 43, 47)	186 (58%)	156 (63%)	151 (62%)
Severe nonproliferative (level 53)	43 (14%)	27 (11%)	25 (10%)
Mild to moderate proliferative (levels 60, 61, 65)	79 (25%)	56 (23%)	62 (25%)
High-risk proliferative (levels 71, 75)	9 (3%)	8 (3%)	6 (2%)

E-ETDRS = electronic Early Treatment Diabetic Retinopathy Study; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = glycosylated hemoglobin; OCT = optical coherence tomography.
Subjects with 2 study eyes are counted in 1 of the triamcinolone groups and in the laser group.
*Missing HbA1c data in 64, 46, and 50 in the laser, 1-mg, and 4-mg groups, respectively.
[†]Missing (or ungradeable) OCT and fundus photograph data as follows for the laser, 1-mg, and 4-mg groups, respectively: central subfield (1, 2, 1), retinal volume (47, 36, 48), cystoid abnormality (3, 4, 2), subretinal fluid (1, 4, 1), retinopathy severity (12, 8, 10).
[‡]Mean of 2 baseline scans.
[§]Mean central subfield thickness was < 250 μm based on reading center grading in 15, 7, and 5 eyes for the laser, 1-mg, and 4-mg groups, respectively.
[‖]Within center or outside of center.

differences in visual acuity among groups. Beginning with the 16-month visit and extending through the primary outcome visit at 2 years, the laser group showed a greater beneficial effect on visual acuity compared with the 2 triamcinolone groups, which were similar to each other (Table 3, available at http://aaojournal.org; Fig 2).

For the 2-year primary outcome, the mean±SD change in the visual acuity letter score from baseline was 1±17 in the laser group, −2±18 in the 1-mg triamcinolone group, and −3±22 in the 4-mg triamcinolone group (for the three 2-group comparisons, mean difference adjusted for baseline visual acuity and prior macular photocoagulation, 95% confidence interval and P value were as follows: laser vs. 1 mg triamcinolone, 3.5 [0.6–6.4], $P =$ 0.02; laser vs. 4 mg triamcinolone, 4.6 [1.7–7.5], $P = 0.002$; 1 mg triamcinolone versus 4 mg triamcinolone, 1.1 [−2.1 to 4.3], $P =$ 0.49; Table 4). A worsening of the visual acuity letter score of 15 or more occurred in 14%, 20%, and 20% of the 3 groups, respectively (P = 0.03, 0.01, 0.82, respectively, for the 3 pairwise comparisons listed previously), and an improvement in the visual acuity letter score by 15 or more occurred in 18%, 14%, and 17% of the 3 groups, respectively (P = 0.10, 0.48, and 0.36, respectively, for the 3 pairwise comparisons listed above).

Limiting the analysis to eyes that were pseudophakic at baseline, mean±SD change from baseline to 2 years in the visual acuity letter score was 2±18 in the laser group (n = 54), 2±17 in the 1-mg triamcinolone group (n = 48), and −1±19 in the 4-mg triamcinolone group (n = 43). When the analysis included eyes that were pseudophakic or had minimal or no cataract by clinician assessment at 2 years, mean±SD change from baseline to 2 years in the visual acuity letter score was 3±16 in the laser group (n = 178), 0±18 in 1-mg triamcinolone group (n = 136), and 0±22 in the 4-mg triamcinolone group (n = 159).

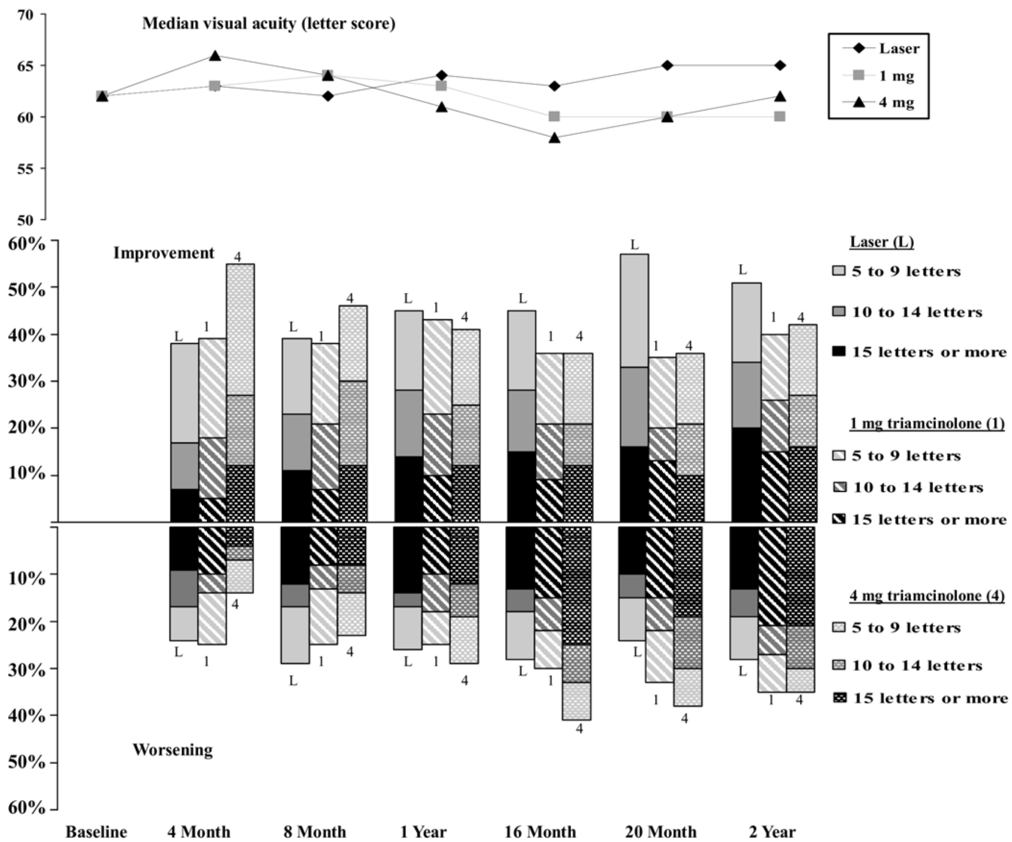

Figure 2. Graph showing the change in visual acuity from baseline to each visit through 2 years according to treatment group. The top portion of the figure displays the median visual acuity in each treatment group. In the bottom portion, the top bars represent the percentage of eyes in each treatment group (solid is laser group [L], striped is 1-mg triamcinolone group [1], dotted is 4-mg triamcinolone group [4]) with an improvement in the visual acuity letter score of 5 to 9 (black segments), 10 to 14 (dark gray segments), and 15 or more (light gray segments); the bottom bars represent the proportion of eyes in each treatment group (solid is laser group [L], striped is 1-mg triamcinolone group [1], dotted is 4-mg triamcinolone group [4]) with a worsening in the visual acuity letter score of 5 to 9 (black segments), 10 to 14 (dark gray segments), and 15 or more (light gray segments).

