

Randomized Trial of Treat and Extend Ranibizumab With and Without Navigated Laser Versus Monthly Dosing for Diabetic Macular Edema: *TREX-DME* 2-Year Outcomes



JOHN F. PAYNE, CHARLES C. WYKOFF, W. LLOYD CLARK, BEAU B. BRUCE, DAVID S. BOYER, AND DAVID M. BROWN, FOR THE TREX-DME STUDY GROUP

- **PURPOSE:** To prospectively evaluate a treat and extend algorithm of ranibizumab with and without navigated laser to monthly dosing for center-involving diabetic macular edema.
- **DESIGN:** This was a multicenter, randomized, clinical trial.
- **METHODS:** One hundred fifty eyes were randomized into 3 cohorts: monthly ($n = 30$), treat and extend without laser photocoagulation (TREX; $n = 60$), and treat and extend with angiography-guided laser photocoagulation (GILA; $n = 60$). Monthly cohort eyes received ranibizumab 0.3 mg every 4 weeks. TREX and GILA cohort eyes received 4 monthly injections of ranibizumab 0.3 mg followed by a treat and extend dosing strategy. GILA cohort eyes also received navigated focal laser at month 1 and again every 3 months as needed. The primary outcomes included the mean change in best-corrected visual acuity and central retinal thickness and the number of injections from baseline to 2 years.
- **RESULTS:** At 2 years, mean best-corrected visual acuity and central retinal thickness improved by 7.5, 9.6, and 9.0 letters ($P = .75$) and 139, 140, and 175 μm ($P = .09$), in the monthly, TREX, and GILA cohorts, respectively. The mean number of injections was significantly reduced in both the TREX (18.9) and GILA (17.5) cohorts compared with the monthly cohort (24.7, $P < .001$). Between the TREX and GILA cohorts, there was no significant difference in the mean treatment interval, mean maximal treatment interval, or percentage of eyes extended to 12 weeks. The total 2-year incidence of Anti-Platelet Trialists' Collaboration events was 6.7%.
- **CONCLUSION:** The treat and extend algorithm of ranibizumab in the TREX-DME trial resulted in significantly

fewer injections and yielded visual and anatomic gains comparable to monthly dosing at 2 years. (*Am J Ophthalmol* 2019;202:91–99. © 2019 Elsevier Inc. All rights reserved.)

NUMEROUS CLINICAL TRIALS HAVE DEMONSTRATED the safety and effectiveness of consistent dosing of anti-vascular endothelial growth factor (anti-VEGF) medications for diabetic macular edema (DME).^{1–8} While monthly dosing has shown to be effective at reducing retinal thickness and improving vision, the application of this approach in busy clinical settings and in patients with complex comorbid conditions can be challenging. A recent survey of retina specialists suggested that the most frequent treatment regimens of intravitreal anti-VEGF injections for retinal vascular disease are either an as-needed or treat and extend strategy.⁹ The goal of treat and extend dosing is to titrate the anti-VEGF dosing based on an individual's clinical response.^{10,11} Decreasing the treatment burden while providing clinically significant visual and anatomic improvements is of paramount importance. A growing emphasis has been placed on practice efficiency and cost containment while maintaining optimal visual outcomes.

Individualized treat and extend dosing has not been rigorously investigated for DME. To date, only a few clinical trials have assessed the efficacy of this treatment regimen for DME.^{12–15} The RETAIN (Efficacy and Safety of Ranibizumab in Two “Treat and Extend” Treatment Algorithms Versus Ranibizumab As Needed in Patients With Macular Edema and Visual Impairment Secondary to Diabetes Mellitus) trial used ranibizumab 0.5 mg and the authors concluded that their treatment strategy was a feasible approach for those with DME.¹² The REACT (The Safety and Efficacy of Intravitreal Ranibizumab for Diabetic Macular Edema Previously Treated with Intravitreal Bevacizumab: A Randomized Dual-Arm Comparative Dosing Trial) trial, which studied patients with persistent DME that was refractory to bevacizumab, showed that patients improved similarly with either monthly or treat and extend regimens of ranibizumab.¹³ The Treat and Extend Protocol in Patients with Diabetic Macular Edema



Supplemental material available at www.AJO.com.

Accepted for publication Feb 6, 2019.

From the Palmetto Retina Center, West Columbia, South Carolina, USA (J.F.P., W.L.C.); Retina Consultants of Houston, Blanton Eye Institute, Houston Methodist Hospital, Houston, Texas, USA (C.C.W., D.M.B.); Emory University, Atlanta, Georgia, USA (B.B.B.); and the Retina-Vitreous Associates Medical Group, Los Angeles, California, USA (D.S.B.).

Inquiries to: John F. Payne, Palmetto Retina Center, 124 Sunset Ct, West Columbia, SC 29169 USA; e-mail: jpayne@palmettoretina.com

(TRES-DME), which used a unique treat and extend algorithm, was the first prospective, randomized, controlled trial using ranibizumab 0.3 mg (Lucentis 0.3 mg; Genentech, South San Francisco, California, USA) in a treat and extend fashion for DME.¹⁴ Through 1 year in TRES-DME, treat and extend dosing with and without navigated laser significantly decreased the number of injections given while providing similar visual and anatomic outcomes compared to monthly dosing.¹⁴ The purpose of this article is to investigate the long-term outcomes of treat and extend dosing of ranibizumab with and without navigated laser for DME in the TRES-DME trial.

