Original Investigation

# Persistent Macular Thickening After Ranibizumab Treatment for Diabetic Macular Edema With Vision Impairment

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**IMPORTANCE** The prevalence of persistent diabetic macular edema (DME) after months of anti–vascular endothelial growth factor therapy and its effect on visual acuity are unknown.

**OBJECTIVE** To assess subsequent outcomes of eyes with DME persisting for 24 weeks after initiating treatment with 0.5 mg of ranibizumab.

**DESIGN, SETTING, AND PARTICIPANTS** We performed post hoc, exploratory analyses of a randomized clinical trial from March 20, 2007, through January 29, 2014, from 117 of 296 eyes (39.5%) randomly assigned to receive ranibizumab with persistent DME (central subfield thickness ≥250 µm on time domain optical coherence tomography) through the 24-week visit.

**INTERVENTIONS** Four monthly intravitreous injections of ranibizumab and then as needed per protocol.

**MAIN OUTCOMES AND MEASURES** Cumulative 3-year probabilities of chronic persistent DME (failure to achieve a central subfield thickness <250 µm and at least a 10% reduction from the 24-week visit on at least 2 consecutive study visits) determined by life-table analyses, and at least 10 letter (≥2 line) gain or loss of visual acuity among those eyes.

**RESULTS** The probability of chronic persistent DME among eyes with persistent DME at the 24-week visit decreased from 100% at the 32-week visit to 81.1% (99% CI, 69.6%-88.6%), 55.8% (99% CI, 42.9%-66.9%), and 40.1% (99% CI, 27.4%-52.4%) at the 1-, 2-, and 3-year visits, respectively. At 3 years, visual acuity improved in eyes with and without chronic persistent DME through the follow-up period, respectively, by a mean of 7 letters and 13 letters from baseline. Among 40 eyes with chronic persistent edema through 3 years, 17 (42.5%) (99% CI, 23.1%-63.7%) gained 10 letters or more from baseline, whereas 5 (12.5%) (99% CI, 2.8%-31.5%) lost 10 letters or more from baseline.

**CONCLUSIONS AND RELEVANCE** These data suggest less than half of eyes treated for DME with intravitreous ranibizumab have persistent central-involved DME through 24 weeks after initiating treatment. Among the 40% that then have chronic persistent central-involved DME through 3 years, longer-term visual acuity outcomes appear to be slightly worse than in the 60% in which DME does not persist. Nevertheless, when following the treatment protocol used in this trial among eyes with vision impairment from DME, long-term improvement in visual acuity from baseline is typical and substantial (≥2-line) loss of visual acuity is likely uncommon through 3 years, even when central-involved DME chronically persists.

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Invited Commentary

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Several phase 3 studies[1-4] have found that anti-vascular endothelial growth factor (VEGF) therapy, with or without macular laser treatment, is superior to laser treatment alone for improving vision and decreasing retinal thickness in eyes with center-involved diabetic macular edema (DME) and vision impairment. However, not all eyes in these studies manifest complete resolution of DME during follow-up despite anti-VEGF treatment and focal/grid laser. In the Diabetic Retinopathy Clinical Research Network (DRCR.net) study, approximately 40% of eyes receiving ranibizumab injections with prompt or deferred focal/grid laser had a central subfield thickness ≥250 microns on time domain (TD) optical coherence tomography (OCT) at 2 years.[5] Treatment protocols in this study,[1,5] as well as another,[3] allow a treating ophthalmologist to observe eyes with stable DME without additional anti-VEGF treatment despite the absence of complete resolution of DME after multiple injections. These findings suggest that physicians treating patients with ranibizumab may have many patients with persistent DME despite previous months of repeated anti-VEGF intravitreous injections. To further our understanding of persistent DME after many months of anti-VEGF therapy, including its prevalence over time and effect on visual acuity, the DRCR.net conducted a post hoc exploratory analysis of ranibizumab-treated eyes from a DRCR.net trial evaluating laser treatment, ranibizumab, and intravitreous triamcinolone for DME.[1]

**Key Points**

**Question:** What was the outcome of eyes with diabetic macular edema (DME) persisting 24 weeks after initiating treatment with 0.5-mg of ranibizumab?

**Findings:** In this post hoc analysis of a randomized clinical trial, 40% of eyes with persistent DME at 24 weeks after initiating treatment with ranibizumab had chronic persistent DME through 3 years, and vision outcomes were only slightly worse than the 60% in which DME did not persist.

**Meaning:** Substantial (≥2-line) vision loss is uncommon at 3 years despite chronic persistent DME after initiating ranibizumab treatment.

