Five-Year Outcomes of Ranibizumab With Prompt or Deferred Laser Versus Laser or Triamcinolone Plus Deferred Ranibizumab for Diabetic Macular Edema

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• PURPOSE: To compare long-term vision and anatomic effects of ranibizumab with prompt or deferred laser vs laser or triamcinolone + laser with very deferred ranibizumab in diabetic macular edema (DME).

• DESIGN: Randomized clinical trial.

• METHODS: Eight hundred and twenty-eight study eyes (558 [67%] completed the 5-year visit), at 52 sites, with visual acuity 20/32 to 20/320 and DME involving the central macula were randomly assigned to intravitreous ranibizumab (0.5 mg) with either (1) prompt or (2) deferred laser; (3) sham injection + prompt laser; or (4) intravitreous triamcinolone (4 mg) + prompt laser. The latter 2 groups could initiate ranibizumab as early as 74 weeks from baseline, for persistent DME with vision impairment. The main outcome measures were visual acuity, optical coherence central subfield thickness, and number of injections through 5 years.

• RESULTS: At 5 years mean (± standard deviation) change in Early Treatment Diabetic Retinopathy Study visual acuity letter scores from baseline in the ranibizumab + deferred laser (N = 111), ranibizumab + prompt laser (N = 124), laser/very deferred ranibizumab (N = 198), and triamcinolone + laser/very deferred ranibizumab (N = 125) groups were 10 ± 13, 8 ± 13, 5 ± 14, and 7 ± 14, respectively. The difference (95% confidence interval) in mean change between ranibizumab + deferred laser and laser/very deferred ranibizumab and triamcinolone + laser/very deferred ranibizumab was 4.4 (1.2–7.6, $P = .001$) and 2.8 (−0.9 to 6.5, $P = .067$), respectively, at 5 years.

• CONCLUSIONS: Recognizing limitations of follow-up available at 5 years, eyes receiving initial ranibizumab therapy for center-involving DME likely have better long-term vision improvements than eyes managed with laser or triamcinolone + laser followed by very deferred ranibizumab for persistent thickening and vision impairment. (Am J Ophthalmol 2016;164:57–68.

AS PREVIOUSLY REPORTED BY THE DIABETIC RETINOPathy Clinical Research Network (DRCR.net), the ranibizumab plus prompt or deferred laser groups were more effective than laser alone, or intravitreous triamcinolone plus prompt laser, for diabetic macular edema (DME) treatment.[1] In this study, the ranibizumab plus prompt or deferred laser groups were continued on their original structured re-treatment algorithm through 5 years, at which time the visual acuity and optical coherence tomography (OCT) outcomes identified at 2 years were maintained.[2]

Based on the 1-year trial results, study participants originally assigned to sham injections plus prompt laser ("laser") or triamcinolone plus prompt laser ("triamcinolone + laser") were given an opportunity to initiate very deferred (between 1.5 and 3 years following enrollment) intravitreous ranibizumab plus continued focal/grid laser (if indicated). This report compares visual acuity and OCT outcomes through 5 years among eyes assigned to the ranibizumab plus deferred laser group to the laser/very deferred ranibizumab and the triamcinolone + laser/very deferred ranibizumab groups. All comparisons are made with reference to the ranibizumab plus deferred laser group, as this management strategy is presently favored by DRCR.net because it may offer greater vision benefits when directly compared with ranibizumab plus prompt laser. Eyes managed with ranibizumab and prompt laser are included for completeness.[2] The short-term vision and anatomic outcomes following the initiation of very deferred ranibizumab therapy also are explored.

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Dec 16, 2015.

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0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2015.12.025

METHODS

THE STUDY PROCEDURES HAVE BEEN REPORTED, AND ARE summarized below.[3] The study adhered to the tenets of the Declaration of Helsinki. The Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by multiple institutional review boards. The study is listed on www.clinicaltrials.gov under identifier NCT00445003 (website registration date 03/06/2007). The protocol is available on the DRCR.net website (www.drcr.net; date accessed: February 5, 2015). Participants had at least 1 eye with approximate Snellen equivalent visual acuity of 20/32-20/320 and DME involving the central macula. Prior DME treatment was permitted if performed in compliance with a protocol-defined washout period. At baseline, 828 eyes were assigned to 1 of 4 treatment groups (sham + prompt focal/grid laser, ranibizumab + prompt laser, ranibizumab + deferred [≥24 weeks] laser, or triamcinolone + prompt laser).

Visits occurred every 4 weeks through the first year, and then every 4–16 weeks through 5 years, depending on visual acuity, OCT, and the participant's last treatment date. Retreatment at each visit was based on protocol-specific criteria.[3] Based on the 1-year visual acuity and OCT outcomes showing superior results in eyes assigned to the ranibizumab groups, the protocol was revised to allow participants assigned to laser or triamcinolone + laser the opportunity to initiate intravitreous ranibizumab between approximately 1.5 and 3 years (variation owing to enrollment date). These groups are referred to herein as laser/very deferred ranibizumab and triamcinolone + laser/very deferred ranibizumab. Eyes with a letter score <78 (Snellen equivalent 20/32 or worse) and a central subfield thickness ≥250 μm (using Stratus or Stratus OCT-equivalent values) were considered for treatment with ranibizumab; however, initiating ranibizumab was at the investigator's discretion. Once ranibizumab was initiated, investigators were required to follow the ranibizumab treatment algorithm.

• **STATISTICAL ANALYSIS:** For all outcome analyses, the ranibizumab + deferred laser group was compared with the other 3 treatment groups. A longitudinal discrete time mixed-model analysis incorporating discrete generalized estimating equations to account for correlated data from participants with 2 study eyes was used to compare visual acuity and OCT central subfield thickness change from baseline through the 5-year visit among treatment groups. All analyses were adjusted for the baseline value of the outcome and number of study eyes. Visual acuity changes were truncated to ±30 letters to minimize the effects of outliers. Generalized linear regression models were used to analyze binary variables. The Bonferroni method was used to adjust confidence intervals for the 3 pairwise treatment comparisons; *P* values less than .0167 were considered statistically significant. SAS 9.4 (SAS, Cary, North Carolina, USA) was used for all analyses.

Safety data include all randomized participants, irrespective of extension study participation and eligibility. All other analyses excluded 26 study eyes of 18 participants from 1 clinical site in which a majority of eyes at baseline were judged not to meet the OCT eligibility criterion of central subfield thickness ≥250 μm when graded manually at a central reading center. Systemic adverse events and death among participants with 2 study eyes (1 eye in the laser group and the other eye in either of the original ranibizumab groups or the triamcinolone + laser group) were assigned to the appropriate drug exposure group. Data for all events that occurred among participants contributing a single study eye were analyzed according to the original treatment assignment, recognizing that very deferred ranibizumab was administered to many participants in the laser and the triamcinolone + laser groups by the 5-year visit.