METHODS

TRES-DME IS A PHASE I/II, MULTICENTER, RANDOMIZED, controlled clinical trial (US Food and Drug Administration Investigational New Drug 119146; ClinicalTrials.gov identifier NCT01934556).¹⁴ The study protocol and procedures were prospectively approved by a centralized institutional review board (Sterling IRB, Atlanta, Georgia, USA) and conducted at 3 sites in the United States. All study conduct adhered to the tenets of the Declaration of Helsinki and was in compliance with the Health Insurance Portability and Accountability Act. The TRES-DME study methods were previously reported.¹⁴ Briefly, subjects with center-involving DME and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) between 79–24 letters (20/25 to 20/320 Snellen equivalent) were randomized by a computer algorithm in a 1:2:2 fashion to receive either monthly dosing of ranibizumab 0.3 mg for 2 years (monthly cohort; n = 30) or a prespecified treat and extend dosing algorithm of ranibizumab 0.3 mg without navigated focal laser (TRES cohort; n = 60) or with navigated focal laser (GILA cohort; n = 60). Eyes were excluded if they had received previous intravitreal injections of anti-VEGF medications or corticosteroids within the previous 12 weeks or had any previous focal macular laser photocoagulation treatment.

All study eyes received 0.05-mL intravitreal injections of ranibizumab 0.3 mg administered monthly (28 ± 7 days) for 4 treatments, and those in the monthly cohort continued to receive monthly treatments throughout the first 2 years. At week 12, eyes in the TRES and GILA cohorts were eligible to enter the treat and extend dosing phase if the central retinal thickness (CRT) was ≤ 325 μm . The CRT was defined as the average retinal thickness of the central 1 mm around the fovea using Heidelberg Spectralis spectral-domain optical coherence tomography (SD-OCT; Heidelberg Engineering, Heidelberg, Germany). Eyes with CRT > 325 μm at week

12 continued monthly therapy until the CRT achieved was ≤ 325 μm . When the study eye entered the treat and extend phase (either at week 12 or when the CRT became ≤ 325 μm) the baseline CRT was recorded and used for treatment interval determination from that point forward. The treatment interval at each visit was extended by 2 weeks, maintained, or decreased by 2 weeks according to the CRT at that visit compared with baseline. [Supplemental Figure 1](#) graphically outlines the treat and extend algorithm used in TRES-DME (Supplemental Material available at [AJO.com](#)). The treatment interval was automatically reduced to 4 weeks if ≥ 15 letters were lost because of DME. Study eyes were not allowed to extend beyond 12 weeks in the first year of the study or beyond 16 weeks in the second year of the study.

Eyes in the GILA cohort also received angiography-guided macular laser photocoagulation on the 532-nm Navilas laser system (OD-OS GmbH, Teltow, Germany) at week 4 and again every 3 months if microaneurysm leakage was present on fluorescein angiography. All microaneurysms identified on the fluorescein angiogram were targeted using registered image overlays and the power level was titrated so that a faint grey burn was visible. Laser treatment was deferred if significant macular ischemia was present or if the leaking microaneurysms were within or at the edge of the foveal avascular zone.

The primary outcome measure was change in mean ETDRS BCVA from baseline. Secondary outcome measures included mean change in CRT, total number of intravitreal injections, percentage of patients gaining or losing 10 or 15 ETDRS letters at month 24, and the incidence and severity of ocular and nonocular adverse events. The total incidence of Anti-Platelet Trialists' Collaboration events was also measured.¹⁶

Description of the statistical computations, including power calculations, have been previously reported.¹⁴ Briefly, the intention to treat principle was used in all analyses. Statistical comparisons were performed with R software (version 3.5.1; R Project for Statistical Computing, [www.r-project.org](#)). Analysis of variance was used to compare continuous outcomes and the χ^2 or Fisher exact test, as appropriate, was used to compare categorical outcomes between the 3 arms of the study. For most analyses, if a subject's observation was missing the last observation was carried forward, except in the case of number of visits which was assumed to be worst case (every 4 weeks) for incompletely observed follow-up time. As a sensitivity analysis, multiple imputation using chained equations was carried out for missing ETDRS and SD-OCT measurements using a mixed effects linear model based on treatment visit week (random slope and intercept) with arm as a fixed effect. One hundred imputed datasets were created with 10 iterations each.