## Methods

The methods for this trial comparing sham and prompt focal/grid laser, intravitreous ranibizumab and prompt laser, intravitreous ranibizumab and deferred (≥24 weeks) laser, and intravitreous triamcinolone and prompt laser have been published in detail elsewhere,[1] with the complete protocol available online (http://drcrnet.jaeb.org/). The protocol and Health Insurance Portability and Accountability Act–compliant informed consent forms were approved by multiple institutional review boards. The study was performed from March 1, 2007, through February 28, 2014. In brief, principal eligibility criteria included eyes with DME confirmed by TD-OCT (Stratus; Carl Zeiss Meditec), CST of at least 250 µm, and a decreased best-corrected electronic visual acuity letter score[6] of 78 through 24 (approximate Snellen equivalent 20/32 to 20/320) following a protocol refraction. Visits were every 4 weeks through the 52-week visit and every 4, 8, or 16 weeks thereafter, depending on the clinical course and treatments received. Injections were required every 4 weeks for the initial 12 weeks of the study and through 20 weeks if DME persisted. Thereafter, injections were repeated every 4 weeks if there was successive improvement in visual acuity (≥5 letters) or OCT (CST decreased by ≥10%) and visual acuity remained worse than 20/20 with a CST of 250 µm or greater. Otherwise, reinjection was at investigator discretion. Focal/grid laser was given with anti-VEGF therapy at baseline in the ranibizumab and prompt laser group. In the ranibizumab and deferred laser group, focal/grid laser was added at 24 weeks or anytime thereafter if there was persistent DME that was no longer improving with ranibizumab and there were areas of thickened macula where laser could be applied, either directly (focal) to microaneurysms or with grid to areas of thickening without microaneurysms. After the initiation of laser treatment within the trial, eyes could receive additional laser treatment every 4 months if edema persisted, and areas were identified in the macula where laser could be applied to thickened retina. Other treatments, such as intravitreous corticosteroids or other anti-VEGF agents, could not be considered unless failure or futility criteria were met. Failure criteria could be met after 6 months if there was a loss of 10 or more letters of visual acuity from baseline due to persistent DME no longer improving when complete focal/grid laser treatment had been applied with at least 13 weeks from the last laser treatment. Futility criteria could be met after 1 year because of persistent DME no longer improving when complete focal/grid laser treatment had been applied with at least 29 weeks from the last complete laser treatment.

The main focus of the present analysis is to evaluate OCT and best-corrected visual acuity changes beyond 24 weeks in the subgroup of participants with persistent macular thickening through 24 weeks despite receipt of at least 4 intravitreous ranibizumab injections required during this period. This analysis will determine how many of these eyes, referred to as the persistent DME cohort, manifest chronic persistent DME over time (**Box**). Eyes with persistent DME through 24 weeks were considered to have chronic persistent DME until they achieved a CST less than 250 µm and 10% or greater reduction relative to the 24-week study visit on at least 2 consecutive study visits subsequent to the 24-week visit. To increase the likelihood that eyes were correctly classified with respect to chronic persistent DME between the 28- and 52-week visits, all analyses excluded participants who missed more than 2 visits during this time. After excluding 65 eyes with a baseline CST less than 250 µm, fewer than 4 injections before 24 weeks, or missing more than 2 visits between 28 and 52 weeks, 296 of the 361 eyes randomly assigned to receive ranibizumab remained eligible for this analysis, 117 vs 179 of which were classified as the cohort with and without persistent DME at 24 weeks, respectively (eFigure in the Supplement). Participants were censored at the date of the prior annual visit if there were fewer than 4 visits between annual visits (the protocol required a minimal number of 4 visits between the annual visits). Four eyes that received alternative treatment for

**Box. Definitions of Persistent DME and Chronic Persistent DME**

**Persistent DME**

Eyes with OCT CST of 250 µm or greater (stratus OCT equivalence values) at all completed visits through the 24-week visit despite receipt of at least 4 of the potential 6 protocol-mandated intravitreous ranibizumab injections during this period. In addition, to be included in this cohort, eyes missed no more than 2 visits between the 28-week and 1-year visits.

**Chronic Persistent DME**

Eyes with persistent DME as defined above that have not yet achieved a CST less than 250 µm (stratus equivalence values) and 10% or greater reduction relative to the 24-week study visit on at least 2 consecutive study visits subsequent to the 24-week visit as of a given time point. Eyes with fewer than 4 visits between annual visits or that receive alternative treatment(s) for DME were censored.

Abbreviations: CST, central subfield thickness; DME, diabetic macular edema; OCT, optical coherence tomography.

DME (eg, intravitreous corticosteroid injections) during study follow-up, all of which met criteria for failure or futility, were censored on the date of first receiving the alternative treatment.