There was no evidence of substantially different results in subgroups of sufficient size based on baseline visual acuity, baseline OCT-measured central subfield thickening, and history of prior focal/grid photocoagulation for DME (Table 5).

There were 72 subjects who had 1 eye assigned to the laser group and 1 eye in the 1-mg triamcinolone group and 75 subjects who had 1 eye in the laser group and 1 eye in the 4-mg triamcinolone group. For the laser plus 1-mg triamcinolone subjects, the mean paired difference in change in visual acuity letter score at 2 years was 4.4 (95% confidence interval, −0.2 to 9.0) and for the laser plus 4-mg triamcinolone subjects, the mean paired difference was 4.5 (95% confidence interval, −1.4 to 10.3), in each case favoring the laser group.

Effect of Treatment on Retinal Thickening

The OCT results generally paralleled the visual acuity results, with a greater beneficial effect seen at the 4-month visit in the 4-mg triamcinolone group compared with the other 2 groups, a greater beneficial effect in the laser group compared with the other 2 groups during the second year, and no difference between the 2 triamcinolone groups during the second year (Table 6, available at http://aaojournal.org; Fig 3). The OCT central subfield thickness decreased from baseline to 2 years by a mean of 139±148 μm in the laser group, 86±167 μm in the 1-mg triamcinolone group ($P<0.001$ compared with the laser group), and 77±160 μm in the 4-mg triamcinolone group ($P<0.001$ compared with the laser group and 0.91 compared with the 1-mg triamcinolone group); 67%, 46%, and 48% of eyes, respectively, had a decrease in retinal thickening of 50% or more ($P<0.001$, $P<0.001$, and $P = 0.60$, respectively, for the 3 pairwise comparisons), and 53%, 34%, and 38% had central subfield thickness of less than 250 μm ($P<0.001$, $P<0.001$ and $P = 0.55$, respectively, for the 3 pairwise comparisons). A tendency for a greater reduction in OCT-measured retinal thickening in the laser group than in the triamcinolone groups was present regardless of the degree of retinal thickening at baseline (Table 7). Results were similar comparing the change in OCT-measured retinal volume among treatment groups (Table 7).

Adverse Events

Major ocular adverse events are summarized in Table 8. There were no cases of endophthalmitis or inflammatory pseudoendophthalmitis after any of the 1649 intravitreal injections (1583 in study eyes in the triamcinolone groups, 23 in study eyes in the laser group, and 43 in nonstudy eyes). Silicone oil droplets were noted in 77 (30%) eyes in the 1-mg triamcinolone group (841 injections given) and 59 (23%) eyes in the 4-mg triamcinolone group (742 injections given). Although some subjects were symptomatic with floaters, there was no indication of an adverse effect of the silicone

Table 4. Change in Visual Acuity at 2-Year Primary Outcome*

Change in Visual Acuity (Letters)	Laser (n = 330)	1 mg (n = 256)	4 mg (n = 254)
Mean±SD	1±17	−2±18	−3±22
Median (25th, 75th percentile)	4 (−6, 11)	1 (−11, 9)	2 (−11, 11)
Distribution of change at 2 yrs (%)			
≥15-letter improvement	18%	14%	17%
14- to 10-letter improvement	13%	11%	11%
9- to 5-letter improvement	16%	14%	15%
Same ±4 letters	24%	27%	23%
5–9 letters worse	10%	9%	6%
10–14 letters worse	5%	6%	8%
≥15 letters worse	14%	20%	20%

SD = standard deviation.
P values for 2-group comparisons of difference in mean change: laser vs. 1 mg = 0.02, laser vs. 4 mg = 0.002, 1 mg vs. 4 mg = 0.49.
P values for 2-group comparisons of proportion with 15-letter or more worsening: laser vs. 1 mg = 0.03, laser vs. 4 mg = 0.01, 1 mg vs. 4 mg = 0.82.
Hochberg's procedure was used to determine statistical significance by the following prespecified plan. After ordering the *P* values of the 3 comparisons from highest to lowest ($P1>P2>P3$), statistical significance was determined as follows: If $P1\leq0.049$ (includes an adjustment of 0.001 to account for DSMC data reviews), all comparisons were considered statistically significant; otherwise, if $P2\leq(0.049/2) = 0.0245$, then $P2$ and $P3$ were considered statistically significant; otherwise, if $P3\leq(0.049/3) = 0.0163$, then it was considered statistically significant.
*Visits occurring between 609 and 852 days from randomization were included as 2-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 2-year target date were used. For other eyes without any 2-year data (58 eyes in the laser group, 36 eyes in the 1 mg triamcinolone group, and 50 eyes in the 4 mg triamcinolone group), the last observation carried forward method was used to impute data for the primary analysis. Refraction was performed before the best-corrected visual acuity measurement used in this analysis in 89%, 86%, 88% of eyes in the laser, 1 mg triamcinolone, and 4 mg triamcinolone groups, respectively. For other eyes, a refraction from the prior visit was used.

oil on the eye. There were no systemic adverse events with a difference in frequency among the 3 groups that could not be attributed to chance.

With regard to ocular hypertension and glaucoma, there were more eyes in the 4-mg triamcinolone group (40%) than in the 1-mg triamcinolone group (20%) or laser group (10%) that had 1 of the following at 1 or more visits: (1) elevation in intraocular pressure of 10 mmHg or more from baseline, (2) intraocular pressure of 30 mmHg or more, (3) initiation of intraocular pressure-lowering medications (if not being treated at study entry) or a diagnosis of glaucoma ($P<0.001$ for all 3 pairwise comparisons). Glaucoma surgery was performed in 4 eyes in the 4-mg triamcinolone group (filtering procedure in 2 eyes, laser trabeculoplasty in 1 eye, and ciliary body destruction in 1 eye). At the 2-year visit, mean intraocular pressure was 16 mmHg in all groups; treatment to lower intraocular pressure was being used by 3%, 6%, and 13% of eyes in the laser, 1-mg triamcinolone, and 4-mg triamcinolone groups, respectively.