RESULTS

OF THE ORIGINAL 673 PARTICIPANTS, 520 (77%) PROVIDED consent to extend follow-up from 3 to 5 years (646 of 828 study eyes; 78%). Excluding deaths, the 5-year study visit was completed by 77% of the entire cohort and 94% of study eyes of participants agreeing to the extension study. Completion rates appeared balanced by treatment group (Supplemental Table 1, available at AJO.com). Systemic and ocular baseline characteristics for extension study participants were similar among the 4 treatment groups (data not shown), and a comparison of those who completed the 5-year visit to those who did not is reported in Table 1.

• **STUDY TREATMENT DURING FOLLOW-UP:** At 5 years, the median number of ranibizumab injections for the ranibizumab + deferred laser group was 17. During years 4 and 5, the median number of injections was 1 and 0, with 55% and 48% of eyes, respectively, in the ranibizumab + deferred laser group, receiving at least 1 additional ranibizumab injection. The median number of injections administered to these eyes was 4 and 3 injections during years 4 and 5, respectively. Table 2 shows similar ranibizumab administration in the ranibizumab + prompt laser eyes.

Very deferred ranibizumab was initiated in 130 eyes (57%) and 89 eyes (62%) originally assigned to laser and triamcinolone + laser, respectively, of participants who consented to the extension phase. Nearly half of the eyes managed with very deferred ranibizumab received the initial dose between the 2- and 3-year visit (Supplemental Table 2, available at AJO.com). At 5 years, among eyes receiving ranibizumab, the median number of ranibizumab injections was 8 and 9 in the laser and triamcinolone + laser groups, respectively (Table 2). Table 2 shows the infrequent administration of intravitreous triamcinolone to the triamcinolone + laser group beyond the 3-year visit. No substantive differences in

TABLE 1. Baseline Characteristics Comparing Participants Who Completed the 5-Year Extension Study Visit[a] to Those Who Did Not From a Randomized Trial Comparing Ranibizumab With Prompt or Deferred Laser, Laser With Deferred Ranibizumab, and Triamcinolone Plus Deferred Ranibizumab in Eyes With Vision Impairment From Center-Involved Diabetic Macular Edema

		Did Not Complete 5-Year Extension Study Visit	
	Completed 5-Year Extension Study Visit	Consented to Be in Extension Study[b]	Did Not Consent to Be in Extension Study[c]
	N = 558 Eyes (450 Participants)	N = 88 Eyes (70 Participants)	N = 182 Eyes (153 Participants)
Baseline Characteristics			
Sex: women, n (%)	247 (44%)	34 (39%)	75 (41%)
Age (y), median (25^{th}, 75^{th} percentile)	63 (57, 69)	63 (56, 70)	65 (56, 72)
Race, n (%)			
White	409 (73%)	68 (77%)	123 (68%)
Black	86 (15%)	13 (15%)	39 (21%)
Hispanic	49 (9%)	6 (7%)	15 (8%)
Asian	8 (1%)	1 (1%)	2 (1%)
Native Hawaiian/other Pacific Islander	1 (<1%)	0	0
Multiracial	1 (<1%)	0	2 (1%)
Unknown/not reported	4 (<1%)	0	1 (<1%)
Diabetes type, n (%)			
Type 1	39 (7%)	9 (10%)	17 (9%)
Type 2	509 (91%)	78 (89%)	156 (86%)
Uncertain	10 (2%)	1 (1%)	9 (5%)
Duration of diabetes (y), median (25^{th}, 75^{th} percentile)	17 (10, 23)	15 (12, 25)	17 (10, 24)
Insulin used, n (%)	323 (58%)	54 (61%)	122 (67%)
HbA1c[d] (%), median (25^{th}, 75^{th} percentile)	7.3 (6.5, 8.2)	7.0 (6.2, 8.3)	7.7 (6.8, 8.8)
Prior cardiovascular event,[e] n (%)	156 (28%)	42 (48%)	78 (43%)
Hypertension,[e] n (%)	449 (80%)	79 (90%)	151 (83%)
Number of study eyes, n (%)			
1 study eye	342 (61%)	52 (59%)	124 (68%)
2 study eyes	216 (39%)	36 (41%)	58 (32%)
Prior PRP, n (%)	136 (24%)	21 (24%)	31 (17%)
Prior treatment for DME, n (%)	371 (66%)	52 (59%)	119 (65%)
Prior photocoagulation for DME, n (%)	340 (61%)	45 (51%)	107 (59%)
Prior IVT for DME, n (%)	81 (15%)	21 (24%)	25 (14%)
Prior vitrectomy for DME, n (%)	23 (4%)	5 (6%)	11 (6%)
Prior peribulbar triamcinolone for DME, n (%)	24 (4%)	2 (2%)	5 (3%)
Prior anti-VEGF for DME, n (%)	58 (10%)	13 (15%)	18 (10%)
IOP (mm Hg), median (25^{th}, 75^{th} percentile)	16 (14, 18)	16 (14, 18)	16 (14, 18)
Lens status phakic (clinical examination), n (%)	393 (70%)	45 (51%)	117 (64%)
E-ETDRS visual acuity (letter score), median (25^{th}, 75^{th} percentile)	66 (57, 73)	67 (56, 73)	62 (53, 71)
Central subfield thickness on OCT[f] (μm), median (25^{th}, 75^{th} percentile)	395 (321, 498)	376 (311, 491)	373 (298, 471)
Retinal volume on OCT[f] (mm^3), median (25^{th}, 75^{th} percentile)	8.5 (7.7, 9.9)	8.5 (7.7, 9.2)	8.5 (7.6, 9.7)
Retinopathy severity level on fundus photograph (ETDRS severity scale),[f] n (%)			
No DR/minimal NPDR (10, 12, 14, 15, 20)	9 (2%)	2 (2%)	0
Mild/moderate NPDR (35, 43)	123 (23%)	21 (24%)	32 (18%)
Moderately severe/severe NPDR (47, 53)	240 (45%)	30 (35%)	81 (47%)
Mild-/moderate-/high-risk PDR (60, 61, 65, 71)	160 (30%)	33 (38%)	61 (35%)
Characteristics at last completed visit			
Timing of last completed visit, wk, median (25th, 75th percentile)	257 (254, 262)	188 (155, 215)	88 (51, 154)

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TABLE 1. Baseline Characteristics Comparing Participants Who Completed the 5-Year Extension Study Visit[a] to Those Who Did Not From a Randomized Trial Comparing Ranibizumab With Prompt or Deferred Laser, Laser With Deferred Ranibizumab, and Triamcinolone Plus Deferred Ranibizumab in Eyes With Vision Impairment From Center-Involved Diabetic Macular Edema (*Continued*)

		Did Not Complete 5-Year Extension Study Visit	
	Completed 5-Year Extension Study Visit	Consented to Be in Extension Study[b]	Did Not Consent to Be in Extension Study[c]
	N = 558 Eyes (450 Participants)	N = 88 Eyes (70 Participants)	N = 182 Eyes (153 Participants)
E-ETDRS visual acuity (letter score), median (25^{th}, 75^{th} percentile)	75 (63, 82)	74 (63, 81)	67 (53, 76)
Central subfield thickness on OCT (μm), median (25^{th}, 75^{th} percentile)[g]	254 (209, 308)	238 (195, 287)	239 (195, 298)

DME = diabetic macular edema; DR = diabetic retinopathy; E-ETDRS = Electronic Early Treatment Diabetic Retinopathy Study; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = hemoglobin A1c; IOP = intraocular pressure; IVT = intravitreal triamcinolone; MA = microaneurysms; NPDR = nonproliferative diabetic retinopathy; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; PRP = panretinal scatter photocoagulation; VEGF = vascular endothelial growth factor.