Cumulative probabilities, with corresponding 99% CIs, of chronic persistent DME through the 1-, 2-, and 3-year visits were calculated using the life-table method. Statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc).

## Results

Select baseline and 24-week characteristics of eyes with and without persistent DME through the 24-week visit are provided in **Table 1**. Baseline CST and macular volume were greater in the eyes with persistent DME. The median (interquartile range [IQR]) approximate Snellen equivalent visual acuity at 24 weeks was 20/40 (20/32-20/50) among the persistent DME eyes and 20/32 (20/25-20/50) in the eyes without persistent DME. Change in visual acuity from baseline to the 24-week visit was similar for the eyes with and without persistent DME (mean [99% CI], +8 [+6 to +11] and +8 [+6 to +10] letters, 49 [41.9%] and 70 [43.5%] with ≥10-letter gain, and 2 [1.7%] and 5 [3.1%] with ≥10-letter loss, respectively).

Eyes with persistent DME through the 24-week visit had a similar number of injections from the 24-week to the 1-year visit, with a median (IQR) of 5 (3-6) injections regardless of whether the eye had chronic persistent DME or not (**Table 2**). Cumulatively, the median number (IQR) of injections by 3 years was 17 (12-26) and 16 (12-22) in those with and without chronic persistent DME, respectively. In addition, 25 of 40 study participants (62.5%) and 44 of 60 study participants (73.3%) with and without chronic persistent DME, respectively, received focal/grid laser from 24 weeks to 3 years (Table 2), including 12 of 21 participants (57.1%) and 22 of 32 participants (68.8%), respectively, in the group assigned randomly to receive ranibizumab with deferred focal/grid laser.

**Table 1. Selected Baseline and 24-Week Characteristics for Eyes With and Without Persistent DME at All Study Visits Through the 24-Week Study Visit[a]**

| Characteristic | Patients With DME (n = 117) | Patients Without DME (n = 179) |
|---|---|---|
| Female sex | 46 (39.3) | 78 (43.6) |
| Age, median (IQR), y | 64 (58 to 71) | 63 (57 to 70) |
| Race | | |
| White | 94 (80.3) | 125 (69.8) |
| African American | 14 (12.0) | 30 (16.8) |
| Hispanic or Latino | 6 (5.1) | 19 (10.6) |
| Asian | 0 | 2 (1.1) |
| Native Hawaiian or other Pacific Islander | 0 | 1 (0.6) |
| Multiracial | 2 (1.7) | 0 |
| Unknown or not reported | 1 (0.9) | 2 (1.1) |
| Diabetes mellitus | | |
| Type 1 | 7 (6.0) | 14 (7.8) |
| Type 2 | 109 (93.2) | 161 (89.9) |
| Uncertain type | 1 (0.9) | 4 (2.2) |
| Duration of diabetes, median (IQR), y | 16 (10 to 21) | 18 (12 to 26) |
| Insulin used | 66 (56.4) | 115 (64.2) |
| $HbA_{1c}$, median (IQR), %[b] | 7.2 (6.5 to 8.4) | 7.5 (6.7 to 8.4) |
| Prior cardiovascular event[c] | 40 (34.2) | 59 (33.0) |
| Hypertension[c] | 95 (81.2) | 149 (83.2) |
| No. of study eyes | | |
| 1 | 77 (65.8) | 132 (73.7) |
| 2[d] | 40 (34.2) | 47 (26.3) |
| Prior | | |
| PRP | 28 (23.9) | 48 (26.8) |
| Treatment (any type) for DME | 75 (64.1) | 118 (65.9) |
| Laser for DME | 68 (58.1) | 108 (60.3) |
| IVT for DME | 22 (18.8) | 26 (14.5) |
| Vitrectomy for DME | 4 (3.4) | 6 (3.4) |
| Peribulbar triamcinolone for DME | 4 (3.4) | 8 (4.5) |
| Anti-VEGF for DME | 15 (12.8) | 22 (12.3) |
| Lens status (clinical examination) | | |
| Phakic | 76 (65.0) | 129 (72.1) |
| IOL AC | 1 (0.9) | 1 (0.6) |
| IOL PC | 40 (34.2) | 49 (27.4) |
| IOP, median (IQR), mm Hg | 16 (14 to 18) | 16 (14 to 19) |
| VA letter score (approximate Snellen equivalent), median (IQR) | | |
| Baseline | 65 (58 to 71) 20/50 (20/80 to 20/40) | 65 (56 to 71) 20/50 (20/80 to 20/40) |
| 24 wk[e] | 73 (64 to 78) 20/40 (20/50 to 20/32) | 74 (65 to 80) 20/32 (20/50 to 20/25) |
| 24-wk Change in VA letter score from baseline[e] | | |
| Median (IQR) | 7 (2 to 12) | 8 (4 to 13) |
| Mean (SD) | 8 (10) | 8 (9) |
| ≥10-Letter gain | 49 (41.9) | 70 (43.5) |
| 5- to 9-Letter gain | 24 (20.5) | 41 (25.5) |
| Within 4-letter gain or loss | 37 (31.6) | 40 (24.8) |
| 5- to 9-Letter loss | 5 (4.3) | 5 (3.1) |
| ≥10-Letter loss | 2 (1.7) | 5 (3.1) |