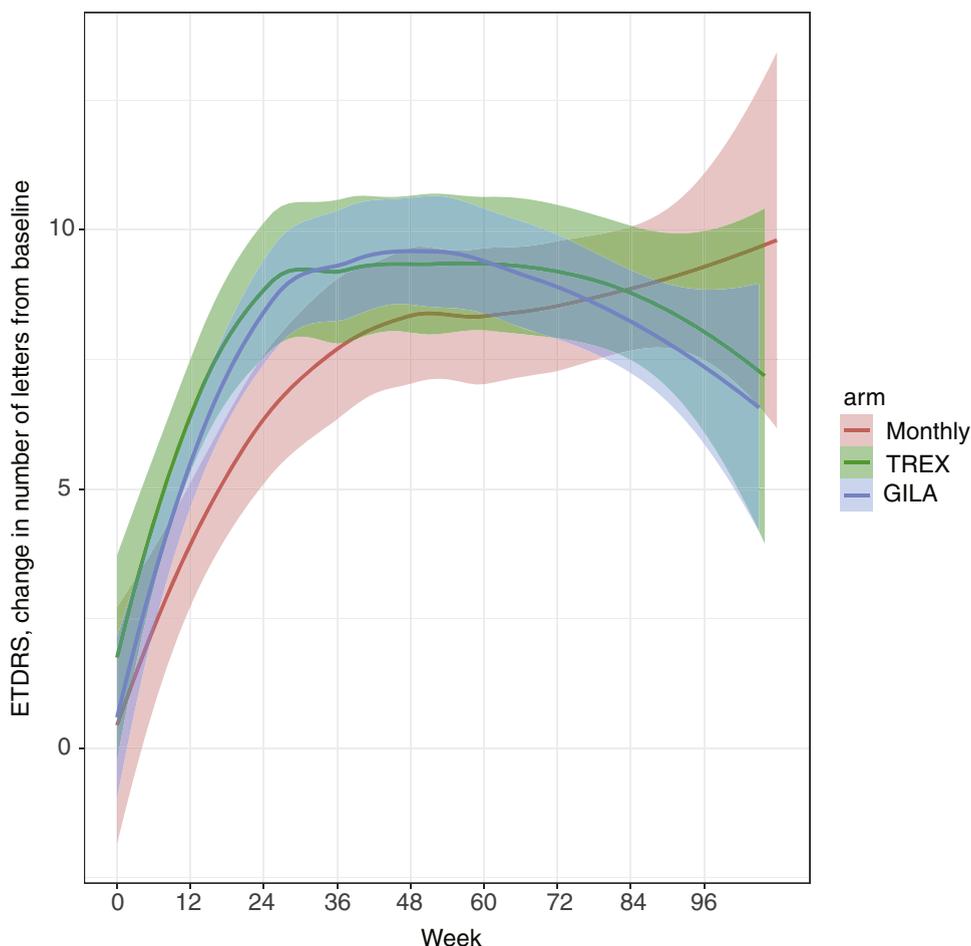


FIGURE 1. Locally weighted regression analysis for change in best-corrected visual acuity over time.

RESULTS

ONE HUNDRED FIFTY EYES WERE ENROLLED BETWEEN November 2013 and April 2015. Baseline demographics at screening were well balanced between the 3 cohorts.¹³ One hundred thirty-six eyes (91%) and 119 eyes (79%) completed the 1-year and 2-year endpoint visits, respectively. Supplemental Figure 2 shows a diagram of patient flow through the first 2 years of the study (Supplemental Material available at AJO.com). Sixteen subjects (21 eyes, 14%) were lost to follow-up and 2 subjects (2 eyes, 1%) withdrew consent before the 2-year endpoint. Baseline demographics were well balanced between the groups and previously reported.¹⁴

- **VISUAL ACUITY OUTCOMES:** Overall, the BCVA gains achieved at month 12 remained stable through the second year (Figure 1). At month 24, mean BCVA improved from baseline by 7.5, 9.6, and 9.0 letters in the monthly, TREX, and GILA cohorts, respectively ($P = .75$). Visual acuity gains were similar and there was no difference between the cohorts when multiple imputations were performed to

include eyes that did not reach the 2-year endpoint visit. Table shows a summary of the visual and anatomic outcomes as well as the number of injections per cohort. Figure 1 shows a locally weighted regression analysis for change in BCVA over time.

A similar number of eyes gained 1, 2, and 3 lines of vision in each of the 3 cohorts. Of those who reached the 2-year endpoint, 13 (52%) eyes in the monthly cohort, 28 (64%) eyes in the TREX cohort, and 32 (64%) eyes in the GILA cohort gained 1 line of vision. Similarly, 12 (48%) eyes in the monthly cohort, 19 (43%) eyes in the TREX cohort, and 22 (44%) eyes in the GILA cohort gained 2 lines of vision. Six (24%) eyes in the monthly cohort, 12 (27%) eyes in the TREX cohort, and 15 (30%) eyes in the GILA cohort gained 3 lines of vision. More eyes in the monthly cohort lost 1 and 2 lines of vision compared with the other 2 cohorts, but these numbers were small. Five (20%) eyes in the monthly cohort lost 1 line of vision compared with 1 (2%) eye in the TREX cohort and 3 (6%) eyes in the GILA cohort. Two (8%) eyes in the monthly cohort lost 2 lines of vision compared with 1 (2%) eye in the TREX cohort and no eyes in the GILA cohort. None

TABLE. Summary of Mean Visual and Anatomic Outcomes and the Number of Intravitreal Injections Given in the 3 Study Cohorts

	Cohort			P Value
	Monthly (n = 30)	TREX (n = 60)	GILA (n = 60)	
ETDRS BCVA at screening (Snellen equivalent)	65.1 (20/60)	64.1 (20/70)	65.1 (20/60)	.88
Change in ETDRS BCVA (letters)				
Month 12	8.6	9.6	9.5	.80
Month 24	7.5	9.6	9.0	.75
Month 24 (imputational analysis ^a)	8.6	10.3	10.1	.52
CRT at screening (μm)	434	475	480	.31
Change in CRT (μm)				
Month 12	-123	-146	-166	.47
Month 24	-139	-140	-175	.09
Month 24 (imputational analysis ^a)	-150	-159	-187	.30
No. of injections at month 12	13.1	10.7	10.1	<.001 ^b
No. of injections at month 24	24.7	18.9	17.5	<.001 ^c

BCVA = best-corrected visual acuity; CRT = central retinal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study.