Among phakic eyes at baseline, cataract surgery was performed before the 2-year outcome visit in more eyes in the 4-mg triamcinolone group (51%) than in the 1-mg triamcinolone group (23%) or in the laser group (13%; $P<0.001$ for all 3 pairwise comparisons).

There were no differences among groups in the change of glycosylated hemoglobin from baseline to 1 year or 2 years (data not shown).

Discussion

This phase III randomized clinical trial compared 1-mg and 4-mg doses of preservative-free triamcinolone with focal/grid photocoagulation as treatments for eyes with DME and visual acuity ranging from 20/40 to 20/320. At 4 months, a greater positive treatment response on visual acuity was seen in the 4-mg triamcinolone group compared with the other 2 groups. However, by 1 year, there was little difference in visual acuity between the groups, and at the time of the 2-year primary outcome assessment, visual acuity and safety (with respect to intraocular pressure and cataract) were significantly better in the laser group than in either the 1-mg triamcinolone or 4-mg triamcinolone groups. There was no significant difference between the 1-mg triamcinolone and 4-mg triamcinolone groups in visual acuity at 2 years. Treatment group differences in the change in retinal thickening generally mirrored the effect on visual acuity, with initially a greater reduction in the 4-mg triamcinolone group, an eventual greater reduction in the laser group, and no difference between the 2 triamcinolone groups at 2 years.

The lesser efficacy of triamcinolone on visual acuity relative to focal/grid photocoagulation at 2 years is unlikely to be the result of corticosteroid-induced lens changes alone, in view of the OCT results and because an analysis limited to eyes that were pseudophakic or without lens changes judged clinically relevant did not demonstrate a benefit of triamcinolone compared with focal/grid photocoagulation. Likewise, a benefit of triamcinolone relative to photocoagulation was not seen in prespecified subgroups of sufficient size based on baseline visual acuity, retinal thickening, or a history of prior macular photocoagulation. Among the small number of eyes with the most severe visual acuity loss at baseline (20/200 to 20/320), most of the eyes in the 4-mg triamcinolone group had an improvement in visual acuity at 2 years. However, the number of such eyes was too small (n = 13) for a meaningful assessment of the treatment effect relative to focal/grid photocoagulation.

With respect to the safety of the intravitreal injections, through 2 years of follow-up, there were no cases of infectious or noninfectious endophthalmitis after an injection of the preservative-free triamcinolone preparation used in this study. A relatively high incidence of detection of silicone oil droplets in the vitreous after intravitreal injections (approximately one quarter of eyes treated with intravitreal triamcinolone) was noted. This is a recognized occurrence after intravitreal injection using siliconized syringes.[48] Although some subjects were symptomatic from floaters because of the silicone oil droplets, we have not identified any adverse effects on the eye attributable to the silicone oil. Consistent with other reports,[22,49,50] the 4-mg triamcinolone injections were associated with an increased incidence of both elevation of intraocular pressure and development of cataract requiring surgery. Most cases of elevated intraocular pressure were controlled adequately with ocular hypotensive medications, but in the 4-mg triamcinolone group, 2 cases required a filtering procedure, 1 case required a laser trabeculoplasty, and 1 case required a ciliary body destructive procedure.

Table 5. Change in Visual Acuity at 2-Year Primary Outcome among Subgroups

Subgroup	N (N imputed) Laser, 1 mg, 4 mg Groups	Change in Visual Acuity, Median (25th, 75th Percentile)			≥10-Letter Worsening (%)			≥10-Letter Improvement (%)		
		Laser	*1 mg*	*4 mg*	*Laser*	*1 mg*	*4 mg*	*Laser*	*1 mg*	*4 mg*
Baseline visual acuity letter score (approximate Snellen equivalent)										
73–60 (20/32-2–20/63)	189 (29), 149 (21), 149 (22)	1 (−9, 8)	−1 (−12, 7)	2 (−12, 7)	23	28	33	23	17	16
59–36 (20/63-1–20/200+1)	129 (27), 94 (13), 92 (23)	7 (−3, 17)	3 (−9, 13)	4 (−11, 14)	12	24	26	43	33	39
35–24 (20/200–20/320-1)*	12 (2), 13 (2), 13 (5)	7 (−6, 14)	8 (0, 22)	21 (15, 40)	17	15	0	42	46	77
Baseline central subfield thickness (μm)†										
<400	166 (25), 121 (16), 130 (20)	4 (−4, 11)	2 (−6, 10)	2 (−11, 10)	16	19	29	31	26	25
400–500	80 (17), 67 (8), 63 (12)	5 (−7, 14)	−1 (−12, 8)	5 (−8, 11)	23	28	21	36	22	30
>500	83 (16), 66 (11), 60 (18)	1 (−8, 11)	−2 (−19, 8)	0 (−21, 12)	22	38	37	28	23	30
Prior photocoagulation for diabetic macular edema										
No prior laser	132 (29), 102 (17), 96 (23)	2 (−8, 11)	1 (−13, 10)	0 (−18, 8)	23	27	40	32	27	24
Prior laser	198 (29), 154 (19), 158 (27)	4 (−5, 12)	0 (−10, 8)	3 (−8, 12)	16	25	22	31	23	30

Imputation for missing values using last observation carried forward.
*Median baseline central subfield thickness was 435, 599, and 501 μm in the laser, 1-mg, and 4-mg groups, respectively.
†Baseline central subfield thickness was missing for 4 eyes.