(continued)

Table 1. Selected Baseline and 24-Week Characteristics for Eyes With and Without Persistent DME at All Study Visits Through the 24-Week Study Visit[a] (continued)

| Characteristic | Patients With DME (n = 117) | Patients Without DME (n = 179) |
|---|---|---|
| Central subfield thickness on OCT, median (IQR), μm | | |
| Baseline | 422 (364 to 535) | 365 (292 to 461) |
| 24 wk[h] | 309 (270 to 357) | 227 (199 to 255) |
| 24-wk[i] Change in central subfield thickness from baseline on OCT, median (IQR), μm[f] | −99 (−176 to −40) | −128 (−213 to −65) |
| OCT volume, median (IQR), $mm^3$ | | |
| Baseline[g] | 8.7 (7.7 to 10.0) | 8.2 (7.3 to 9.6) |
| 24 wk[j] | 7.5 (7.0 to 8.5) | 7.1 (6.6 to 7.5) |
| 24-wk Change in OCT volume from baseline, median (IQR), $mm^3$ | −1.1 (−1.7 to −0.5) | −1.0 (−2.2 to −0.6) |
| Baseline retinopathy severity on fundus photographs (ETDRS diabetic retinopathy severity level)[j] | | |
| Diabetic retinopathy absent, minimal NPDR (10, 12, 14, 15, 20) | 3 (2.7) | 4 (2.4) |
| Mild or moderate NPDR (35, 43) | 30 (26.6) | 39 (22.9) |
| Moderately severe or severe NPDR (47) | 46 (40.7) | 72 (42.4) |
| Mild-, moderate-, or high-risk PDR (60, 61, 65, 71) | 34 (30.1) | 55 (32.4) |

Abbreviations: AC IOL, anterior chamber intraocular lens; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; $HbA_{1c}$, hemoglobin $A_{1c}$; IOP, intraocular pressure; IQR, interquartile range; IVT, intravitreous triamcinolone; NPDR, nonproliferative diabetic retinopathy; OCT, optical coherence tomography; PC IOL, posterior chamber intraocular lens; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VA, visual acuity; VEGF, vascular endothelial growth factor.

SI conversion factor: To convert $HbA_{1c}$ to a proportion of 1.0, multiply by 0.01.

[a] Data are presented as number (percentage) of study participants unless otherwise indicated. All eyes had baseline central subfield thickness of 250 μm or greater, at least 4 intravitreous ranibizumab injections before the 24-week visit, and 2 or fewer missed visits between the 28-week and 1-year visits.

[b] Missing for 1 and 4 study participants, respectively.

[c] Medical history of condition.

[d] Contralateral study eye is not assigned to ranibizumab.

[e] Missing for 0 and 18 eyes, respectively.

[f] Missing for 0 and 19 eyes, respectively.

[g] Missing or ungradable for 15 and 40 eyes, respectively.

[h] Missing for 2 and 19 eyes, respectively.

[i] Missing for 15 and 55 eyes, respectively.

[j] Missing or ungradable for 4 and 9 eyes, respectively.

Table 2. Number of Injections and Laser Treatment Sessions Administered Throughout Follow-up to Eyes With Persistent DME Through Week 24[a]

