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Randomized Trial of Treat and Extend Ranibizumab with and without Navigated Laser for Diabetic Macular Edema

TREX-DME 1 Year Outcomes

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Purpose: To compare monthly dosing with a treat and extend algorithm using ranibizumab 0.3 mg with and without angiography-guided macular laser photocoagulation for center-involving diabetic macular edema (DME).

Design: Multicenter, prospective, randomized clinical trial.

Participants: A total of 150 eyes from 116 subjects were randomized into 3 cohorts: Monthly (n = 30), TReat and EXtend without macular laser photocoagulation (TREX; n = 60), and treat and extend with angiography-Gulded macular LAser photocoagulation (GILA; n = 60).

Methods: Monthly cohort eyes received ranibizumab 0.3 mg every 4 weeks. Eyes in the TREX and GILA cohorts received 4 monthly injections of ranibizumab 0.3 mg followed by a treat and extend algorithm based on disease activity. Eyes in the GILA cohort also received angiography-guided macular laser photocoagulation at month 1 and again every 3 months for microaneurysm leakage.

Main Outcome Measures: Change in mean best-corrected visual acuity (BCVA), mean central retinal thickness (CRT), number of injections from baseline to 1 year, and percentage gaining/losing 2 and 3 lines of vision.

Results: Baseline demographics were well balanced among the cohorts. A total of 137 eyes (91%) completed the 1-year end point visit. At 1 year, the mean BCVA improved by 8.6, 9.6, and 9.5 letters in the Monthly, TREX, and GILA cohorts, respectively ($P = 0.8$). There was no significant difference between the cohorts in the percentage gaining/losing 2 and 3 lines of vision. The CRT improved by 123 μm, 146 μm, and 166 μm in the Monthly, TREX, and GILA cohorts, respectively ($P = 0.47$). The mean number of macular laser treatments in the GILA cohort at 1 year was 2.9 (range, 1–4). The number of injections was significantly reduced in both the TREX (10.7) and GILA (10.1) cohorts compared with the Monthly cohort (13.1, $P < 0.001$). There were no cases of endophthalmitis, and the total incidence of Anti-Platelet Trialists' Collaboration events was 4.7%.

Conclusions: This prospective, randomized trial found that treat and extend dosing of ranibizumab 0.3 mg with and without angiography-guided macular laser photocoagulation significantly decreased the number of injections given while providing similar visual and anatomic outcomes compared with monthly dosing at 1 year. Adding angiography-guided laser photocoagulation to this dosing algorithm did not significantly improve outcomes at 1 year. *Ophthalmology 2016;■:1–8 © 2016 by the American Academy of Ophthalmology*

Supplemental material is available at www.aaojournal.org.

The RIDE/RISE phase III clinical trials demonstrated the safety, effectiveness, and superiority of monthly ranibizumab (Lucentis 0.3 mg; Genentech, South San Francisco, CA) over sham injections with as-needed conventional focal laser photocoagulation for the treatment of center-involving diabetic macular edema (DME) causing visual acuity loss.[1] Although the most robust visual outcomes have been achieved with consistent monthly dosing, less frequent dosing has been shown to effectively reduce retinal thickness and improve vision.[2–5] Treat and extend dosing allows for incremental increases in treatment intervals with the aim of identifying the longest possible interval without disease recurrence.[6] The current study is the first prospective, randomized, controlled trial using ranibizumab 0.3 mg in a treat and extend fashion for DME. The primary purpose of this trial was to compare the efficacy of a treat and extend dosing algorithm, with and without angiography-guided focal laser treatment, with monthly dosing for center-involved DME.

There continues to be a debate on the role of focal laser therapy for center-involving DME in the setting of consistent vascular endothelial growth factor (VEGF) blockade. The

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Diabetic Retinopathy Clinical Research Network showed that at 5 years, focal/grid laser treatment at the initiation of ranibizumab is no better than deferred laser treatment for at least 6 months in eyes with center-involving DME.[4] Recent advances in computer-assisted tracking systems have enabled the development of a computer-guided laser targeting device. The navigated laser photocoagulator, also known as the NAVILAS laser system (OD-OS GmbH, Teltow, Germany), has been shown to be more accurate and provide better visual gains compared with conventional focal laser therapy.[7,8] A secondary objective of this study was to assess whether angiography-guided focal laser treatment with the NAVILAS laser system can effectively decrease the treatment burden of ranibizumab for DME.

