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Scatter Photocoagulation Does Not Reduce Macular Edema or Treatment Burden in Patients with Retinal Vein Occlusion

The RELATE Trial

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Purpose: To determine whether scatter and grid laser photocoagulation (laser) adds benefit to ranibizumab injections in patients with macular edema from retinal vein occlusion (RVO) and to compare 0.5-mg with 2.0-mg ranibizumab.

Design: Randomized, double-masked, controlled clinical trial.

Participants: Thirty-nine patients with central RVO (CRVO) and 42 with branch RVO (BRVO).

Methods: Subjects were randomized to 0.5 mg or 2.0 mg ranibizumab every 4 weeks for 24 weeks and re-randomized to pro re nata ranibizumab plus laser or ranibizumab alone.

Main Outcome Measures: Mean change from baseline best-corrected visual acuity (BCVA) at week 24 for BCVA at weeks 48, 96, and 144 for second randomization.

Results: Mean improvement from baseline BCVA at week 24 was 15.5 and 15.8 letters in the 0.5-mg and 2.0-mg CRVO groups, and 12.1 and 14.6 letters in the 0.5-mg and 2.0-mg BRVO groups. For CRVO, but not BRVO, there was significantly greater reduction from baseline mean central subfield thickness (CST) in the 2.0-mg versus 0.5-mg group (396.1 vs. 253.5 μm; $P = 0.03$). For the second randomization in CRVO patients, there was no significant difference from week 24 BCVA in the ranibizumab plus laser versus the ranibizumab only groups at week 48 (−3.3 vs. 0.0 letters), week 96 (+0.69 vs. −1.6 letters), or week 144 (+0.4 vs. −6.7 letters), and a significant increase from week 24 mean CST at week 48 (+94.7 vs. +15.2 μm; $P = 0.05$) but not weeks 96 or 144. For BRVO, there was a significant reduction from week 24 mean BCVA in ranibizumab plus laser versus ranibizumab at week 48 (−7.5 vs. +2.8; $P < 0.01$) and week 96 (−2.0 vs. +4.8; $P < 0.03$), but not week 144, and there were no differences in mean CST change from week 24 at weeks 48, 96, or 144. Laser failed to increase edema resolution or to reduce the ranibizumab injections between weeks 24 and 144.

Conclusions: In patients with macular edema resulting from RVO, there was no short-term clinically significant benefit from monthly injections of 2.0-mg versus 0.5-mg ranibizumab injections and no long-term benefit in BCVA, resolution of edema, or number of ranibizumab injections obtained by addition of laser treatment to ranibizumab. *Ophthalmology 2015;■:1−12 © 2015 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Central retinal vein occlusions (CRVOs) occur as a result of thrombosis of the main outflow vessel of the eye and result in retinal hemorrhages, cotton wool patches, and variable amounts of retinal nonperfusion throughout the retina. Branch retinal vein occlusions (BRVOs) occur as a result of thrombosis of a branch of the central retinal vein resulting in similar findings throughout the portion of the retina drained by the occluded vessel. The predominant cause of vision loss acutely in patients with CRVO or BRVO is macular edema. Although there is much that we do not understand regarding the pathogenesis of CRVOs and BRVOs, it is well established that vascular endothelial growth factor (VEGF) is an important contributor to macular edema.[1−3] In fact, although suppression of VEGF is highly effective in the treatment of neovascular age-related macular degeneration (AMD)[4,5] and diabetic macular edema,[6−8] effectiveness is probably greatest in patients with macular edema resulting from retinal vein occlusion (RVO) early in the course after occlusion.[1−3] In patients with CRVO, the mean improvement from baseline

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best-corrected visual acuity (BCVA) was 12.7 and 14.9 letters, respectively, after monthly injections of 0.3 mg or 0.5 mg ranibizumab for 6 months,[3] and in 2 independent studies in which 2.0 mg aflibercept was injected monthly for 6 months, it was 17.3 and 18.0 letters, respectively.[9,10] In patients with BRVO, the mean improvement from baseline BCVA was 16.6 and 18.3 letters, respectively, after monthly injections of 0.3 mg or 0.5 mg ranibizumab for 6 months[2] and 17.0 letters after monthly injections of 2.0 mg aflibercept for 6 months.[11] An important unanswered question is whether injections of 2.0 mg ranibizumab provide greater benefit than injection of 0.5 mg ranibizumab.