| Variable | Chronic Persistent DME[b] | |
|---|---|---|
| | Yes | No |
| No. of injections | | |
| 24 wk to before 1 y[c] | | |
| No. of eyes | 95 | 22 |
| Median (IQR) | 5 (3-6) | 5 (3-6) |
| Mean (SD) | 4 (2) | 4 (2) |
| 1 y to before 2 y[d] | | |
| No. of eyes | 61 | 48 |
| Median (IQR) | 5 (2-8) | 2 (1-5) |
| Mean (SD) | 5 (4) | 3 (3) |
| 2 y to before 3 y[e] | | |
| No. of eyes | 40 | 60 |
| Median (IQR) | 3 (1-6) | 2 (0-4) |
| Mean (SD) | 4 (3) | 2 (3) |
| Before 1 y[c] | | |
| No. of eyes | 95 | 22 |
| Median (IQR) | 10 (9-12) | 11 (8-12) |
| Mean (SD) | 10 (2) | 10 (2) |
| Before 2 y[d] | | |
| No. of eyes | 61 | 48 |
| Median (IQR) | 15 (12-20) | 13 (11-16) |
| Mean (SD) | 15 (5) | 14 (4) |
| Before 3 y[e] | | |
| No. of eyes | 40 | 60 |
| Median (IQR) | 17 (12-26) | 16 (12-22) |
| Mean (SD) | 18 (8) | 17 (6) |
| Laser treatments, No. of eyes (%) | | |
| 24 wk to before 1 y[c] | 60 (63.2) | 11 (50.0) |
| 1 y to before 2 y[d] | 28 (45.9) | 16 (33.3) |
| 2 y to before 3 y[e] | 11 (27.5) | 13 (21.7) |
| 24 wk to before 3 y[e] | 25 (62.5) | 44 (73.3) |
| 24 wk to before 3 y[e] | | |
| No. of laser treatments, median (IQR) | 1 (0-3) | 1 (0-3) |
| No. of laser treatments, mean (SD) | 1.8 (2.0) | 1.7 (1.6) |
| Before 3 y[e] | 31 (77.5) | 50 (83.3) |

Abbreviations: DME, diabetic macular edema; IQR, interquartile range.

[a] All eyes had baseline central subfield thickness of 250 μm or greater, at least 4 injections before the 24-week visit, and no more than 2 missed visits between the 28-week and 1-year visits.

[b] Eyes meeting criteria for no DME at a given visit shift into the no column at that visit and remain there at subsequent visits.

[c] Limited to participants completing the 1-year visit.

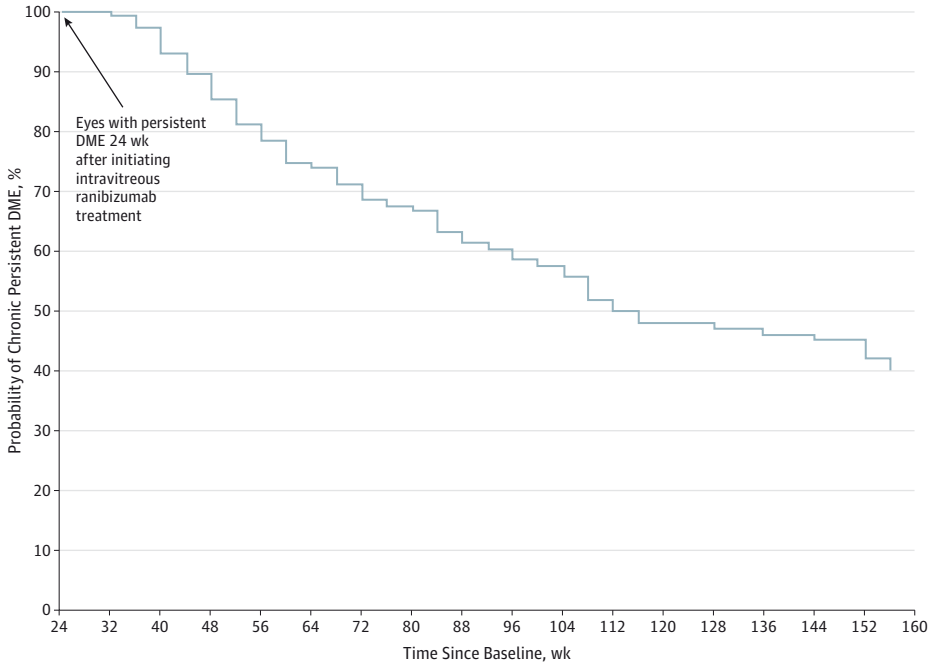
[d] Limited to participants completing the 2-year visit and having at least 4 visits between the 1- and 2-year visits and no nonprotocol treatment before 2 years.

[e] Limited to participants completing the 3-year visit and having at least 4 visits between the 1- and 2-year visits, at least 4 visits between the 2- and 3-year visits, and no alternative treatment before 3 years.

The **Figure** shows the probabilities of chronic persistent DME during the 3 years of follow-up in eyes with persistent DME through 24 weeks. At 1 year 81.1% (99% CI, 69.6%-88.6%) had chronic persistent DME, whereas by 3 years 40.1% (99% CI, 27.4%-52.4%) had chronic persistent DME. In the 40 eyes with chronic persistent DME through 3 years, the median (IQR) CST was 396 (347-474) μm at baseline and 278 (258-327) μm at 3 years.