Methods

The Treat and Extend Protocol in Patients with Diabetic Macular Edema (TREX-DME) is a phase I/II, multicenter, randomized, controlled clinical trial. The protocol was registered at www.clinicaltrials.gov (NCT01934556). The study protocol and procedures were approved by a centralized institutional review board and conducted at Palmetto Retina Center (West Columbia, SC), Retina Consultants of Houston (Houston, TX), and Retina-Vitreous Associates Medical Group (Los Angeles, CA). All study conduct adhered to the tenets of the Declaration of Helsinki and was in compliance with the Health Insurance Portability and Accountability Act. Written informed consent was obtained for each subject at the time of screening. Inclusion criteria consisted of subjects with diabetes mellitus and center-involving DME with Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) between 79 and 24 letters (20/25−20/320 Snellen equivalent). Eyes with prior intravitreal injections of anti-VEGF medications or corticosteroids within the previous 12 weeks and eyes with prior focal macular laser photocoagulation treatment were excluded from study participation.

At enrollment, eyes were randomized with a computer program in a 1:2:2 fashion into 1 of 3 cohorts: Monthly cohort (Monthly; 30 eyes); TReat and EXtend without macular laser photocoagulation (TREX; 60 eyes); and treat and extend with angiography-GuIded macular LAser photocoagulation (GILA; 60 eyes). If both eyes of a subject were enrolled, the eyes were randomized to different treatment groups. At all visits, subjects underwent ETDRS BCVA testing at 4 m, slit-lamp and dilated ophthalmic examination, and spectral-domain optical coherence tomography (SD OCT) imaging using the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). The SD OCT segmentations were image-tracked using Heidelberg Spectralis volume scans (20×20, 49 lines, 768 A-scans per line) with 9-times image averaging. The central retinal thickness (CRT), which is the average retinal thickness of the central 1 mm around the fovea, was used for treatment interval determinations in the TREX and GILA cohorts. Fluorescein angiography, using the Heidelberg Spectralis fundus camera or NAVILAS laser system, was performed at screening, year 1, and year 2, as well as when indicated for the angiography-guided laser treatment in the GILA cohort.

All study eyes received 0.05 ml intravitreal injections of ranibizumab 0.3 mg administered monthly (28±7 days) for 4 treatments. Eyes in the Monthly cohort continued to receive monthly treatments throughout the first 2 years. At week 12, eyes in the TREX and GILA cohorts that had a CRT ≤325 μm began a treat and extend dosing algorithm based on anatomic disease activity. Eyes with a CRT >325 μm at week 12 continued to receive monthly treatments until the CRT achieved was 325 μm or less. At that time, those eyes began the treat and extend dosing strategy.

Figure 1 outlines the treat and extend dosing algorithm used to determine treatment intervals for the TREX and GILA cohorts. When the study eye entered the treat and extend phase (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. Of note, a new baseline CRT was established if the retinal thickness had improved by >20% from baseline for 3 consecutive visits and there was <50 μm of variability among those 3 visits. The treatment interval was automatically reduced to 4 weeks if ≥15 letters were lost because of DME. Study eyes were not allowed to extend treatment beyond 12 weeks in the first year of the study.

Eyes in the GILA cohort also received angiography-guided macular laser photocoagulation on the 532 nm NAVILAS laser system 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. The spot size was maintained at 100 μm in all eyes, but the laser power and duration were left to the investigator's discretion. Laser treatment was deferred if significant macular ischemia was present or the leaking microaneurysms were within or at the edge of the foveal avascular zone.

For intravitreal ranibizumab injections, topical anesthetic with proparacaine 0.5% ophthalmic solution, tetracaine 0.5% ophthalmic solution, or lidocaine 3.5% ophthalmic gel was instilled in the eye on the ocular surface. The periocular skin, eyelids, and eyelashes were disinfected with 10% povidone-iodine swabs, and 5% povidone-iodine ophthalmic solution was applied to the ocular surface. After intravitreal injection, finger-counting testing was performed to confirm central retina artery perfusion, and intraocular pressure was measured within 30 minutes (±15 minutes) of injection.

The primary outcome measure was change in mean ETDRS BCVA from baseline. Secondary outcome measures included the mean change in CRT, total number of intravitreal injections, percentage of patients gaining or losing 10 or 15 ETDRS letters at month 12, and incidence and severity of ocular and nonocular adverse events. The total incidence of Anti-Platelet Trialists' Collaboration events also was measured.[9]

A sample size of 30 eyes in the Monthly cohort and 60 eyes in the TREX and GILA cohorts had >80% power to detect a 9-letter difference between any of the cohorts on the basis of a 2-sided family-wise significance of 0.05 divided evenly among 3 two-sample t tests (significant level 0.0167), assuming a standard deviation of 11 letters. The intention-to-treat principle was used in all analyses. Statistical comparisons were performed with R version 3.2.4 (R Project for Statistical Computing, www.r-project.org). Analysis of variance was used to compare continuous outcomes, and the chi-square or Fisher exact test, as appropriate, was used to compare categoric outcomes among 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 the 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.