^aImputational modeling to include those eyes which did not meet the specified endpoint.

^bP value was <.001 between the TREX and monthly cohorts and between the GILA and monthly cohorts. P value was 0.25 between the TREX and GILA cohorts.

^cP value was <.001 between the TREX and monthly cohorts and between the GILA and monthly cohorts. P value was .27 between the TREX and GILA cohorts.

of the study eyes lost 3 lines of vision at the 2-year endpoint.

The treatment interval in the TREX and GILA cohorts was automatically reduced to 4 weeks if the ETDRS BCVA decreased by ≥ 15 letters between visits. Eleven (18%) eyes in the TREX cohort and 7 (12%) eyes in the GILA cohort lost ≥ 15 letters at any point over the 2-year study period, compared with 1 eye (3%) in the monthly cohort. Of the 11 eyes in the TREX cohort that lost 15 letters at any time point, 8 eyes ultimately recovered vision to within 1 line of the vision before vision loss, and 3 eyes partially recovered vision but not to within 1 line. Of the 7 eyes in the GILA cohort, 6 eyes ultimately recovered vision to within 1 line of the vision before vision loss, and 1 eye partially recovered vision but not to within 1 line. The 1 eye in the monthly cohort recovered vision to within 1 line of the vision before vision loss at the next visit. Of the 4 eyes with persistent vision loss (3 eyes in the TREX cohort and 1 eye in the GILA cohort), 1 was caused by a macular hole. The other 3 patients missed their scheduled visit window and presented 2 weeks later than originally expected. All 3 experienced increased edema, were treated with ranibizumab per the study protocol, and exhibited partial visual recovery to within 2 lines of their preceding vision within 3 visits.

• **ANATOMIC OUTCOMES:** Anatomic improvements in each cohort seen at month 12 were maintained at month 24. At month 24, mean CRT decreased by 139, 140, and 175 μm compared with baseline in the monthly, TREX,

and GILA cohorts, respectively ($P = .09$). The results were similar when multiple imputation was performed to include those eyes not reaching the 2-year endpoint visit. Figure 2 shows a locally weighted regression analysis for change in CRT over time.

• **TREATMENT BURDEN:** Forty-nine (82%) of the eyes in the TREX cohort and 55 (92%) of the eyes in the GILA cohort were eligible for the treat and extend dosing phase by the 2-year endpoint. Of those reaching the 2-year endpoint, only 5 eyes (9%) in the TREX cohort and 3 eyes (5%) in the GILA cohort maintained a 4-week interval throughout the study. At month 12, the mean number of intravitreal injections administered was 13.1, 10.7, and 10.1 in the monthly, TREX, and GILA cohorts, respectively ($P < .001$ for TREX/monthly and GILA/monthly; $P = .25$ for TREX/GILA). In the second year of study, the mean number of injections was 11.6, 8.2, and 7.4 in the monthly, TREX, and GILA cohorts, respectively ($P < .001$ for TREX/monthly and GILA/monthly; $P = .322$ for TREX/GILA). In total, through 24 months, the mean number of intravitreal injections was 24.7, 18.9, and 17.5 in the monthly, TREX, GILA cohorts, respectively ($P < .001$ for TREX/monthly and GILA/monthly; $P = .27$ for TREX/GILA).

Figure 3 shows a locally weighted regression analysis for treatment interval over the first 2 years of study. The mean treatment interval was 4.3, 6.2, and 6.7 weeks in the monthly, TREX, and GILA cohorts, respectively ($P < .001$ for TREX/monthly and GILA/monthly;