Visual acuity improvement from baseline to 3 years (**Table 3**) averaged +10 (99% CI, +7 to +14) letters in all eyes with persistent DME at 24 weeks. The improvement was greater in the 60 eyes that did not have chronic persistent DME through 3 years (mean of +13 letters; 99% CI, +9 to +17; ≥10-letter gain in 36 [60.0%]; 99% CI, 42.6% to 75.8%; ≥10-letter loss in 2 [3.3%]; 99% CI, 0.2% to 14.6%) compared with the 40 who had

Figure. Probability of Chronic Persistent Diabetic Macular Edema (DME)




| | Weeks | | |
|---|---|---|---|
| | 24-52 | 56-104 | 108-156 |
| No. of eyes at risk at beginning of interval | 117 | 91 | 58 |
| No. of events in interval | 22 | 28 | 15 |
| No. of censored patients in interval[a] | 4 | 5 | 3 |
| Reason censored | All censored at 52 wk due to insufficient visits between 52- and 104-wk visit | 2 received alternative treatments<br>3 censored at 104 wk due to insufficient visits between 104- and 156-wk visit | 2 received alternative treatments<br>1 lost to follow-up |
| Cumulative probability of chronic persistent DME up to end of interval (99% CI), % | 81.1 (69.6-88.6) | 55.8 (42.9-66.9) | 40.1 (27.4-52.4) |

An event is defined as a central subfield thickness less than 250 µm and a 10% or greater reduction relative to the 24-week study visit on at least 2 consecutive study visits subsequent to the 24-week visit.

[a] Five participants excluded from 104- or 156-week cross-sectional analyses as noted in the eFigure in the Supplement due to insufficient visits or lost to follow-up are not censored in the time to event analysis because of meeting the definition of no longer chronic persistent DME by 52 weeks.

chronic persistent DME through 3 years (mean of +7 letters; 99% CI, +1 to +13; ≥10-letter gain in 17 [42.5%]; 99% CI, 23.1% to 63.7%; ≥10-letter loss in 5 [12.5%]; 99% CI, 2.8% to 31.5%; $P$ = .02 for $t$ test comparing means, $P$ = .10 and .11 for Fisher exact tests comparing ≥10-letter gain and loss, respectively). The median visual acuity letter score (approximate Snellen equivalent) at 3 years was 76 (20/32; IQR, 80-57 [20/25-20/80]) in the eyes with chronic persistent DME compared with 79 (20/25; IQR, 83-72 [20/20-20/40]) in the eyes without chronic persistent DME ($P$ = .05 for Wilcoxon rank sum test comparing medians).

## Discussion

This exploratory analysis of eyes with persistent DME through 24 weeks after initiation of anti-VEGF therapy estimates that 40.1% (99% CI, 27.4%-52.4%) (Figure) will have chronic persistent DME through 3 years when following a visit and treatment schedule as was performed in this protocol.[1,5] Regardless of status by 3 years, vision in eyes that had persistent DME through 24 weeks improved from baseline to 3 years (+7 and +13 letters in those with and without chronic persistent DME through 3 years). A substantial number of eyes gained at least 10 letters (42.5% and 60.0%, respectively), whereas only a small number of eyes lost at least 10 letters (12.5% and 3.3%, respectively). Eyes that had resolution of DME for at least 2 consecutive visits between 24 weeks and 3 years appear to have better 3-year visual acuity outcomes compared with eyes that have chronic persistent DME through 3 years. However, because of the limited number of participants meeting the outcomes, we cannot conclude this definitively.

These results were observed after a retreatment regimen in which injections were required every 4 weeks only if there was successive improvement in visual acuity (≥5 letters) or OCT (CST change of ≥10%) and vision remained worse than 20/20 with a CST of 250 µm or greater starting at 24 weeks after initiating ranibizumab treatment. Otherwise, reinjection was at

Table 3. Visual Acuity and Change in Visual Acuity Throughout Follow-up for Eyes With Persistent DME Through the 24-Week Visit[a]