The table reports baseline characteristics stratified by whether the participant completed or did not complete the 5-year visit of participants in a randomized trial of ranibizumab with prompt or deferred laser vs laser or triamcinolone plus deferred ranibizumab for diabetic macular edema.

[a]Visits occurring between window 244 and 276 weeks from randomization were included as 5-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 5-year target date were used.

[b]Includes the following between enrollment in the extension and the 5-year visit: deaths (50), withdrawals from the study (21), loss to follow-up (15), unknown (2).

[c]Includes those who discontinued from the study prior to the opportunity to re-consent.

[d]Missing HbA1c data for 16, 1, and 16 eyes, respectively.

[e]Medical history of condition.

[f]Missing (or ungradable) OCT and fundus photograph data as follows for the completer and noncompleters (with and without extension study), respectively: central subfield (0, 0, 1), retinal volume (118, 22, 48), and retinopathy severity (26, 2, 8).

[g]Missing (or ungradable) OCT data as follows for the completer and noncompleters (with and without extension study), respectively: 18, 10, 17.

baseline characteristics were apparent between eyes that received ranibizumab and those that did not in the very deferred ranibizumab groups (Supplemental Table 3, available at AJO.com).

Focal/grid laser photocoagulation was primarily performed in the first 3 years in all 4 treatment groups; 15%, or fewer eyes, in each group received laser between the 3- and 5-year visit. In the ranibizumab + deferred laser group, in which laser was not required, 56% never received laser during this 5-year study; for all other treatment groups, the 5-year median total number of laser sessions ranged from 3 to 4 (Table 2).

• **VISUAL ACUITY:** Figure 1 shows the mean visual acuity change from baseline over time by original treatment group assignment. The differences between the vision gains observed in the ranibizumab + deferred laser vs the very deferred ranibizumab groups progressively narrowed between years 2 and 5. The mean changes in visual acuity letter scores from baseline to the 5-year visit were +10 for ranibizumab + deferred laser, +8 for ranibizumab + prompt laser, +5 for laser, and +7 for triamcinolone + laser (Table 3). After adjustment for baseline visual acuity and number of eyes, the difference in mean change (95% confidence interval [CI]) in visual acuity letter score at the 5-year visit between the ranibizumab + deferred laser group and the laser/very deferred ranibizumab or triamcinolone + laser/very deferred ranibizumab was 4.4 (1.2–7.6, $P = .001$) and 2.8 (−0.9 to 6.5, $P = .067$), respectively. At 5 years, the laser/very deferred ranibizumab eyes had a lower percentage of eyes with ≥10 letter improvement from baseline in visual acuity relative to the ranibizumab + deferred laser group (relative risk [RR] 0.71, 95% CI 0.55–0.91) (Table 3 and Supplemental Figure, available at AJO.com). An area under the curve analysis was also conducted since the eyes managed with very deferred ranibizumab achieved their larger vision gains later in the follow-up period relative to eyes managed with ranibizumab from study entry; this methodology evaluates vision gains that are averaged over time and showed superior outcomes with ranibizumab + deferred laser (Table 3).

RETINAL THICKNESS

AT 5 YEARS THE LASER/VERY DEFERRED RANIBIZUMAB group had the thinnest OCT measurements (central subfield thickness and macular volume) and largest absolute decrease in central subfield thickness from baseline. The

TABLE 2. Intravitreous Injections and Laser Sessions At and Beyond the 3-Year Study Visit From a Randomized Trial Comparing Ranibizumab With Prompt or Deferred Laser, Laser With Deferred Ranibizumab, and Triamcinolone Plus Deferred Ranibizumab in Eyes With Vision Impairment From Center-Involved Diabetic Macular Edema

	Laser/Very Deferred Ranibizumab	Ranibizumab + Prompt Laser	Ranibizumab + Deferred Laser	Triamcinolone + Laser/Very Deferred Ranibizumab
Injections				
156-week visit[a]	N = 233	N = 144	N = 147	N = 150
Treated with ranibizumab from baseline to 156-week visit, n (%)	93 (40%)	144 (100%)	147 (100%)	55 (37%)
Ranibizumab injections from baseline to 156-week visit in those eyes, median (IQR)	5 (3, 7)	12 (8, 17)	15 (9, 22)	6 (3, 8)
Treated with triamcinolone from baseline to 156-week visit, n (%)	–	–	–	150 (100%)
Triamcinolone injections from baseline to 156-week visit in those eyes, median (IQR)				4 (3, 6)
Treated with ranibizumab from 104- to 156-week visit, n (%)	89 (38%)	82 (57%)	99 (67%)	51 (34%)
Ranibizumab injections from 104- to 156-week visit in those eyes, median (IQR)	4 (2, 6)	3 (2, 5)	4 (2, 6)	5 (3, 7)
Treated with triamcinolone from 104- to 156-week visit, n (%)	–	–	–	44 (29%)
Triamcinolone injections from 104- to 156-week visit in those eyes, median (IQR)				1 (1, 3)
208-week visit[b]	N = 205	N = 127	N = 122	N = 131
Treated with ranibizumab from baseline to 208-week visit, n (%)	112 (55%)	127 (100%)	122 (100%)	76 (58%)
Ranibizumab injections from baseline to 208-week visit in those eyes, median (IQR)	7 (5, 12)	12 (9, 20)	17 (10, 25)	8 (5, 12)
Treated with triamcinolone from baseline to 208-week visit, n (%)	–	–	–	131 (100%)
Triamcinolone injections from baseline to 208-week visit in those eyes, median (IQR)				4 (3, 6)
Treated with ranibizumab from 156- to 208-week visit, n (%)	85 (41%)	58 (46%)	67 (55%)	68 (52%)
Ranibizumab injections from 156- to 208-week visit in those eyes, median (IQR)	5 (3, 8)	3 (1, 5)	4 (2, 6)	5 (3, 8)
Treated with triamcinolone from 156- to 208-week visit, n (%)	–	–	–	13 (10%)
Triamcinolone injections from 156 to 208 week visit in those eyes - median (IQR)				1 (1, 2)
260-week visit[c]	N = 198	N = 124	N = 111	N = 125
Treated with ranibizumab from baseline to 260-week visit, n (%)	114 (58%)	124 (100%)	111 (100%)	77 (62%)
Ranibizumab injections from baseline to 260-week visit in those eyes, median (IQR)	8 (5, 15)	13 (9, 24)	17 (11, 27)	9 (6, 16)
Treated with triamcinolone from baseline to 260-week visit, n (%)	–	–	–	125 (100%)
Triamcinolone injections from baseline to 260-week visit in those eyes, median (IQR)				4 (3, 6)
Treated with ranibizumab from 208- to 260-week visit, n (%)	70 (35%)	47 (38%)	53 (48%)	57 (46%)
Ranibizumab injections from 208- to 260-week visit in those eyes, median (IQR)	3 (2, 6)	4 (2, 5)	3 (2, 5)	4 (2, 7)
Treated with triamcinolone from 208- to 260-week visit, n (%)	–	–	–	5 (4%)
Triamcinolone injections from 208- to 260-week visit in those eyes, median (IQR)				2 (1, 3)
Laser				
156-week visit[a]	N = 233	N = 144	N = 147	N = 150
Number of focal/grid laser treatments from baseline to 156-week visit				
Median (25^{th}, 75^{th} percentiles)	4 (2, 5)	3 (2, 4)	0 (0, 2)	3 (2, 5)
Did not receive laser, n (%)	1 (<1%)	0	79 (54%)	0
208-week visit[b]	N = 205	N = 127	N = 122	N = 131
Number of focal/grid laser treatments from baseline to 208-week visit				
Median (25^{th}, 75^{th} percentiles)	4 (2, 6)	3 (2, 5)	0 (0, 2)	3 (2, 6)
Did not receive laser, n (%)	0	0	68 (56%)	0