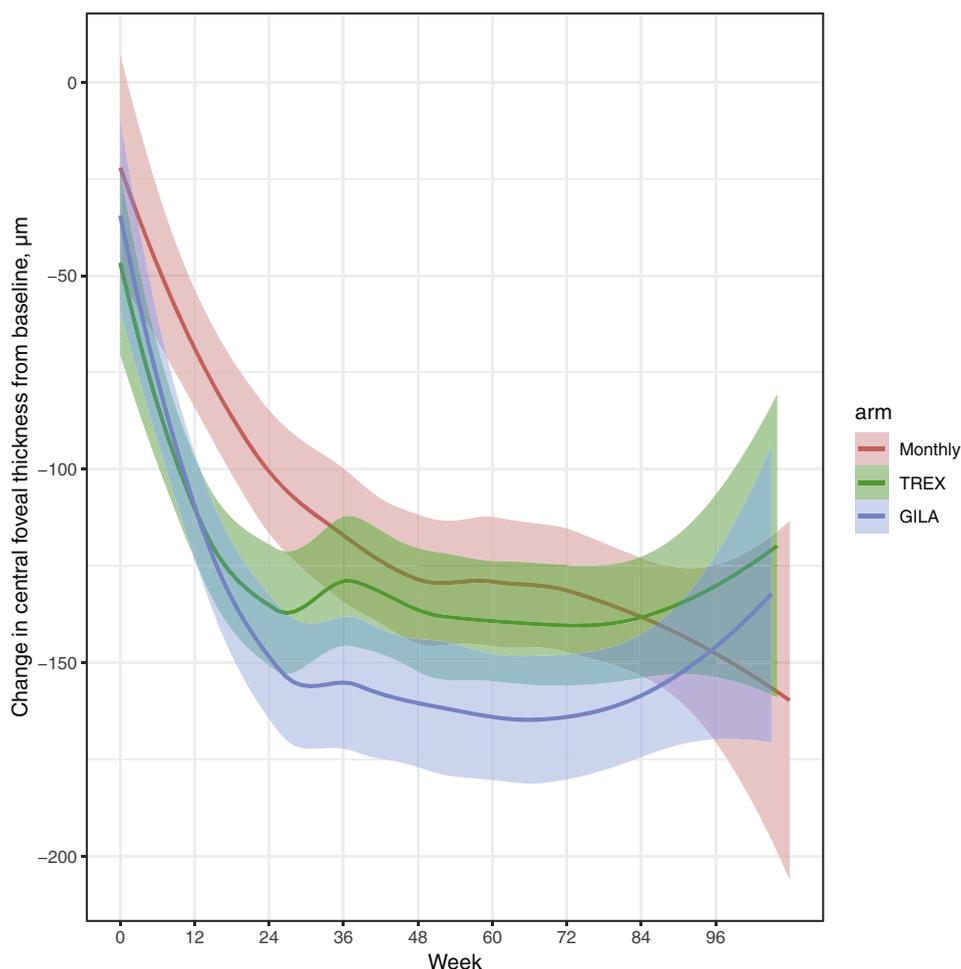


FIGURE 2. Locally weighted regression analysis for change in central retinal thickness over time.

$P = .31$ for TREX/GILA). The mean maximal interval achieved in the TREX cohort was 10.1 weeks compared with 11.1 weeks in the GILA cohort. Twenty-six (43%) of the TREX eyes and 29 (48%) of the GILA eyes were able to be extended to ≥ 12 weeks at any point over the 2-year study period.

A total of 175 and 117 navigated focal laser treatments were performed in the first and second years in the GILA cohort. The mean number of laser treatments per patient year in the GILA cohort was 3.1 and 1.9 in the first and second years of the study, respectively. The mean number of laser spots per laser treatment in the second year of the study was 44 (range 5–254 laser spots). The mean laser power was 77 mW (range 50–250 mW), and the mean laser duration was 93 ms (range 20–110 ms). The laser spot size was maintained at 100 μm for all laser sessions.

• **SAFETY DATA:** No new safety signals were identified. The most common ocular adverse events were eye discomfort or discharge, posterior vitreous detachment or vitreous floaters, and cataract progression. There were no cases of

endophthalmitis. The total 2-year incidence of Anti-Platelet Trialists' Collaboration events was 6.7%. There were 6 cases of acute myocardial infarction (4 in the TREX cohort and 2 in the GILA cohort) and 3 cases of acute cerebrovascular accident (1 in the TREX cohort, 1 in the GILA cohort, and 1 in the TREX/GILA cohorts). One patient died of unknown causes and was included as an Anti-Platelet Trialists' Collaboration event. Six subjects (8 eyes, 5%) died before reaching the 2-year endpoint visit, and 2 of these had both eyes enrolled in the study (1 subject in the monthly and GILA cohorts and 1 subject in the TREX and GILA cohorts). The remaining 4 deaths occurred in subjects who had 1 eye enrolled in the TREX cohort. One of the deaths was from unknown causes; none of the other deaths were considered to be related to study medication or study procedure. A complete list of the causes of death before the 2-year endpoint is shown in [Supplemental Table 1](#) (Supplemental Material available at [AJO.com](#)). A complete summary of the adverse events and serious adverse events over the first 2 years of the study