The 4-mg triamcinolone dose was evaluated because it was the dose most commonly used in clinical practice at the time the trial was initiated. The 1-mg dose was included because this dose was likely to exceed the concentration necessary to saturate the glucocorticoid receptors in the cell cytoplasm completely.[51,52] Also, it was hoped that adverse effects on the lens and intraocular pressure might be less frequent. Indeed, the 1-mg triamcinolone group had fewer side effects with respect to glaucoma and cataract than the 4-mg triamcinolone group. Although the 4-mg group was superior to the 1-mg group with respect to vision at 4 months and superior to the 1-mg group with respect to retinal thickening up to 1 year, no differences in visual acuity or retinal thickening were detected after 2 years of follow-up. The retreatment protocol encouraged frequent reinjection, with reinjection of triamcinolone at 4-month intervals as long as edema was present, visual acuity or retinal thickening had not improved substantially since the last injection, futility criteria were not met (see "Methods"), or an

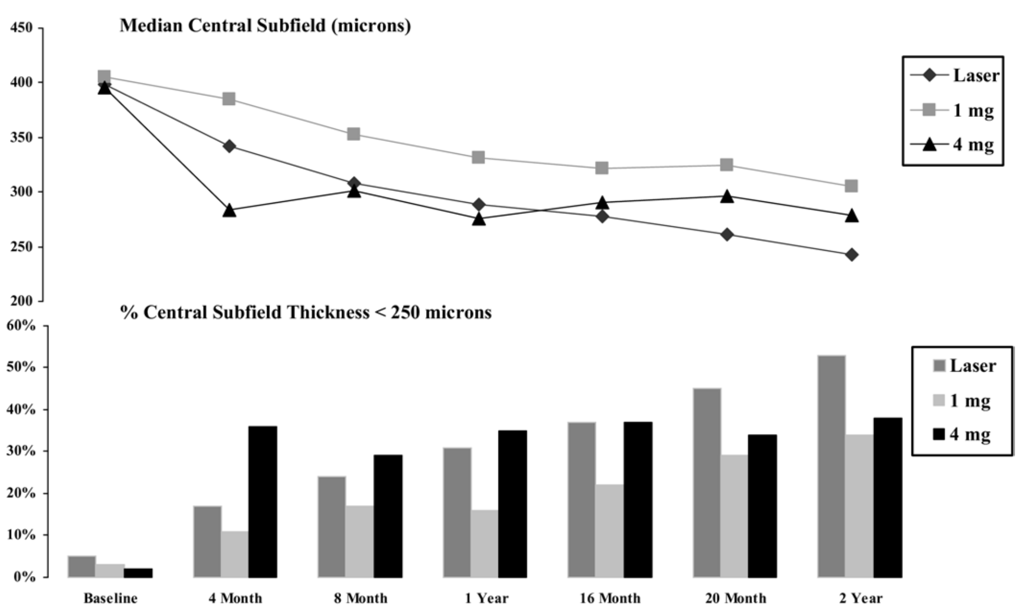

Figure 3. Graph showing the effect of treatment on the central subfield thickness, measured with optical coherence tomography (OCT), at each visit according to treatment group. The top portion of the figure displays the median thickness in each treatment group. The bars in the bottom portion represent the proportion of eyes in each treatment group with thickness of less than 250 μm.

Table 7. Retinal Thickening* at 2 Years Overall and Stratified by Baseline Central Subfield Thickness

	Laser	1 mg	4 mg
Overall			
Central subfield	n = 261	n = 207	n = 193
Thickness (μm), median (25th, 75th percentile)	243 (197, 326)	305 (231, 406)	279 (228, 430)
Change from baseline (μm), mean±SD†	−139±148	−86±167	−77±160
Change from baseline (μm), median (25th, 75th percentile)	−131 (−217, −49)	−74 (−168, −3)	−76 (−175, 11)
Thickening decreased by ≥50%†	67%	46%	48%
Thickness <250 μm†	53%	34%	38%
Retinal volume	n = 164	n = 133	n = 120
Change from baseline, mean±SD†	−1.4±1.7	−0.7±1.7	−0.4±1.7
Change from baseline, median (25th, 75th percentile)	−1.1 (−2.2, −0.4)	−0.6 (−1.3, 0.1)	−0.6 (−1.4, 0.4)
Baseline thickness <400 μm			
Central subfield	n = 139	n = 98	n = 104
Thickness (μm), median (25th, 75th percentile)	235 (198, 288)	265 (225, 341)	263 (227, 349)
Change from baseline (μm), mean±SD	−74±90	−32±104	−20±124
Change from baseline (μm), median (25th, 75th percentile)	−86 (−137, −18)	−36 (−101, 18)	−42 (−102, 24)
Thickening decreased by ≥50%	64%	46%	47%
Thickness <250 μm	60%	42%	44%
Retinal volume	n = 90	n = 61	n = 71
Change from baseline, mean±SD	−0.8±1.3	−0.4±0.8	−0.2±1.5
Change from baseline, median (25th, 75th percentile)	−0.6 (−1.4, −0.2)	−0.2 (−0.8, 0.1)	−0.5 (−1.2, 0.3)
Baseline thickness 400–500 μm			
Central subfield	n = 58	n = 55	n = 49
Thickness (μm), median (25th, 75th percentile)	243 (189, 365)	352 (239, 406)	326 (234, 440)
Change from baseline (μm), mean±SD	−154±129	−80±162	−91±147
Change from baseline (μm), median (25th, 75th percentile)	−193 (−251, −69)	−92 (−177, −29)	−105 (−200, 5)
Thickening decreased by ≥50%	67%	44%	49%
Thickness <250 μm	52%	27%	29%
Retinal volume	n = 35	n = 36	n = 34
Change from baseline, mean±SD	−1.6±1.6	−0.5±1.2	−0.5±1.6
Change from baseline, median (25th, 75th percentile)	−1.3 (−2.5, −0.7)	−0.7 (−1.2, 0.1)	−0.8 (−1.4, 0.2)
Baseline thickness >500 μm			
Central subfield	n = 64	n = 54	n = 40
Thickness (μm), median (25th, 75th percentile)	301 (199, 423)	408 (245, 552)	367 (223, 563)
Change from baseline (μm), mean±SD	−265±177	−192±211	−209±178
Change from baseline (μm), median (25th, 75th percentile)	−259 (−373, −169)	−204 (−355, −52)	−247 (−322, −97)
Thickening decreased by ≥50%	72%	48%	50%
Thickness <250 μm	41%	26%	33%
Retinal volume	n = 39	n = 36	n = 15
Change from baseline, mean±SD	−2.5±2.0	−1.6±2.6	−0.7±2.6
Change from baseline, median (25th, 75th percentile)	−2.4 (−3.7, −1.2)	−1.3 (−3.3, −0.6)	−1.7 (−2.5, 1.1)

SD = standard deviation.
Nos. include only eyes with a central subfield or retinal volume value at both baseline and the follow-up visit.
*Retinal thickening defined as observed thickness minus average normal thickness. Average central subfield thickness of normals defined as 201 μm. Twenty-seven eyes (15 in laser group, 7 in 1-mg group, and 5 in 4-mg group) with baseline central subfield thickness <250 μm not included in calculations of relative change in thickening.
†*P* values (not adjusted for multiple comparisons) for treatment group comparisons of laser vs. 1-mg group, laser v. 4-mg group, and 1-mg v. 4-mg groups are as follows. Change in central subfield from baseline: <0.001, <0.001, 0.91; percentage with central subfield thickening reduced by 50% or more: <0.001, <0.001, 0.60; percentage with central subfield thickness <250 μm: <0.001, <0.001, 0.55; change in retinal volume from baseline: <0.001, <0.001, 0.44.