| Variable | Chronic Persistent DME[b] | | | | | |
|---|---|---|---|---|---|---|
| | 1-y Visit[c] | | 2-y Visit[d] | | 3-y Visit[e] | |
| | Yes (n = 95) | No (n = 22) | Yes (n = 61) | No (n = 48) | Yes (n = 40) | No (n = 60) |
| Baseline visual acuity, median (IQR) | | | | | | |
| Letter score | 66 (73 to 57) | 65 (70 to 58) | 67 (73 to 53) | 65 (70 to 59) | 67 (73 to 58) | 65 (71 to 58) |
| Approximate Snellen equivalent | 20/50 (20/40 to 20/80) | 20/50 (20/40 to 20/80) | 20/50 (20/40 to 20/100) | 20/50 (20/40 to 20/63) | 20/50 (20/40 to 20/80) | 20/50 (20/40 to 20/80) |
| Follow-up visual acuity | | | | | | |
| Letter score, median (IQR) | 75 (81 to 66) | 75 (81 to 69) | 74 (81 to 65) | 76 (81 to 70) | 76 (80 to 57) | 79 (83 to 72) |
| Approximate Snellen equivalent, median (IQR) | 20/32 (20/25 to 20/50) | 20/32 (20/25 to 20/40) | 20/32 (20/25 to 20/50) | 20/32 (20/25 to 20/40) | 20/32 (20/25 to 20/80) | 20/25 (20/20 to 20/40) |
| Letter score, mean (SD) | 71 (13) | 72 (12) | 70 (17) | 73 (13) | 70 (14) | 75 (13) |
| Approximate Snellen equivalent, mean (SD lines, assuming 5 letters per line) | 20/40 (2.6) | 20/40 (2.4) | 20/40 (3.4) | 20/32 (2.6) | 20/40 (2.8) | 20/32 (2.6) |
| Change in visual acuity from baseline visit | | | | | | |
| Letters, median (IQR) | 8 (3 to 15) | 8 (4 to 15) | 8 (2 to 17) | 11 (5 to 17) | 5 (−2 to 16) | 12 (8 to 21) |
| Letters, mean (SD) | 9 (12) | 11 (11) | 8 (17) | 11 (13) | 7 (14) | 13 (12) |
| ≥10-Letter gain, No. (%) | 42 (44.2) | 10 (45.5) | 26 (42.6) | 28 (58.3) | 17 (42.5) | 36 (60.0) |
| 5- to 9-Letter gain, No. (%) | 25 (26.3) | 4 (18.2) | 13 (21.3) | 8 (16.7) | 3 (7.5) | 14 (23.3) |
| Within ±4 letters, No. (%) | 19 (20.0) | 8 (36.4) | 15 (24.6) | 9 (18.8) | 12 (30.0) | 5 (8.3) |
| 5- to 9-Letter loss, No. (%) | 5 (5.3) | 0 | 2 (3.3) | 2 (4.2) | 3 (7.5) | 3 (5.0) |
| ≥10-Letter loss, No. (%) | 4 (4.2) | 0 | 5 (8.2) | 1 (2.1) | 5 (12.5) | 2 (3.3) |
| Change in visual acuity from 24-wk visit | | | | | | |
| Letters, median (IQR) | 1 (−4 to 5) | 3 (1 to 6) | 1 (−4 to 6) | 2 (−2 to 6) | 0 (−7 to 4) | 5 (−3 to 9) |
| Letters, mean (SD) | 0 (9) | 3 (6) | −1 (14) | 2 (10) | −2 (12) | 3 (10) |
| ≥10-Letter gain, No. (%) | 7 (7.4) | 4 (18.2) | 9 (14.8) | 5 (10.4) | 5 (12.5) | 13 (21.7) |
| 5- to 9-Letter gain, No. (%) | 18 (18.9) | 3 (13.6) | 10 (16.4) | 8 (16.7) | 3 (7.5) | 17 (28.3) |
| Within ±4 letters, No. (%) | 50 (52.6) | 13 (59.1) | 28 (45.9) | 28 (58.3) | 21 (52.5) | 22 (36.7) |
| 5- to 9-Letter loss, No. (%) | 11 (11.6) | 1 (4.5) | 8 (13.1) | 4 (8.3) | 4 (10.0) | 5 (8.3) |
| ≥10-Letter loss, No. (%) | 9 (9.5) | 1 (4.5) | 6 (9.8) | 3 (6.3) | 7 (17.5) | 3 (5.0) |

Abbreviations: DME, diabetic macular edema; IQR, interquartile range.

[a] All eyes had baseline central subfield thickness of 250 µm or greater, at least 4 injections before the 24-week visit, and no more than 2 missed visits between the 28-week and 1-year visits.

[b] Eyes meeting criteria for no DME at a given visit shift into the no column at that visit and remain there at subsequent visits.

[c] Limited to participants completing the 1-year visit in the plus or minus 8-week analysis window (actual IQR, 49-54 weeks).

[d] Limited to participants completing the 2-year visit in the plus or minus 16-week analysis window (actual IQR, 99-107 weeks) and having at least 4 visits between the 1-year and 2-year visits and no nonprotocol treatment before 2 years.

[e] Limited to participants completing the 3-year visit in the plus or minus 16-week analysis window (actual IQR, 145-165 weeks) and having at least 4 visits between the 1-year and 2-year visits at least 4 visits between the 2-year and 3-year visits and no nonprotocol treatment before 3 years.

investigator discretion. Regardless of DME status by 3 years, eyes that had chronic persistent DME through 24 weeks received a moderate number of injections by 3 years (mean total of 16 to 17 injections of a maximum potential of 39).