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TABLE 2. Intravitreous Injections and Laser Sessions At and Beyond the 3-Year Study Visit From a Randomized Trial Comparing Ranibizumab With Prompt or Deferred Laser, Laser With Deferred Ranibizumab, and Triamcinolone Plus Deferred Ranibizumab in Eyes With Vision Impairment From Center-Involved Diabetic Macular Edema (*Continued*)

	Laser/Very Deferred Ranibizumab	Ranibizumab + Prompt Laser	Ranibizumab + Deferred Laser	Triamcinolone + Laser/Very Deferred Ranibizumab
Eyes without focal/grid laser treatments from 156- to 208-week visit, n (%)	181 (88%)	111 (87%)	111 (91%)	111 (85%)
260-week visit[c]	N = 198	N = 124	N = 111	N = 125
Number of focal/grid laser treatments from baseline to 260-week visit				
Median (25th, 75th percentiles)	4 (2, 6)	3 (2, 5)	0 (0, 2)	3 (2, 6)
Did not receive laser, n (%)	0	0	62 (56%)	0
Eyes without focal/grid laser treatments from 208- to 260-week visit, n (%)	177 (89%)	112 (90%)	108 (97%)	109 (87%)

The table reports the number of injections and laser sessions during the course of the study from a randomized trial of ranibizumab with prompt or deferred laser vs laser or triamcinolone plus deferred ranibizumab for diabetic macular edema.

[a]Limited to study participants that completed the 156-week visit; includes participants who did and did not provide consent for the extension study.

[b]Limited to study participants that completed the 208-week visit.

[c]Limited to study participants that completed the 260-week visit.

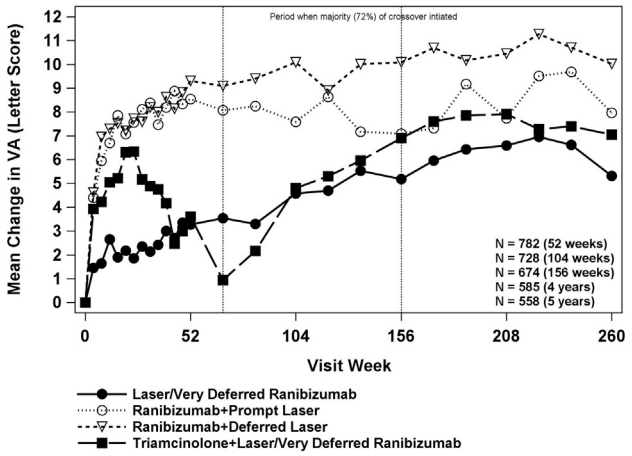

FIGURE 1. Mean change in visual acuity letter score over 5 years from a randomized trial comparing ranibizumab with prompt or deferred laser, laser with deferred ranibizumab, and triamcinolone plus deferred ranibizumab in eyes with vision impairment from center-involved diabetic macular edema.

average difference in central subfield thickness change favored laser/very deferred ranibizumab by 32 μm relative to the ranibizumab + deferred laser group (95%CI: 2–61, $P = .009$). None of the other between-group differences were statistically significant at 5 years (Figure 2, Table 4). At the 5-year visit, approximately two-thirds of all eyes, irrespective of treatment assignment, had central subfield thickness less than the study entry criterion (250 μm on Stratus or equivalent spectral-domain OCT) and few eyes (≤6%) had 1 logOCT step (approximately 20%) worsening from baseline.

• **VISUAL ACUITY AND RETINAL THICKNESS IN PSEUDOPHAKIC EYES AT BASELINE:** Within the subset of eyes that were pseudophakic at baseline, the visual acuity changes through 5 years in the triamcinolone + laser/very deferred ranibizumab group differed for several years from that of the full triamcinolone cohort, but by 5 years the trend suggested they behaved more similarly to the full triamcinolone cohort (Figure 3, Left). Within pseudophakic eyes, the mean change (95% CI) in visual acuity at 5 years was +6 [+3, +9] in the laser/very deferred ranibizumab group (n = 67), +10 [+6, +14] in the ranibizumab + prompt laser group (n = 34), +10 [+4, +16] in the ranibizumab + deferred laser group (n = 28), and +6 [+1, +11] in the triamcinolone + laser/very deferred ranibizumab group (n = 36). Mean reductions in thickness through the 5-year visit in pseudophakic eyes were similar to the full cohort within each treatment arm (Figure 3, Right).

• **SHORT-TERM EFFECT OF VERY DEFERRED RANIBIZUMAB:** Short-term effects of very deferred ranibizumab injections for DME were evaluated by analyzing eyes in the laser/very deferred ranibizumab and triamcinolone + laser/very deferred ranibizumab groups for whom ranibizumab was initiated and who had at least 24 weeks of follow-up after ranibizumab initiation (n = 118 and 81, respectively). Following ranibizumab initiation, the median (25th, 75th percentile) number of ranibizumab injections delivered to this cohort during the 24-week period following ranibizumab initiation

TABLE 3. Visual Acuity at the 4- and 5-Year Visit From a Randomized Trial Comparing Ranibizumab With Prompt or Deferred Laser, Laser With Deferred Ranibizumab, and Triamcinolone Plus Deferred Ranibizumab in Eyes With Vision Impairment From Center-Involved Diabetic Macular Edema