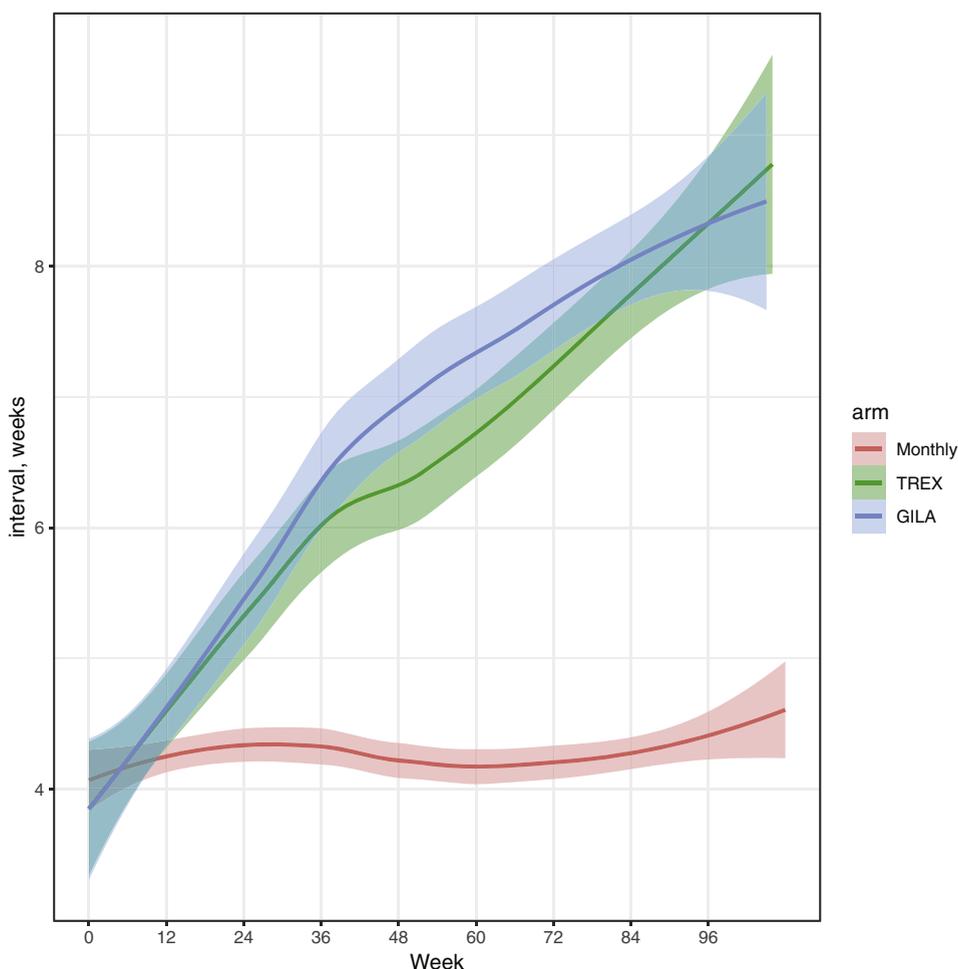


FIGURE 3. Locally weighted regression analysis for treatment interval over time.

are shown in Supplemental Tables 2 and 3, respectively (Supplemental Material available at AJO.com).

DISCUSSION

TREAT AND EXTEND DOSING HAS BEEN SHOWN TO BE A suitable approach for DME, neovascular age-related macular degeneration, and retinal vein occlusions with macular edema.¹⁷ A recent meta-analysis of the efficacy of treat and extend dosing described some of the advantages and disadvantages of a treat and extend approach compared with as-needed treatment.¹⁷ The advantages included fewer disease recurrences, better long-term visual outcomes and disease stability, fewer patient visits and lower costs, and a more predictable injection workload, while the disadvantages included the possibility for overtreatment, the inability to identify the patient who may remain stable without treatment, and limited evidence. TREX-DME, the first randomized clinical trial of ranibizumab 0.3 mg

for DME, demonstrated that the algorithm used resulted in significantly fewer injections and yielded visual and anatomic gains comparable to those obtained with monthly dosing at 2 years. In addition, TREX-DME found no value of laser supplementation of treat and extend ranibizumab treatment of DME. Treat and extend dosing reduced the number of ranibizumab injections from 25 to 18 over 2 years. The study power is low or moderate only, and while it may have missed an injection-reducing effect of laser, the effect is not likely to be of a clinically significant magnitude. The number of injections over 2 years is high compared with the Diabetic Retinopathy Clinical Research Network Protocol T study, where it was 12 for the ranibizumab cohort.

The 2-year TREX-DME results were similar to those of the RETAIN trial, which used ranibizumab 0.5 mg for DME.¹² The mean change in BCVA at month 24 in the RETAIN trial was +8.3 and +6.5 letters compared with +9.0 and +9.6 letters in TREX-DME. It should be noted that the treatment regimen in the RETAIN trial consisted of ≥ 3 monthly intravitreal injections until vision

stability was achieved and then subjects were extended by 4-week intervals as long as vision was maintained. Disease recurrence, which was defined as vision loss from disease activity as determined by the examining physician, triggered a return to monthly injections. Fewer injections were given with this approach (a mean of 12.4 and 12.8 in the treat and extend groups over 2 years) compared with the current trial. The algorithm in TREX-DME was more conservative, with the fewest number of injections allowed over the 2-year study period being 11. This conservative approach was chosen because of the lack of experience with treat and extend dosing for DME at the time of trial design.

The findings from TREX-DME were also comparable to those of the 1-year results from the REACT and EVADE clinical trials. The REACT trial assessed both monthly and treat and extend dosing of ranibizumab in eyes with bevacizumab-resistant DME.¹³ At month 12, the monthly cohort gained 2.7 letters after a mean of 10.9 injections compared with 8.4 letters after a mean of 9.6 injections in the treat and extend cohort. This study was somewhat limited by the small sample sizes ($n = 12$ and 15 eyes) and the 1-year follow-up. The EVADE trial, which used aflibercept and the same treat and extend algorithm as TREX-DME, demonstrated favorable visual outcomes in the treat and extend cohort (+12.5 letters with 10.1 injections) compared with the fixed interval cohort (+6.8 letters with 8.8 injections) at 1 year.¹⁵ Both of these trials are consistent with the findings of TREX-DME, that treat and extend dosing is a reasonable approach for DME.