adverse event such as increased intraocular pressure had not occurred that precluded retreatment at that visit. The occurrence of elevated intraocular pressure may have limited the number of reinjections in some subjects. The early treatment effect of triamcinolone relative to focal/grid photocoagulation found in the current study is consistent with many published case series[50,53,54] and a small randomized trial showing such an effect.[55] One other small randomized trial reported no significant difference comparing focal/grid photocoagulation and 4 mg intravitreal triamcinolone after 4 months or 12 months.[49]

The trial had a sample size that was sufficiently large so that it is highly unlikely that a true 2-year benefit of triamcinolone over focal/grid photocoagulation went undetected, particularly because the results favored the photocoagulation group. The treatment groups were well balanced with regard to baseline factors. Although investigators and subjects were not masked to treatment group with respect to photocoagulation versus triamcinolone, it is unlikely that this was a source of bias favoring the photocoagulation group, because the prestudy presumption was that intravitreal triamcinolone may be a better treatment than focal/grid

Table 8. Number of Major Ocular Adverse Events During 2 Years of Follow-up

	Laser (n = 330 Eyes, n = 23 4-mg Injections)	1 mg (n = 256 Eyes, n = 841 Injections)	4 mg (n = 254 Eyes, n = 742 Injections)
Endophthalmitis*	0	0	0
Pseudoendophthalmitis	0	0	0
Retinal detachment†	2	2	4
Retinal vein occlusion†	3	1	2
Retinal artery occlusion†	1	0	0
Anterior ischemic optic neuropathy†	0	1	0
Vitrectomy‡	31	26	19
Elevated IOP/glaucoma (%)			
Increase ≥10 mmHg from baseline§	12 (4)	41 (16)	85 (33)
IOP ≥30 mmHg§	3 (1)	22 (9)	53 (21)
Initiation of IOP-lowering medication§	25 (8)	31 (12)	76 (30)
Open-angle glaucoma	2 (1)	2 (1)	7 (3)
Glaucoma filtering surgery	0	0	2 (1)
Laser trabeculoplasty	0	0	1 (<1)
Ciliary body destruction	0	0	1 (<1)
No. of eyes meeting 1 or more of the above	33 (10)	51 (20)	102 (40)
Cataract surgery‖			
No. phakic at baseline	262	203	197
No. (%) with cataract surgery	34 (13)	47 (23)	101 (51)

IOP = intraocular pressure.
*One case of endophthalmitis occurred after vitrectomy, not related to injection of study drug.
†Not necessarily related to treatment.
‡Includes vitrectomy for diabetic macular edema, vitreous hemorrhage, or other cause.
§At any follow-up visit through the 2-year examination.
‖Before the 2-year examination or 2 years from randomization if the 2-year visit was not completed.

photocoagulation. Visual acuity was measured using a computerized system and OCT scans were graded at a reading center masked to treatment group, reducing the potential for bias in these assessments. The consistency between the visual acuity and OCT results adds further credence to the validity of the findings. The study completion rate of 83% (88% if deaths are excluded) was lower than expected, but we have no indication that this significantly influenced the results. The completion rate was similar among the treatment groups, and analyses using 3 different methods for handling missing data produced similar results.

Based on data from the ETDRS, it seems likely that the visual acuity outcome with each of the 3 treatment regimens is superior to the expected untreated course. The best estimate of the untreated course of visual acuity in eyes with DME for comparison with the treatment groups in the current study comes from the treatment group in the ETDRS in which focal/grid photocoagulation was deferred. Among 235 ETDRS eyes in that group that had definite center thickening on fundus photographs, a visual acuity letter score of less than 74 (worse than 20/32), and mild to moderate nonproliferative retinopathy at baseline, the median visual acuity letter score at 2 years was decreased from baseline by −6, with 12% improving 10 letters or more and 43% worsening 10 letters or more (Ferris FL, unpublished data, 2008). This was a substantially worse outcome than that observed in any of the 3 treatment groups. It is important to note that in the current study, some eyes had more severe retinopathy than those included in this analysis of ETDRS data. Further support for the positive long-term effect on visual acuity and retinal thickening of intravitreal triamcinolone comes from a randomized trial conducted by Gillies et al.[50] These authors reported a beneficial effect on visual acuity and retinal thickening of 4 mg intravitreal triamcinolone compared with sham injections after 2 years of follow-up in a randomized trial involving 69 eyes of 43 subjects previously treated with focal/grid photocoagulation with persistent DME and visual acuity of 20/30 or worse. The conclusions from the Gillies et al study cannot be compared directly with the conclusions from the current study because only approximately half of the control group eyes in the Gillies et al study received focal/grid photocoagulation during the study, and collectively these eyes fared much worse than the laser group in the current study.

The results of the current study elevate the importance of focal/grid photocoagulation in managing DME across a wide range of visual acuities and a wide range of retinal thicknesses, even in eyes with prior macular photocoagulation for DME. It is important to note that eyes with prior macular photocoagulation were enrolled in this trial only if judged by the investigator to have the potential to benefit from additional laser treatment. Although the ETDRS demonstrated that focal/grid photocoagulation improves the visual outcome of DME, it largely has been believed that the benefit was in reducing the frequency of vision loss and not in improving visual acuity. However, this general conclusion ignores the fact that most eyes in the ETDRS had normal or near normal visual acuity and thus did not have the potential for substantial visual acuity improvement. In a subset of 114 ETDRS eyes meeting the aforementioned criteria that were treated with immediate focal/grid photocoagulation, the results were similar to the findings in the current study. This ETDRS subset of eyes had a median change in the visual acuity letter score from baseline to 2 years of +4, with 29% improving 10 or more letters and 16% worsening 10 or more letters (Ferris FL, unpublished data, 2008). A prior DRCR.net study evaluating macular photocoagulation regimens also demonstrated that visual acuity improvement is not uncommon after focal/grid photocoagulation for DME.[43] In the 46 eyes in that study with a baseline visual acuity letter score of 73 or less (20/40 or worse) and central subfield thickness of 250 μm or more that were in the focal/grid photocoagulation group, the median change in the visual acuity letter score from baseline to 1 year was +6, with 37% of eyes improving 10 or more letters and 9% worsening 10 or more letters (unpublished data, 2008).