	Laser/Very Deferred Ranibizumab	Ranibizumab + Prompt Laser	Ranibizumab + Deferred Laser	Triamcinolone + Laser/Very Deferred Ranibizumab
4-year visit[a]	N = 205	N = 127	N = 122	N = 131
Visual acuity - letter score				
Median (25^{th}, 75^{th})	74 (64, 80)	76 (63, 82)	76 (71, 83)	74 (63, 82)
Mean ± standard deviation	70 ± 15	71 ± 18	74 ± 13	71 ± 13
≥20/40, n (%)	142 (69%)	89 (70%)	98 (80%)	89 (68%)
≤20/200, n (%)	7 (3%)	8 (6%)	3 (2%)	3 (2%)
Change from baseline				
Median (25^{th}, 75^{th})	+8 (0, +15)	+9 (+1, +17)	+11 (+5, +19)	+10 (+1, +15)
Mean ± standard deviation	+7 ± 13	+8 ± 13	+10 ± 13	+8 ± 12
Difference in mean change from ranibizumab + deferred laser[b]	3.6	2.8		2.9
(95% CI)[b,c]	(0.8 to 6.4)	(−0.7 to 6.3)		(−0.5 to 6.2)
[*P* value][b]	[.002]	[.055]		[.040]
Distribution of visual acuity change, n (%)				
≥15 letter improvement	55 (27%)	41 (32%)	45 (37%)	38 (29%)
14–10 letter improvement	36 (18%)	20 (16%)	23 (19%)	31 (24%)
9–5 letter improvement	42 (20%)	23 (18%)	24 (20%)	19 (15%)
Same ± 4 letters	41 (20%)	27 (21%)	19 (16%)	27 (21%)
5–9 letters worse	9 (4%)	4 (3%)	4 (3%)	5 (4%)
10–14 letters worse	6 (3%)	5 (4%)	2 (2%)	4 (3%)
≥15 letters worse	16 (8%)	7 (6%)	5 (4%)	7 (5%)
Difference in proportion with ≥10 letter improvement, vs ranibizumab +deferred laser (95% CI)[c]	12% (−1% to 25%)	7% (−8% to 22%)		4% (−11% to 19%)
Relative risk (95% CI)[c]	0.80 (0.63–1.02)	0.86 (0.64–1.14)	1.00	0.94 (0.73–1.20)
5-year visit[d]	N = 198	N = 124	N = 111	N = 125
Visual acuity - letter score				
Median (25^{th}, 75^{th})	73 (61, 80)	76 (65, 82)	77 (68, 82)	74 (62, 82)
Mean ± standard deviation	68 ± 18	71 ± 18	74 ± 14	70 ± 17
≥20/40, n (%)	119 (60%)	85 (69%)	83 (75%)	84 (67%)
≤20/200, n (%)	10 (5%)	7 (6%)	2 (2%)	7 (6%)
Change from baseline				
Median (25^{th}, 75^{th})	+7 (−1, +14)	+9 (+3, +16)	+12 (+4, +19)	+9 (−1, +16)
Mean ± standard deviation	+5 ± 14	+8 ± 13	+10 ± 13	+7 ± 14
Difference in mean change from ranibizumab + deferred laser[b]	4.4	2.0		2.8
(95% CI)[b,c]	(1.2 to 7.6)	(−1.6 to 5.7)		(−0.9 to 6.5)
[*P* value][b]	.001	.186		.067
Average visual acuity change over 5 years, using AUC method, median (25^{th}, 75^{th})	+6 (−1, +11)	+9 (+4, +14)	+10 (+5, +15)	+6 (0, +11)
Difference in mean AUC vs ranbizumab + deferred laser	+4.9	+1.7		+4.1
[*P* value]	<.001	.13		<.001
Distribution of visual acuity change				
≥15 letter improvement	48 (24%)	34 (27%)	42 (38%)	41 (33%)
14–10 letter improvement	32 (16%)	24 (19%)	22 (20%)	21 (17%)
9–5 letter improvement	40 (20%)	24 (19%)	18 (16%)	17 (14%)
Same ± 4 letters	40 (20%)	28 (23%)	13 (12%)	26 (21%)
5–9 letters worse	14 (7%)	3 (2%)	7 (6%)	4 (3%)
10–14 letters worse	4 (2%)	4 (3%)	3 (3%)	5 (4%)
≥ 15 letters worse	20 (10%)	7 (6%)	6 (5%)	11 (9%)

Continued on next page

TABLE 3. Visual Acuity at the 4- and 5-Year Visit From a Randomized Trial Comparing Ranibizumab With Prompt or Deferred Laser, Laser With Deferred Ranibizumab, and Triamcinolone Plus Deferred Ranibizumab in Eyes With Vision Impairment From Center-Involved Diabetic Macular Edema (*Continued*)

	Laser/Very Deferred Ranibizumab	Ranibizumab + Prompt Laser	Ranibizumab + Deferred Laser	Triamcinolone + Laser/Very Deferred Ranibizumab
Difference in proportion with ≥10 letter improvement, vs ranbizumab + deferred laser (95% CI)[c]	17% (3%–30%)	11% (−5% to 26%)		8% (−7% to 24%)
Relative risk (95% CI)[c]	0.71 (0.55–0.91)	0.79 (0.60–1.05)	1.00	0.85 (0.65–1.11)

AUC = area under the curve.

The table reports visual acuity outcomes at the 4- and 5-year visit from participants in a randomized trial of ranibizumab with prompt or deferred laser vs laser or triamcinolone plus deferred ranibizumab for diabetic macular edema.

Change in visual acuity truncated to ±30 letters.

[a]Visits occurring between 192 and 224 weeks (1344 and 1568 days) from randomization were included as 4-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 4-year target date were used. All analyses were limited to eyes completing the 4-year visit, with the exception of the longitudinal model in which all available visits (excluding 1-week safety visits) from all study eyes were included.

[b]From longitudinal model adjusting for baseline visual acuity and correlation between 2 study eyes.

[c]95% CI adjusted for multiple comparisons.

[d]Visits occurring between 244 and 276 weeks (1708 and 1932 days) from randomization were included as 5-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 5-year target date were used. All analyses were limited to eyes completing the 4-year visit, with the exception of the longitudinal model in which all available visits (excluding 1-week safety visits) from all study eyes were included.

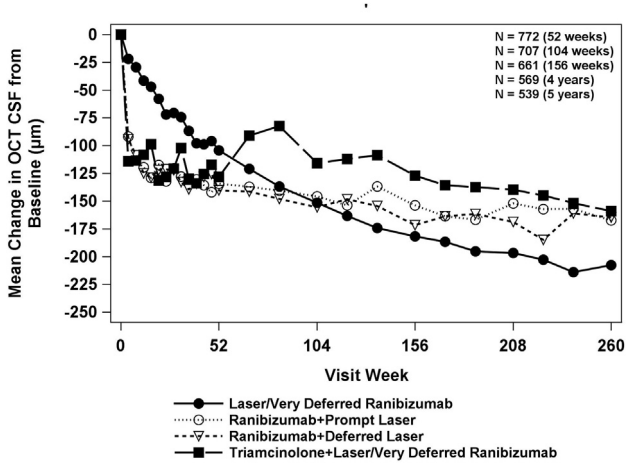

FIGURE 2. Mean change in optical coherence tomography central subfield thickness over 5 years from a randomized trial comparing ranibizumab with prompt or deferred laser, laser with deferred ranibizumab, and triamcinolone plus deferred ranibizumab in eyes with vision impairment from center-involved diabetic macular edema.

was 5 (4, 5) in both groups (Supplemental Table 4). Only about one-third of the eyes in each group received any laser during this 24-week follow-up interval, most of which only had 1 additional laser session.