Initially, it was believed that intraocular injections of VEGF antagonists would be needed in patients with RVO for only a relatively short period until recanalization or collateral formation eliminated the need for treatment; however, long-term follow-up demonstrated that this was not the case.[12–14] In the RETAIN study (Extended follow-up of patients with macular edema due to b***R***anch r***ET***inal vein occlusion or centr***A***l retinal ve***I***n occlusio***N*** previously treated with intravitreal ranibizumab), with a mean follow up of 49 months, 14 of 32 CRVO patients (44%) and 17 of 34 BRVO patients (50%) had edema resolution and no longer required ranibizumab injections.[14] The vein occlusion is merely the initiating event that causes retinal ischemia and high levels of VEGF, and the high levels of VEGF cause additional capillary closure and worsening ischemia, resulting in a positive feedback loop and disease worsening over time in some patients.[15,16] Scatter photocoagulation reduces retinal ischemia, suggesting that it may provide a way to interrupt the positive feedback loop in patients with RVO and reduce the need for injections of a VEGF antagonist. In this study, we addressed 2 experimental questions: (1) whether injections of 2.0 mg ranibizumab provide greater short-term benefit than injections of 0.5 mg ranibizumab in patients with macular edema resulting from RVO; and (2) whether scatter photocoagulation promotes resolution of macular edema, reduces the need for VEGF antagonists, and improves outcomes in patients with RVO.

Methods

The Ranibizumab Dose Comparison (0.5 mg and 2.0 mg) and the Role of Laser in the Management of Retinal Vein Occlusion (RELATE; ClinicalTrials.gov identifier, NCT01003106) was an investigator-initiated, double-masked, randomized trial sponsored by Genentech, Inc. (South San Francisco, CA), was designed to compare the effects of monthly injections of 0.5 mg ranibizumab with monthly injections of 2.0 mg ranibizumab for 24 weeks in patients with macular edema resulting from RVO and also to determine whether scatter and grid laser photocoagulation (laser treatment) reduces the need for injections and improves long-term outcomes. To address these 2 independent study questions, there were 2 randomizations: 1 at baseline and 1 at week 24 (Fig 1, available at www.aaojournal.org). Eighty-one patients with RVO (39 with CRVO and 42 with BRVO) were enrolled at a single center (The Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, MD) and were randomized to receive injections of 0.5 mg or 2.0 mg ranibizumab at baseline, with primary end point at 24 weeks when patients were re-randomized to pro re nata (PRN) arms: ranibizumab plus laser or ranibizumab only for recurrent macular edema resulting from RVO. The study was conducted in accordance with the Declaration of Helsinki, applicable United States Food and Drug Administration regulations, and the Health Insurance Portability and Accountability Act. The study protocol was approved by the Johns Hopkins University Institutional Review Board before study initiation, and all participating patients provided informed consent.

Patient Eligibility and Exclusion Criteria

Eligible patients were aged 18 years or older, had BCVA of 20/40 to 20/200, and had central subfield thickness (CST) of 250 μm or more measured by time-domain optical coherence tomography (OCT) using a StratusOCT3 device (Carl Zeiss Meditec, Dublin, CA) in the study eye because of macular edema resulting from RVO and no other cause. Patients were excluded if they had an anti-VEGF injection within 1 month, an intraocular steroid injection within 4 months, or ocular surgery within 3 months.

Randomizations

The study was powered to detect a difference in BCVA of 5 letters or more between RVO patients treated with laser plus ranibizumab versus ranibizumab alone with a probability of 95% or more, and it was determined that the same number of patients would allow detection of a difference of 5 letters or more in BCVA between RVO patients treated with 2.0 mg versus 0.5 mg ranibizumab at 6 months with a probability of 95% or more. Patients were randomized to receive injections of 0.5 mg ranibizumab (22 with BRVO, 19 with CRVO) or 2.0 mg ranibizumab (20 with BRVO and 20 with CRVO) at baseline and weeks 4, 8, 12, 16, and 20. The random allocation sequence was generated using Windows (Microsoft, Inc., Redmond, WA) version 5.0 of block randomization software; the program generated block-stratified assignments with user-selected block size. The pseudorandom number generator is a linear congruent algorithm of Park and Miller with Bays-Durham shuffling. It has a period of more than 2 billion. For the first randomization, the block size was 2, 4, and 8. At week 24, the patients were re-randomized into the laser plus ranibizumab versus ranibizumab only group with a block size of 2, 2, and 2. Treatment groups were double masked until week 24, with patients, care providers, and those assessing outcomes all masked to ranibizumab dose. The only unmasked member of the study team was responsible for enrolling and assigning participants to interventions. After week 24, the patients and investigators were not masked with regard to the second randomization group, but visual acuity examiners remained masked.

Study Protocol

At each study visit, BCVA was measured by Early Treatment Diabetic Retinopathy Study protocol,[17] and whereas time-domain OCT was used for eligibility to ensure comparability with prior studies, spectral-domain OCT was carried out with the Spectralis device (Heidelberg Engineering, Inc., Heidelberg, Germany) for outcome analysis. The primary outcome was the mean change from baseline BCVA letter score at week 24. Secondary outcomes were the percentage of patients with letter score improvement of 15 or more and mean improvement in CST.

At week 24, patients were re-randomized to ranibizumab plus laser or ranibizumab alone. In each group, patients received an injection of their originally assigned dose of ranibizumab at each study visit at which there was foveal thickening, intraretinal or subretinal fluid in the macula, or both thickening and fluid.