With respect to any deleterious effects of focal/grid photocoagulation on visual acuity, there has been no indication of an attenuation of the beneficial effect of photocoagulation through 2 years of follow-up. Results from the ETDRS[8] focal/grid photocoagulation group showing no deterioration of visual acuity through 3 years support the expectation that deterioration of visual acuity will not be seen during the third year of follow-up in the current study. The fact that photocoagulation was administered by a wide range of treating physicians in the DRCR network based on a written protocol without grading of photographs to confirm adherence to protocol enhances the generalizability of the study results.

The photocoagulation treatment regimen used in the current study, which was a modification of the regimen used in the ETDRS, encouraged frequent retreatment at 4-month intervals whenever there was persistent or new edema that had not been treated previously and had not improved substantially since the last treatment. In view of the importance of focal/grid photocoagulation in treating DME, as reaffirmed by this study, additional studies are needed to develop a better understanding of when photocoagulation treatment is complete and the optimal interval for repeating treatment. To this end, the DRCR.net is currently conducting a study evaluating whether a less intensive photocoagulation retreatment algorithm offers enough promise to warrant a clinical trial comparing such treatment with the more intensive retreatment criteria used in this study. Pending such a study, it is not known whether a less aggressive approach of deferring retreatment with focal/grid photocoagulation as long as there is evidence of improvement in visual acuity or retinal thickening may produce results similar to the current study.

Although the results of the current study confirm the ETDRS finding that focal/grid photocoagulation has a substantial beneficial effect on DME, there is certainly a role for better treatments in the future, because approximately half of the study eyes in the photocoagulation group still had central retinal thickening at 2 years, with approximately 1 in 5 having worsened 10 letters or more from baseline and only approximately 1 in 3 having improved by 10 letters or more. The fact that the 4-mg intravitreal triamcinolone group had a greater positive treatment response on visual acuity and retinal thickening at 4 months, whereas the photocoagulation group had a greater positive response later, raises the possibility that combining focal/grid photocoagulation with intravitreal triamcinolone may produce greater benefit for DME than either focal/grid photocoagulation or intravitreal triamcinolone alone. A DRCR.net study currently is evaluating a combination of intravitreal triamcinolone and focal/grid photocoagulation, a combination of ranibizumab and photocoagulation, and ranibizumab alone in eyes with characteristics similar to those included in the current study (protocol available at www.drcr.net; date accessed, June 5, 2008).

In conclusion, although intravitreal triamcinolone likely improves visual acuity over 2 years compared with the expected untreated course, the results of this study demonstrate that focal/grid photocoagulation not only is more effective over at least 2 years than intravitreal triamcinolone with respect to both visual acuity and OCT-measured retinal thickening, but also is associated with far fewer adverse events, particularly elevation of intraocular pressure and lens changes. Based on these results, the strongest scientific evidence currently supports focal/grid photocoagulation as the most effective treatment for patients with DME who have similar characteristics to the cohort in this clinical trial. The results of this study also support that focal/grid photocoagulation currently should be the benchmark against which other treatments are compared in clinical trials of DME.

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Footnotes

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Writing Committee. Lead authors: Michael S. Ip, Allison R. Edwards, Roy W. Beck, Neil M. Bressler; additional writing committee members (in alphabetical order): Lloyd Paul Aiello, David J. Browning, Michael J. Elman, Scott M. Friedman, Frederick L. Ferris, Adam R. Glassman, Craig Kollman, Angela Price.

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Appendix: 1

Participating Diabetic Retinopathy Clinical Research Network Clinical Sites

Sites are listed in order by number of subjects enrolled into the study. The number of subjects enrolled is noted in parentheses, preceded by the site location and the site name. Personnel are listed as (I) for investigator, (C) for coordinator, (V) for visual acuity tester, and (P) for photographer.

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Central Florida Retina Institute, Lakeland, Florida (22): Scott M. Friedman (I), Oren Z. Plous (I), Kelly A. Blackmer (C), Jolleen S. Key (C, P, V), Steve D. Carlton (C, P, V), Karen L. Sjoblom (P, V), Damanda A. Fagan (V), Virginia Gregory (P, V), Jessica Maldonado (P), Katie A. Gostischa (P), Allen McKinney (P, V).

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Retina-Vitreous Surgeons of Central New York, PC, Syracuse, New York (20): G. Robert Hampton (I), Samuel C. Spalding (I), Paul F. Torrisi (I), Bryan K. Rutledge (I), Cindy J. Grinnell (C, V), Fayth M. DiSano (C, V), Lynn M. Kwasniewski (V), Tanya C. Czajak (V), Peter B. Hay (P), Jeanne L. Burke (P), Kenneth B. Fyles (P), Bob Corey (P), Lynn A. Capone (P).

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Retina Consultants, Providence, Rhode Island (12): Caldwell W. Smith (I), Harold A. Woodcome (I), Magdalena G. Krzystolik (I), Paul B. Greenberg (I), Robert H. Janigian (I), Collin L. DuCoty (C), Sylvia Varadian (C), Claudia Salinas (V), Sandra Henriques (V), Erika Banalewicz (V), Mark Hamel (P), Alex L. Nagle (P).

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West Texas Retina Consultants P.A., Abilene, Texas (10): Sunil S. Patel (I), S. Young Lee (I), Kristen L. Garcia (C, P, V), Angela Jaimes (C, P, V), Brenda K. Arrington (C, P, V), Brandi L. Dunn (C, P, V), Gwyn R. Nafe (V), Tammy Jones (P), Leah D. Adams (P), Tamara A. Bartlett (P).

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(V), Zuzanna Rozenbajgier (V), Jonathan Shankle (P), Dawn M. Ryan (P), Evica Simjanoski (P).