At the time ranibizumab was initiated, the average visual acuity letter score was 63 in the laser/very deferred ranibizumab group and 67 in the triamcinolone + laser/very deferred ranibizumab group (Snellen equivalent ~20/50). Twenty-four weeks following ranibizumab initiation, there was a mean (95% CI) visual acuity improvement of 3 (2–5) letters and 4 (2–6) letters in the 2 groups, respectively (Figure 4 and Supplemental Table 4, available at AJO.com). The average central subfield thickness at the time of the initial ranibizumab injection was 357 µm in the laser/very deferred ranibizumab group and 361 µm in the triamcinolone + laser/very deferred ranibizumab group. A substantial reduction in central subfield thickness (~60 µm) occurred with the first injection in each group. From week 8 through the remainder of the 24-week follow-up period there was no further notable change in macular thickness; at 24 weeks following ranibizumab initiation central subfield thickness was 57 µm and 78 µm thinner relative to the day of the ranibizumab crossover, respectively. Changes in macular volume paralleled those of central subfield thickness (Supplemental Table 4).

• **SAFETY:** Major systemic safety events through five years are summarized in Supplemental Table 5. Major ocular adverse events, with the exception of those related to elevation in intraocular pressure, were infrequent and similar between groups, including 4 cases of study injection

TABLE 4. Optical Coherence Tomography Retinal Thickness at the 4- and 5-Year Visit From a Randomized Trial Comparing Ranibizumab With Prompt or Deferred Laser, Laser With Deferred Ranibizumab, and Triamcinolone Plus Deferred Ranibizumab in Eyes With Vision Impairment From Center-Involved Diabetic Macular Edema

	Sham + Prompt Laser/Very Deferred Ranibizumab	Ranibizumab + Prompt Laser	Ranibizumab + Deferred Laser	Triamcinolone + Prompt Laser/ Very Deferred Ranibizumab
4-year visit[a]	N = 205	N = 127	N = 122	N = 131
Central subfield thickness, μm				
Median (25th, 75th percentile)	220 (182, 266)	228 (190, 275)	225 (193, 276)	220 (189, 293)
Mean ± standard deviation	239 ± 88	252 ± 110	249 ± 89	257 ± 102
Change in CSF from baseline, μm				
Median (25th, 75th percentile)	−182 (−292, −90)	−144 (−228, −51)	−155 (−236, −59)	−140 (−236, −41)
Mean ± standard deviation	−197 ± 153	−152 ± 173	−169 ± 159	−140 ± 161
Difference in mean change from ranibizumab + deferred laser	21	−1		8
(95% CI)[b,c]	(−5 to 46)	(−32 to 29)		(−38 to 22)
[*P* value][c]	.051	.91		.51
CSF <250 μm on Stratus or spectral-domain equivalent, n (%)	134 (66%)	80 (63%)	76 (64%)	74 (60%)
CSF <150 μm on Stratus or spectral-domain equivalent, n (%)	10 (5%)	8 (6%)	4 (3%)	6 (5%)
≥1 step improvement in logOCT, n (%)	162 (80%)	90 (71%)	88 (75%)	87 (71%)
≥1 step worsening in logOCT, n (%)	4 (2%)	5 (4%)	6 (5%)	12 (10%)
Retinal volume - mm^3				
Median (25th, 75th percentile)	6.9 (6.5, 7.6)	6.8 (6.3, 7.5)	6.9 (6.5, 7.7)	7.1 (6.5, 7.9)
Mean ± standard deviation	7.1 ± 1.0	7.1 ± 1.3	7.1 ± 0.9	7.3 ± 1.2
Change in retinal volume from baseline, mm^3				
Median (25th, 75th percentile)	−1.6 (−2.7, −0.9)	−1.2 (−2.4, −0.7)	−1.5 (−2.8, −0.6)	−1.3 (−2.4, −0.6)
Mean ± standard deviation	−2.1 ± 1.8	−1.6 ± 1.8	−1.9 ± 1.9	−1.6 ± 1.8
5-year visit[d]	N = 198	N = 124	N = 111	N = 125
Central subfield thickness, μm				
Median (25th, 75th percentile)	210 (175, 263)	217 (182, 262)	227 (193, 290)	217 (177, 280)
Mean ± standard deviation	233 ± 98	239 ± 90	256 ± 110	245 ± 99
Change in CSF from baseline, μm				
Median (25th, 75th percentile)	−196 (−307, −99)	−152 (−256, −65)	−160 (−245, −54)	−140 (−236, −78)
Mean ± standard deviation	−208 ± 164	−167 ± 168	−165 ± 165	−159 ± 154
Difference in mean change from ranibizumab + deferred laser	32	17		7
(95% CI)[b,c]	(2 to 61)	(−15 to 48)		(−25 to 39)
[*P* value][c]	.009	.20		.61
CSF <250 μm on Stratus or spectral-domain equivalent, n (%)	130 (68%)	77 (65%)	71 (65%)	80 (66%)
CSF <150 μm on Stratus or spectral-domain equivalent, n (%)	21 (11%)	9 (8%)	8 (7%)	8 (7%)
≥1 step improvement in logOCT, n (%)	159 (84%)	91 (77%)	81 (74%)	94 (78%)
≥1 step worsening in logOCT, n (%)	4 (2%)	4 (3%)	4 (4%)	7 (6%)
Retinal volume, mm^3				
Median (25th, 75th percentile)	6.8 (6.4, 7.5)	6.9 (6.4, 7.4)	6.9 (6.5, 7.6)	6.9 (6.5, 7.5)
Mean ± standard deviation	7.0 ± 1.0	7.0 ± 1.0	7.2 ± 1.4	7.1 ± 1.0

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related endophthalmitis among a total of 8051 ranibizumab injections (0.05%) (Supplemental Table 5, available at AJO.com). Cataract and intraocular pressure adverse events were more likely to occur in the triamcinolone + prompt laser/very deferred ranibizumab group ($P < .001$ from global Fisher exact tests).

DISCUSSION

THIS STUDY DEMONSTRATED THAT VISUAL ACUITY AND retinal thickness improvements obtained with ranibizumab treatment in conjunction with immediate or deferred laser are sustained over time. Initial results of this study, showing

TABLE 4. Optical Coherence Tomography Retinal Thickness at the 4- and 5-Year Visit From a Randomized Trial Comparing Ranibizumab With Prompt or Deferred Laser, Laser With Deferred Ranibizumab, and Triamcinolone Plus Deferred Ranibizumab in Eyes With Vision Impairment From Center-Involved Diabetic Macular Edema (*Continued*)

	Sham + Prompt Laser/Very Deferred Ranibizumab	Ranibizumab + Prompt Laser	Ranibizumab + Deferred Laser	Triamcinolone + Prompt Laser/ Very Deferred Ranibizumab
Change in retinal volume from baseline, mm^3				
Median (25th, 75th percentile)	−1.6 (−2.8, −0.9)	−1.7 (−2.5, −0.7)	−1.8 (−2.8, −0.6)	−1.6 (−2.6, −0.6)
Mean ± standard deviation	−2.1 ± 1.9	−1.7 ± 1.3	−1.9 ± 2.1	−1.8 ± 1.6

CSF = central subfield; OCT = optical coherence tomography.