While the mechanisms of action for focal laser photocoagulation are incompletely understood, it has been theorized that decreased edema may result from direct closure of leaking microaneurysms.¹⁸ Some investigators have suggested that photocoagulation decreases edema by reducing retinal tissue, leading to decreased retinal blood flow through alterations in autoregulation.^{19,20} Others have hypothesized that reduced retinal blood flow and edema is a result of improved oxygenation after laser treatment.²¹ The Diabetic Retinopathy Clinical Research concluded in their 5-year results of Protocol I that eyes receiving focal laser treatment required statistically significantly fewer intravitreal injections (median of 4 fewer injections) to achieve similar outcomes as those not receiving focal laser treatment for center-involved DME with vision impairment.⁵ A challenge in analyzing trials assessing focal laser therapy is that there is considerable difficulty in standardizing “adequate” focal laser burns. In TREX-DME, the Navilas laser system was chosen because it has been shown to be safe and accurate,^{22,23} because it offers the ability to potentially treat both visible microaneurysms and those only visualized on fluorescein angiography, and because the investigators believed there would be more

consistency of laser treatments across multiple clinical sites and investigators. Despite these perceived advantages, the addition of navigated laser to the TREX-DME protocol did not demonstrate a clinically meaningful reduction in the number of intravitreal injections administered or improve visual or anatomic outcomes. While the investigators aimed to keep the laser treatments standardized, it is possible that other factors, such as variations in photocoagulant effect, spot density, proximity to foveal avascular zone, and depth of coagulation influenced the results. Additional studies on the effects of these factors on disease control and visual function may be helpful. It should be noted that formal visual field analyses have not yet been completed for the TREX-DME cohorts.

Both TREX-DME and the RETAIN trial compared the efficacy of treat and extend regimens of intravitreal ranibizumab with and without focal laser treatment.^{12,14} However, there were some differences in the focal laser treatment protocols between these 2 trials. TREX-DME used the Navilas 532-nm navigated laser at month 1 and every 3 months if leaking microaneurysms were visible on fluorescein angiography, whereas the RETAIN trial used standard focal treatment on day 1 and additional treatments were left to the investigator's discretion. The mean number of laser treatments at month 24 was 1.2 in RETAIN vs 5.0 for TREX-DME. Despite the protocol differences, both clinical trials demonstrated similar visual and anatomic outcomes in the groups receiving focal laser treatment with a small numerical reduction in treatment burden of injections. This is in contrast to the study by Liegl and associates²⁴ that found a significant reduction in number of as-needed intravitreal injections after navigated laser treatment. In their study,²⁴ Liegl and associates used a navigated laser that was applied after 3 monthly anti-VEGF injections (compared with week 4 in the current study) and that resulted in a reduction in injection burden at 12 months from 3.9 in the monotherapy group to 0.9 in the combination anti-VEGF/laser group ($P < .001$). The reduction in injections was maintained over the 3-year follow-up period without a compromise in visual acuity.²⁵