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Table 2. Number of Treatments with Randomization Assigned Treatment

	Laser (n = 272)	1 mg (n = 220)	4 mg (n = 205)
Baseline to <1 yr*			
Baseline only, no. (%)	69 (25%)	34 (15%)	51 (25%)
Baseline+4 mos only, no. (%)	76 (28%)	56 (25%)	44 (21%)
Baseline+8 mos only, no. (%)	22 (8%)	22 (10%)	43 (21%)
4 mos+8 mos only, no. (%)	1 (<1%)	0	0
Baseline+4 mos+8 mos, no. (%)	104 (38%)	108 (49%)	67 (33%)
Mean±standard deviation	2.1±0.8	2.3±0.7	2.1±0.8
Total, baseline to <2 yrs			
1	52 (19%)	25 (11%)	25 (12%)
2	65 (24%)	36 (16%)	52 (25%)
3	67 (25%)	54 (25%)	49 (24%)
4	49 (18%)	46 (21%)	39 (19%)
5	28 (10%)	31 (14%)	27 (13%)
6	11 (4%)	28 (13%)	13 (6%)
Mean±standard deviation	2.9±1.4	3.5±1.5	3.1±1.4

Table includes only subjects completing the 2-year visit.
*Too many permutations to detail beyond 8 mos.

Table 3. Change in Visual Acuity at Follow-up Visits*

Change in Visual Acuity (Letters)	Laser	1 mg	4 mg
4 Mos	n = 311	n = 241	n = 244
Mean±SD	0±13	0±13	4±12
Median (25th, 75th percentile)	2 (−4, 7)	2 (−4, 8)	5 (−1, 10)
Distribution of change (%)			
≥15-letter improvement	7%	5%	12%
14- to 10-letter improvement	10%	13%	15%
9- to 5-letter improvement	21%	21%	28%
Same ±4 letters	38%	36%	32%
5–9 letters worse	7%	11%	7%
10–14 letters worse	8%	4%	3%
≥15 letters worse	9%	10%	4%
8 Mos	n = 299	n = 231	n = 226
Mean±SD	0±15	1±12	2±14
Median (25th, 75th percentile)	2 (−6, 9)	2 (−4, 8)	3 (−4, 11)
Distribution of change (%)			
≥15-letter improvement	11%	7%	12%
14- to 10-letter improvement	12%	14%	18%
9- to 5-letter improvement	16%	17%	16%
Same ±4 letters	31%	37%	31%
5–9 letters worse	12%	12%	9%
10–14 letters worse	5%	5%	6%
≥15 letters worse	12%	8%	8%
1 Yr	n = 286	n = 230	n = 221
Mean±SD	1±16	0±15	0±16
Median (25th, 75th percentile)	3 (−5, 10)	3 (−4, 9)	2 (−7, 10)
Distribution of change (%)			
≥15-letter improvement	14%	10%	12%
14- to 10-letter improvement	14%	13%	13%
9- to 5-letter improvement	17%	20%	16%
Same ±4 letters	29%	33%	29%
5–9 letters worse	9%	7%	10%
10–14 letters worse	3%	8%	7%
≥15 letters worse	14%	10%	12%
16 Mos	n = 263	n = 214	n = 208
Mean±SD	1±15	−1±15	−4±18
Median (25th, 75th percentile)	3 (−5, 11)	0 (−8, 8)	0 (−15, 8)
Distribution of change (%)			
≥15-letter improvement	15%	9%	12%
14- to 10-letter improvement	13%	12%	9%
9- to 5-letter improvement	17%	15%	15%
Same ±4 letters	27%	33%	23%
5–9 letters worse	10%	8%	8%
10–14 letters worse	5%	7%	8%
≥15 letters worse	13%	15%	25%
20 Mos	n = 250	n = 211	n = 195
Mean±SD	3±15	−2±17	−4±20
Median (25th, 75th percentile)	6 (−4, 11)	1 (−9, 7)	0 (−12, 7)
Distribution of change (%)			
≥15-letter improvement	16%	13%	10%
14- to 10-letter improvement	17%	7%	11%
9- to 5-letter improvement	24%	15%	15%
Same ±4 letters	19%	32%	26%
5–9 letters worse	9%	11%	8%
10–14 letters worse	5%	7%	11%
≥15 letters worse	10%	15%	19%
2 Yrs	n = 272	n = 220	n = 204
Mean±SD	2±17	−2±17	−4±23
Median (25th, 75th percentile)	5 (−5, 12)	1 (−11, 10)	2 (−12, 11)
Distribution of change (%)			
≥15-letter improvement	20%	15%	16%
14- to 10-letter improvement	14%	11%	11%
9- to 5-letter improvement	17%	14%	15%
Same ±4 letters	22%	25%	22%
5–9 letters worse	9%	8%	5%

(*Continued*)

Table 3. (Continued.)

Change in Visual Acuity (Letters)	Laser	1 mg	4 mg
10–14 letters worse	6%	6%	9%
≥15 letters worse	13%	21%	21%

P Values[‖]	Visit					
	4 Mos	*8 Mos*	*1 Yr*	*16 Mos*	*20 Mos*	*2 Yrs*
Laser vs. 1 mg	0.85	0.46	0.85	0.06[†]	0.002[†]	0.02[†]
Laser vs. 4 mg	<0.001[‡]	0.05[‡]	0.64	<0.001[†]	<0.001[†]	0.002[†]
1 mg vs. 4 mg	0.001[‡]	0.27	0.79	0.08[§]	0.24	0.42