The table reports central subfield thickness outcomes at the 4- and 5-year visit from participants in a randomized trial of ranibizumab with prompt or deferred laser vs laser or triamcinolone plus deferred ranibizumab for diabetic macular edema.

Assessments from spectral-domain OCTs were converted to Stratus equivalent values.

Missing or ungradable as follows for the sham + prompt laser/very deferred ranibizumab group, ranibizumab + prompt laser group, ranibizumab + deferred laser group, and triamcinolone + prompt laser/very deferred ranibizumab group, respectively: central subfield (3, 1, 4, 8), retinal volume (36, 24, 23, 28), and change in retinal volume (69, 50, 38, 53) at 4-year visit; central subfield (8, 6, 1, 4), retinal volume (57, 40, 24, 37), and change in retinal volume (80, 59, 37, 58) at 5-year visit.

[a]Visits occurring between 192 and 224 weeks from randomization were included as 4-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 4-year target date were used. All analyses were limited to eyes completing the 4-year visit, with the exception of the longitudinal model, in which all available visits (excluding 1-week safety visits) from all study eyes were included.

[b]95% CI adjusted for multiple comparisons.

[c]From longitudinal model adjusting for baseline visual acuity and correlation between 2 study eyes.

[d]Visits occurring between 244 and 276 weeks (1708 and 1932 days) from randomization were included as 5-year visits. When more than 1 visit occurred in this window, data from the visit closest to the 5-year target date were used. All analyses were limited to eyes completing the 4-year visit, with the exception of the longitudinal model in which all available visits (excluding 1-week safety visits) from all study eyes were included.

that ranibizumab with immediate or deferred laser was superior to laser alone or triamcinolone plus laser, led to consideration of ranibizumab initiation among eyes originally managed with laser or triamcinolone plus laser. Subsequently, approximately 60% of the eyes originally assigned to laser or triamcinolone + laser were treated with ranibizumab. On average, the treatment groups originally managed with laser and triamcinolone + laser had a gradual improvement in visual acuity after having the opportunity to receive ranibizumab. Despite this approach, at the 5-year visit, these 2 groups, whether phakic or pseudophakic at study entry, did not realize the same improvement in visual acuity as those initially treated with ranibizumab. The difference in visual acuity outcome between ranibizumab + deferred laser vs laser/very deferred ranibizumab or vs triamcinolone + laser/very deferred ranibizumab was observed throughout the 5-year follow-up period even though each strategy substantially reduced macular thickness.

Eyes in the very deferred ranibizumab subgroups that received ranibizumab and had at least 24 weeks of follow-up after initiating ranibizumab had a decrease in central subfield thickness despite the long-standing nature of the DME. This likely represents a ranibizumab effect, as a minority received additional laser or triamcinolone during this period, although a delayed beneficial effect of prior laser treatment cannot be ruled out, nor can the possibility that this is the natural history of the disease. Simultaneous vision improvement was also observed, although the rate of improvement was slower than the rapid improvement seen during the first 6-month treatment period for the eyes originally assigned to ranibizumab at the start of the study. This could stem from permanent function changes from chronic DME or could indicate that the protocol design isolated a subgroup of eyes that are more resistant to any form of treatment.

The outcomes associated with very deferred ranibizumab in this study are consistent with those observed in the RIDE and RISE trials, whereupon eyes managed with a median of 11 ranibizumab injections after a deferral period of 24 months experienced significant improvements in retinal thickness, yet the vision improvement at 36 months fell short relative to eyes initially managed with ranibizumab.[4] In contrast, in the RESTORE study, eyes initially assigned to ranibizumab and those that received ranibizumab following a 12-month deferral period had similar vision outcomes at 36 months.[5] However, RESTORE did not require re-treatment with ranibizumab once vision stabilized and the magnitude of vision improvement in all groups was more modest than that seen in the RIDE, the RISE, or this DRCR.net trial. All 4 studies provide strong evidence of a significant anatomic effect when administering ranibizumab even in a delayed timeline. However, the chronicity of the DME- and/or laser treatment–related

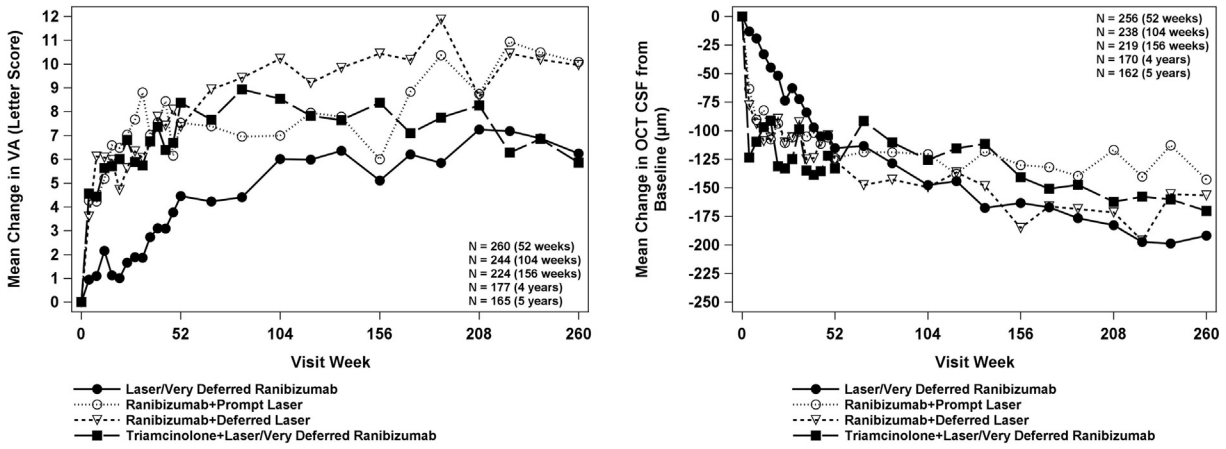

FIGURE 3. Mean change in (Left) visual acuity and (Right) central subfield thickness over 5 years for pseudophakic eyes from a randomized trial comparing ranibizumab with prompt or deferred laser, laser with deferred ranibizumab, and triamcinolone plus deferred ranibizumab in eyes with vision impairment from center-involved diabetic macular edema.