In conclusion, the visual and anatomic gains seen at month 12 using the treat and extend algorithm in TREX-DME, both with and without navigated laser, were maintained through month 24. The addition of navigated laser to the treat and extend regimen of ranibizumab did not significantly improve visual or anatomic outcomes or significantly reduce treatment burden of intravitreal injections. The individualized strategy of treat and extend dosing in TREX-DME yielded comparable visual outcomes with significantly fewer injections and appears to be a reasonable approach for the treatment of center-involved DME with visual loss.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST. Financial Disclosures: J.F.P. has received grant support from Genentech/Roche, Regeneron, OD-OS, Clearside Biomedical, Iconic Pharmaceuticals, Jaeb Center for Health Research, National Eye Institute, Neurotech, Ophthotech, Ophthea, and Santen. C.C.W. has been a consultant for Alcon, Allergan, Alimera, Bayer, Clearside Biomedical, Dutch Ophthalmic Research Center, Genentech, Regeneron, and Roche; has received grant support from Alcon, Allergan, Clearside Biomedical, Genentech, Heidelberg, Novartis, Regeneron, and Roche; and has received lecture fees from Allergan, Bayer, and Regeneron. W.L.C. has been a consultant for Regeneron, Genentech/Roche, OHR, and Santen; has received grant support from Regeneron, Genentech/Roche, Ophthotech, and Santen; and has received lecture fees from Genentech/Roche and Regeneron. B.B.B. has been a consultant for Medimmune and The Data and Safety Monitoring Board service and has received grants from the National Eye Institute (P30-EY006360) and the National Institute of Neurological Disorders and Stroke (R01-NS089694). D.S.B. has been a consultant for Genentech, Optovue, Regeneron, Roche, Novartis, Alcon, Allergan, and Bayer and has received lecture fees from Allergan. D.M.B. has been a consultant for Adverum, Clearside Biomedical, Novartis, Bayer, Genentech, Heidelberg, Regeneron, Roche, Santen, Samsung, Senju, Optos, Zeiss, Ohr Pharmaceuticals, Regenxbio, Chengdukanghong Biotechnology, Apellis, and Stealth Biotherapeutics. Funding/Support: Publication of this article was supported by a research grant from Genentech (ML28724). The funding organizations had no role in the design or conduct of this research. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials. *Ophthalmology* 2013;120(10):2013–2022.
2. Boyer DS, Nguyen QD, Brown DM, Basu K, Ehrlich JS, RIDE and RISE Research Group. Outcomes with as-needed ranibizumab after initial monthly therapy: long-term outcomes of the phase III RIDE and RISE trials. *Ophthalmology* 2015;122(12):2504–2513.e1.
3. Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology* 2015;122(10):2044–2052.
4. Schmidt-Erfurth U, Lang GE, Holz FG, Schlingemann RO, Lanzetta P, Massin P, et al. Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. *Ophthalmology* 2014;121(5):1045–1053.
5. Elman MJ, Ayala A, Bressler NM, Browning D, Flaxel CJ, Glassman AR, et al. Intravitreal ranibizumab for diabetic macular edema with prompt vs deferred laser treatment: 5-year randomized trial results. *Ophthalmology* 2015;122(2):375–381.
6. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology* 2016;123(6):1351–1359.
7. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119(4):789–801.
8. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372(13):1193–1203.
9. Rezaei KA, Gomes AV, Loewenstein A, et al. Global Trends in Retina Survey. Chicago, IL: American Society of Retinal Specialists; 2015.
10. Wyckoff CC, Croft DE, Brown DM, Wang R, Payne JF, Clark L, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. *Ophthalmology* 2015;122(12):2514–2522.
11. Berg K, Pedersen TR, Sandvik L, Bragadóttir R. Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology* 2015;122(1):146–152.
12. Prunte C, Fajnkuchen F, Mahmood S, Ricci F, Hatz K, Studnička J, et al. Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema: the RETAIN study. *Br J Ophthalmol* 2016;100(6):787–795.
13. Ehlers JP, Wang K, Singh RP, Babiuch AS, Schachat AP, Yuan A, et al. A prospective randomized comparative dosing trial of ranibizumab in bevacizumab-resistant diabetic macular edema: the REACT study. *Ophthalmology Retina* 2018;2(3):217–224.
14. Payne JF, Wyckoff CC, Clark WL, Bruce BB, Boyer DS, Brown DM, et al. Randomized trial of treat and extend ranibizumab with and without navigated laser for diabetic macular edema: TREX-DME 1 year outcomes. *Ophthalmology* 2017;124(1):74–81.
15. Dhoot DS. Treat and extend versus bi-monthly dosing with aflibercept for the treatment of diabetic macular edema (EVADE study): year one analysis. In: Oral presentation at: American Society of Retina Specialists Annual Meeting; July 2018. Vancouver, Canada.
16. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308(6921):81–106.
17. Freund KB, Korobelnik JF, Devenyi R, Framme C, Galic J, Herbert E, et al. Treat and extend regimens with anti-VEGF in retinal diseases: a literature review and consensus recommendations. *Retina* 2015;35(8):1489–1506.
18. Shah AM, Bressler NM, Jampol LM. Does laser still have a role in the management of retinal vascular and neovascular diseases. *Am J Ophthalmol* 2011;152(3):332–339.
19. Wilson DJ, Finkelstein D, Quigley HA, Green WR. Macular grid photocoagulation: an experimental study on the primate retina. *Arch Ophthalmol* 1988;106(1):100–105.
20. Arnarsson A, Stefansson E. Laser treatment and the mechanism of edema reduction in branch retinal vein occlusion. *Invest Ophthalmol Vis Sci* 2000;41(3):877–879.

21. Ogata N, Ando A, Uyama M, Matsumura M. Expression of cytokines and transcription factors in photocoagulated human retinal pigment epithelial cells. *Graefes Arch Clin Exp Ophthalmol* 2001;239(2):87–95.
22. Kozak I, Oster SF, Cortes MA, Dowell D, Hartmann K, Kim JS, et al. Clinical evaluation and treatment accuracy in diabetic macular edema using navigated laser photocoagulator NAVILAS. *Ophthalmology* 2011;118(6):1119–1124.
23. Neubauer A, Langer J, Leigl R, Haritoglou C, Wolf A, Kozak I, et al. Navigated macular laser decreases retreatment rate for diabetic macular edema: a comparison with conventional macular laser. *Clin Ophthalmol* 2013;7:121–128.
24. Liegl R, Langer J, Seidensticker F, Reznicek L, Haritoglou C, Ulbig MW, et al. Comparative evaluation of combined navigated laser photocoagulation and intravitreal ranibizumab in the treatment of diabetic macular edema. *PLoS One* 2014;9(12):e113981.
25. Herold TR, Langer J, Vounotrypidis E, Kernt M, Liegl R, Priglinger SG. 3-year-data of combined navigated laser (Navilas) and intravitreal ranibizumab compared to ranibizumab monotherapy in DME patients. *PLoS One* 2018;13(8):e202483.

THE TREX-DME STUDY GROUP

Palmetto Retina Center: John F. Payne, W. Lloyd Clark, John A. Wells III, and David L. Johnson.

Retina Consultants of Houston: Charles C. Wykoff, David M. Brown, Matthew Benz, Eric Chen, Richard H. Fish, Rosa Y. Kim, James C. Major Jr, Ronan E.

O'Malley, Amy C. Scheffler, Ankoor R. Shah, and Tien P. Wong.

Retina-Vitreous Associates Medical Group: David S. Boyer, Roger L. Novack, Thomas G. Chu, Firas Rahhal, Homayoun Tabandeh, Richard H. Roe, Pouya N. Dayani, David Liao, Alexander Walsh, and Daniel D. Esmaili.