The visual acuity improvements for the eyes with chronic persistent DME at 3 years occurred in the setting of substantial decreases in retinal thickness that occurred during follow-up. Among these 40 eyes with chronic persistent DME through 3 years, the median baseline CST decreased from 396 µm (median IQR, 347-474 µm) to 278 µm (median IQR, 258-327 µm). Thus, in half of these eyes, only modest CST persisted at the 3-year visit, consistent with reasonable preservation of the mean vision in eyes with chronic persistent DME.

Limitations of this analysis include the fact that starting at the 24-week visit, investigator discretion was permitted with respect to adding ranibizumab or focal/grid macular laser treatments if an eye had stabilized or reached failure or futility in terms of visual acuity and OCT CST. It is unknown how the treatment decisions that were made at investigator discretion affected the visual acuity and OCT outcomes reported. It also is unknown what would have happened to these eyes had treatment been discontinued at 24 weeks for those with persistent DME, including how many would have had resolution of DME over time just with observation over time or what the outcomes would be if other retreatment protocols were followed.

Other limitations include potential bias from censoring participants receiving alternative treatment, lost to follow-up, or too many missed visits. Those participants may have more medical issues and be at higher risk of chronic persistent DME

and poorer visual acuity outcomes. Hence, the estimate at 3 years of 40.1% of those initially manifesting persistent DME continuing to manifest chronic persistent DME could be an underestimate. The estimate of chronic persistent DME may have alternatively been inflated by retaining eyes that missed visits at which edema might potentially have resolved.

Analyses were not performed on data available beyond 3 years because of small numbers in the subgroup with persistent DME. Furthermore, these analyses only evaluated whether eyes with persistent DME through 24 weeks had resolution of DME by 3 years or chronic persistent DME through 3 years but did not further subdivide resolved cases into those that maintained absence of DME vs those that had recurrence of central-involved DME due to numerous scenarios of resolution and recurrence at various intervals over time.

Although it would be interesting to compare the visual acuity results of the cohort that was the focus of this analysis with the remaining 179 eyes randomly assigned to ranibizumab treatment that did not have persistent DME through 24 weeks, such a comparison would be difficult to evaluate. The persistent DME cohort identified for this analysis had more severe DME reflected in thicker CST measurements at study entry, and the follow-up algorithm was based, in part, on CST changes, which may be affected by baseline CST. Thus, it becomes impossible to parse out the reasons for different outcomes of these cohorts. To reiterate, the objective of this analysis was to assess visual acuity in the long term in eyes for which DME persisted through 24 weeks.

The peer-reviewed literature does not contain a widely accepted definition of persistent DME or chronic persistent DME in the context of anti-VEGF therapy. Had a different definition been used for persistent DME or chronic persistent DME, the results of these analyses may have been somewhat different. Yet another limitation is that these analyses are subgroup analyses, which are exploratory in nature, so they should be viewed as hypothesis generating rather than hypothesis testing. Some of the strengths of the study include the prospective collection of data using standardized data collection and treatment protocols, which involved a large number of eyes treated with intravitreous ranibizumab for a prolonged period.

## Conclusions

Developing treatment strategies to improve visual acuity outcomes among eyes with persistent DME despite repeated anti-VEGF treatment will require additional studies. For example, the DRCR.net is conducting a phase 2 trial in which eyes with persistent DME similar to those defined in this report are assigned randomly to continued anti-VEGF treatment vs combining anti-VEGF with intravitreous corticosteroid treatment. Even if the combination treatment does not lead to improved vision outcomes compared with the outcomes obtained when following the treatment regimen used in this trial, the current results suggest that the anti-VEGF treatment strategy used by the DRCR.net investigators resulted in long-term improvement in visual acuity, regardless of whether there was chronic persistent DME by 3 years. These findings also suggest that when ophthalmologists followed the retreatment and visit regimen used in this study, continued resolution of central-involved edema occurred in many eyes that had not resolved by 24 weeks, with more than half meeting our definition of resolution within 2½ years after the persistent DME was documented 24 weeks after initiating ranibizumab treatment. In addition, the results imply that few eyes lose vision despite chronic persistent DME through at least 3 years after initiating and continuing anti-VEGF treatment in the manner used in this DRCR.net protocol.[1-4] Thus, this analysis reveals that the current DRCR.net anti-VEGF treatment strategy,[1-4] including its approach to permit deferral of additional anti-VEGF in eyes with persistent DME that are stable (no longer improving) starting 24 weeks after initiating therapy unless DME worsens, is unlikely to result in substantial (≥2-line) loss of visual acuity, even when central-involved DME persists through 3 years.

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