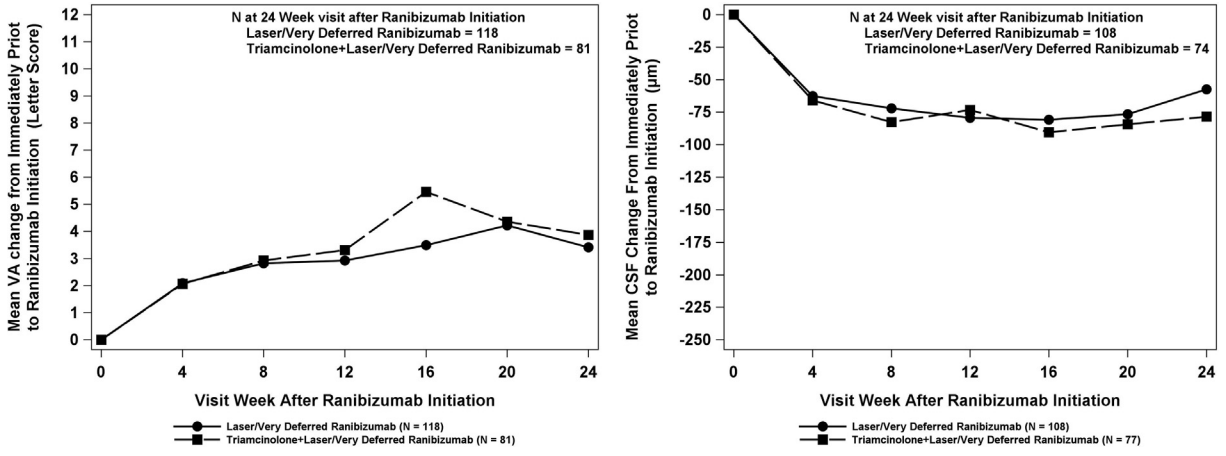

FIGURE 4. Mean change in (Left) visual acuity and (Right) central subfield thickness 24 weeks after initiation of very deferred ranibizumab in eyes with visual acuity impairment from diabetic macular edema randomly assigned to laser or triamcinolone plus laser.

structural damage may result in irreversible vision loss from retinal atrophy, neural cell loss, retinal pigment epithelial changes, and abnormal retinal thinning.

Potential limitations of this study include that although most of the participants who agreed to extend follow-up from 3 years to 5 years completed the 5-year visit (94% excluding deaths), this was only approximately 77% of the original cohort. In addition, the time between study entry and initiation of ranibizumab varied in the very deferred ranibizumab groups. Furthermore, since initiation of deferred ranibizumab was at investigator discretion, it is unknown what factors may have prompted the investigator to decide to initiate ranibizumab vs not initiate ranibizumab and it is unknown how many of the 40% of eyes that did not receive ranibizumab would have benefited from treatment. Although sham + prompt laser was designated as the standard treatment against which all other study treatments were to be compared in the original study protocol, ranibizumab + deferred laser was used as the comparator in this long-term analysis. This post hoc choice of the comparator was based on the observed "best" treatment in this study, considering the likely new clinical standard is anti-VEGF with deferred laser, but may have resulted in overestimation of its benefit relative to the other treatments.

Strengths of the study include the prospective collection of long-term (5 years) outcome data. Furthermore, this is the only trial that included eyes initially managed with intraocular triamcinolone + laser, which then involved late access to ranibizumab, yielding further anatomic and vision gains.

In summary, the benefits of anti-VEGF therapy for managing center-involved DME with vision impairment have been elucidated by several clinical trials. This report compares long-term (5-year) ranibizumab results with eyes managed with either laser or triamcinolone + laser and very deferred ranibizumab within a clinical trial. These data do not support use of ranibizumab in a very deferred manner for management of DME. Eyes assigned to alternate treatment strategies within this trial that received very deferred ranibizumab, when central retinal thickening and vision impairment persisted, did not achieve the same long-term vision improvements when compared with ranibizumab therapy as a first-line treatment strategy.

FUNDING SUPPORT: SUPPORTED THROUGH COOPERATIVE AGREEMENTS FROM THE NATIONAL EYE INSTITUTE AND THE National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland (EY14231, EY23207, and EY18817). The funding organization (National Institutes of Health, Bethesda, MD) participated in oversight of the conduct of the study and review of the manuscript, but not directly in the design or conduct of the study; nor in the collection, management, analysis, or interpretation of the data; nor in the preparation of the manuscript. Genentech (South San Francisco, CA) provided the ranibizumab for the study. In addition, Genentech provided funds to DRCR.net to defray the study's clinical site costs. As described in the Diabetic Retinopathy Clinical Research Network (DRCR.net) Industry Collaboration Guidelines (available at www.drcr.net), the DRCR.net had complete control over the design of the protocol, ownership of the data, and all editorial content of presentations and publications related to the protocol. Financial disclosures: Susan B. Bressler: Novartis (East Hanover, NJ), Research to Prevent Blindness (New York, NY), Boehringer-Ingelheim (Ridgefield, CT), Notal Vision (Chantilly, VA), Bayer (Whippany, NJ) (Research Grants, Expert Testimony). Adam R. Glassman: National Eye Institute (Bethesda, MD) (Grants). Neil M. Bressler: Grants to his institution for research agreements for which he is Principal Investigator: Bayer (Whippany, NJ), Genentech/Roche (South San Francisco, CA), Lumenis (San Jose, CA), Novartis (East Hanover, NJ), Optovue (Fremont, CA), Regeneron (Tarrytown, NY). Frederick L. Ferris: Royalties from Bausch and Lomb (Rochester, NY) for AMD nutritional supplements. Michele Melia: National Eye Institute (Bethesda, MD) (Grants, Personal Fees), National Institute on Deafness and Other Communication Disorders (Bethesda, MD) (Personal Fees), Alimera Sciences (Alpharetta, GA) (Personal Fees). John A. Wells III: Consulting fees from Iconic (South San Francisco, CA) and Panoptica (Mount Arlington, NJ), and travel reimbursement from the Jaeb Center (Tampa, FL); investigator in clinical trials for Ampio (Englewood, CO), Emmes (Rockville, MD), Genentech (South San Francisco, CA), Iconic (South San Francisco, CA), Jaeb Center for Health Research (Tampa, FL), Kalvista (Boston, MA), LPath (San Diego, CA), Neurotech (Cumberland, RI), Ophthotech (New York, NY), Panoptica (Mount Arlington, NJ), Regeneron (Tarrytown, NY), and Santen (Emeryville, CA). The following authors have no financial disclosures: Talat Almukhtar, Joseph M. Googe Jr, Shailesh K. Gupta, and Lee M. Jampol.

Writing Committee financial disclosures: Neil M. Bressler: Grants to investigators at The Johns Hopkins University (Baltimore, MD) are negotiated and administered by the institution (such as the School of Medicine), which receives the grants, typically through the Office of Research Administration. Individual investigators who participate in the sponsored project(s) are not compensated directly by the sponsor, but may receive salary or other support from the institution to support their effort on the projects(s). Dr Bressler is principal investigator of grants at The Johns Hopkins University sponsored by the Bayer (Whippany, NJ), Genentech, Inc (South San Francisco, CA), Novartis Pharma AG (East Hanover, NJ), Regeneron (Tarrytown, NY), and the Emmes Corporation (Rockville, MD) through the Office of Research Administration of the Johns Hopkins University School of Medicine, and has a contract agreement from the American Medical Association to the Johns Hopkins University School of Medicine. A complete list of all DRCR.net investigator financial disclosures can be found at www.drcr.net.

A published list of the Diabetic Retinopathy Clinical Research Network investigators and staff participating in this protocol can be found in *Ophthalmology* 2010;117:1064–1077.e35, with a current list available at www.drcr.net.

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