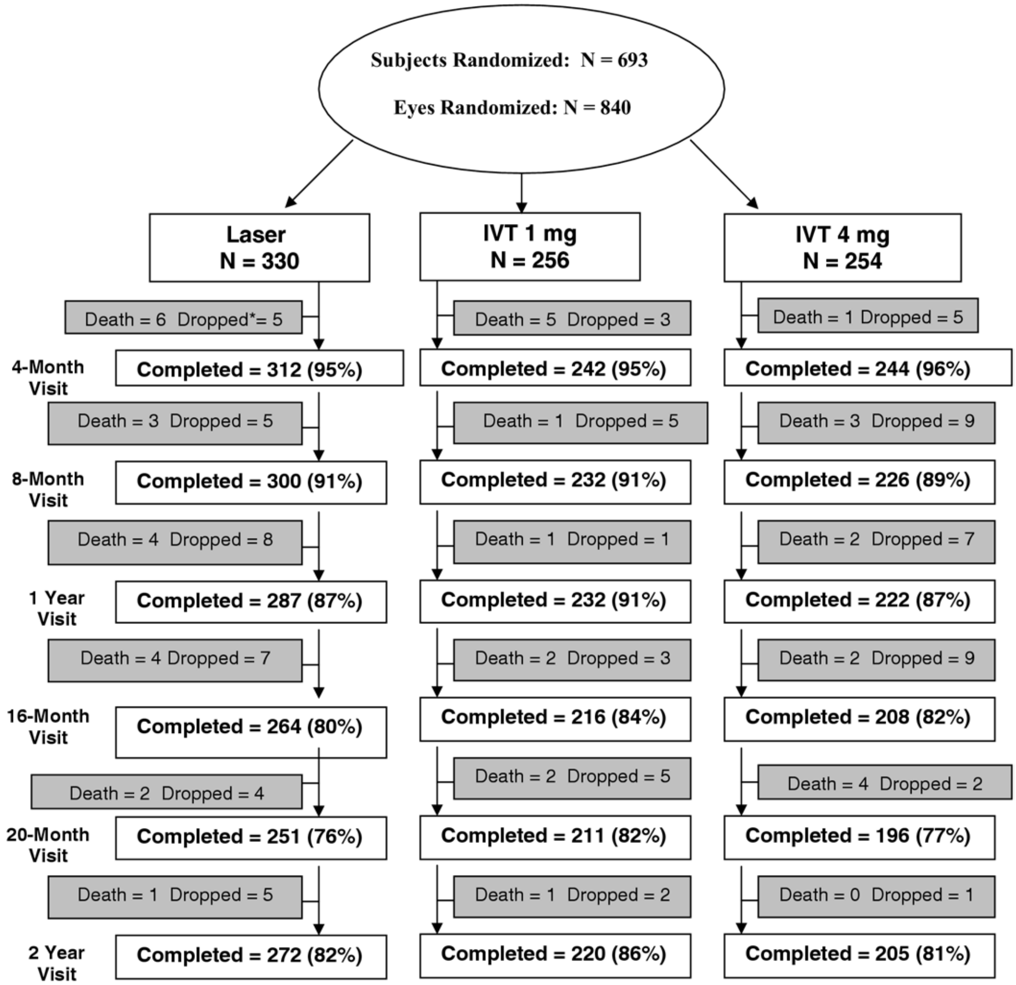
SD = standard deviation.
*Includes data for completed visits with no imputation for missing values.
[†]*P* value favoring laser group.
[‡]*P* value favoring 4-mg group.
[§]*P* value favoring 1-mg group.
[‖]*P* values not adjusted for multiple comparisons.

Table 6. Change in Central Subfield Retinal Thickening* at Follow-up Visits

	Laser	1 mg	4 mg
4 Mos	n = 304	n = 234	n = 242
Thickness (μm), median (25th, 75th percentile)	342 (279, 470)	385 (295, 488)	284 (236, 387)
Change from baseline (μm), mean±SD	−39±109	−16±111	−98±130
Change from baseline (μm), median (25th, 75th percentile)	−33 (−90, 13)	−13 (−62, 41)	−77 (−145, −19)
Thickening decreased by ≥50%	23%	15%	46%
Thickness <250 μm	17%	11%	36%
8 Mos	n = 288	n = 221	n = 220
Thickness (μm), median (25th, 75th percentile)	308 (252, 411)	353 (279, 455)	301 (244, 397)
Change from baseline (μm), mean±SD	−73±136	−35±133	−78±130
Change from baseline (μm), median (25th, 75th percentile)	−60 (−147, 4)	−23 (−101, 38)	−76 (−134, −7)
Thickening decreased by ≥50%	40%	27%	45%
Thickness <250 μm	24%	17%	29%
1 Yr	n = 278	n = 225	n = 213
Thickness (μm), median (25th, 75th percentile)	289 (235, 396)	331 (270, 449)	276 (231, 390)
Change from baseline (μm), mean±SD	−98±144	−55±142	−93±146
Change from baseline (μm), median (25th, 75th percentile)	−85 (−167, −14)	−31 (−137, 25)	−74 (−152, −13)
Thickening decreased by ≥50%	48%	33%	48%
Thickness <250 μm	31%	16%	35%
16 Mos	n = 255	n = 208	n = 191
Thickness (μm), median (25th, 75th percentile)	278 (225, 362)	322 (260, 433)	290 (229, 436)
Change from baseline (μm), mean±SD	−105±149	−62±152	−69±150
Change from baseline (μm), median (25th, 75th percentile)	−100 (−184, −15)	−57 (−141, 10)	−69 (−160, 23)
Thickening decreased by ≥50%	54%	35%	48%
Thickness <250 μm	37%	22%	37%
20 Mos	n = 240	n = 198	n = 179
Thickness (μm), median (25th, 75th percentile)	261 (213, 326)	325 (239, 439)	296 (234, 453)
Change from baseline (μm), mean±SD	−132±143	−69±160	−60±175
Change from baseline (μm), median (25th, 75th percentile)	−119 (−211, −36)	−56 (−155, 23)	−65 (−163, 26)
Thickening decreased by ≥50%	64%	40%	45%
Thickness <250 μm	45%	29%	34%
2 Yrs	n = 261	n = 207	n = 193
Thickness (μm), median (25th, 75th percentile)	243 (197, 326)	305 (231, 406)	279 (228, 430)
Change from baseline (μm), mean±SD	−139±148	−86±167	−77±160
Change from baseline (μm), median (25th, 75th percentile)	−131 (−217, −49)	−74 (−168, −3)	−76 (−175, 11)
Thickening decreased by ≥50%	67%	46%	48%
Thickness <250 μm	53%	34%	38%

	Visit					
***P* Value**§	*4 Mos*	*8 Mos*	*1 Yr*	*16 Mos*	*20 Mos*	*2 Yr*
Laser vs. 1 mg	.01†	<0.001†	<0.001†	<0.001†	<0.001†	<0.001†
Laser vs. 4 mg	<0.001‡	0.98	0.97	0.004†	<0.001†	<0.001†
1 mg vs. 4 mg	<0.001‡	<0.001‡	<0.001‡	0.33	0.86	0.91

SD = standard deviation.
Nos. include only eyes with central subfield value at both baseline and the follow-up visit.
*Retinal thickening defined as observed thickness minus average normal thickness. Average central subfield thickness of normals defined as 201 μm. Twenty-seven eyes (15 in laser group, 7 in 1-mg group, and 5 in 4-mg group) with baseline central subfield thickness of less than 250 μm not included in calculations of relative change in thickening.
†*P* value favoring laser group.
‡*P* value favoring 4-mg group.
§*P* values not adjusted for multiple comparisons.



*Dropped = Withdrew or Lost to Follow
Note: Ns differ from tables 3 and 6 due to not all testing being completed at every visit.

Figure 1. Flow chart showing visit completion rate according to treatment group over the 2 years of follow-up. IVT = intravitreal triamcinolone.