American Academy of Ophthalmology
The Eye M.D. Association

Stereotactic Radiotherapy for Neovascular Age-Related Macular Degeneration

Year 2 Results of the INTREPID Study

*Timothy L. Jackson, PhD, FRCOphth,[1] Usha Chakravarthy, MD, PhD,[2] Jason S. Slakter, MD,[3] Alyson Muldrew, PhD,[4] E. Mark Shusterman, MD,[5] Denis O'Shaughnessy, PhD,[5] Mark Arnoldussen, PhD,[5] Michael E. Gertner, MD,[6] Linda Danielson, MSc,[7] Darius M. Moshfeghi, MD,[8] on behalf of the INTREPID Study Group**

Purpose: To determine the safety and efficacy of low-voltage, external-beam, stereotactic radiotherapy (SRT) for patients with neovascular age-related macular degeneration (AMD).

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

Participants: A total of 230 participants with neovascular AMD who received ≥3 ranibizumab or bevacizumab injections within the preceding year and requiring treatment at enrollment.

Methods: Participants received 16 Gray, 24 Gray, or sham SRT. All arms received pro re nata (PRN) ranibizumab for 12 months, with PRN bevacizumab or ranibizumab thereafter.

Main Outcome Measures: Mean number of PRN injections; best-corrected visual acuity (BCVA); loss of <15 Early Treatment of Diabetic Retinopathy Study letters; change in optical coherence tomography central subfield thickness; and change in angiographic total lesion area and choroidal neovascularization (CNV) area.

Results: At year 2, the 16 and 24 Gray arms received fewer PRN treatments compared with sham (mean 4.5, $P = 0.008$; mean 5.4, $P = 0.09$; and mean 6.6, respectively). Change in mean BCVA was −10.0, −7.5, and −6.7 letters for the 16 Gray, 24 Gray, and sham arms, respectively, with 46 (68%), 51 (75%), and 58 participants (79%), respectively, losing <15 letters. Mean central subfield thickness decreased by 67.0 μm, 55.4 μm, and 33.3 μm, respectively. Mean total active lesion area increased by 1.0, 4.2, and 2.7 mm^2, respectively. Mean CNV area decreased by 0.1 mm^2 in all groups. An independent reading center detected microvascular abnormalities in 6 control eyes and 29 SRT eyes, of which 18 were attributed to radiation; however, only 2 of these possibly affected vision. An exploratory subgroup analysis found that lesions with a greatest linear dimension ≤4 mm (the size of the treatment zone) and a macular volume greater than the median (7.4 mm^3) were more responsive to SRT, with 3.9 PRN injections versus 7.1 in comparable sham-treated participants ($P = 0.001$) and mean BCVA 4.4 letters superior to sham ($P = 0.24$).

Conclusions: A single dose of SRT significantly reduces intravitreal injections over 2 years. Radiation can induce microvascular change, but in only 1% of eyes does this possibly affect vision. The best response occurs when AMD lesions fit within the treatment zone and they are actively leaking. *Ophthalmology 2015;122:138-145 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Neovascular age-related macular degeneration (AMD) is a leading cause of blindness in the developed world, with some studies finding that dry and neovascular AMD together account for more blind registrations than all other eye diseases combined.[1–4] The standard of care for neovascular AMD involves intravitreal injections of drugs targeting vascular endothelial growth factor (VEGF), but for most patients this necessitates ongoing hospital review and repeated intravitreal injections.[5,6]

Radiation has been investigated as an alternative treatment option,[7] but recent studies present apparently conflicting results.[8–13] The Choroidal Neovascularization Secondary to AMD Treated with Beta Radiation Epiretinal Therapy (CABERNET) trial was a pivotal randomized controlled trial (RCT) of epimacular brachytherapy (EMB) used for treatment-naïve neovascular AMD.[9,12] Those in the radiation arm received 24 Gray of EMB delivered via a pars plana vitrectomy using an endoscopic probe held over the macula for approximately 3 to 4 minutes. The trial failed to meet either of its co-primary 2-year end points.[12]

By contrast, the IRay in Conjunction with Anti-VEGF Treatment for Patients with Wet AMD (INTREPID) RCT met its primary end point, showing a statistically significant, one-third reduction in anti-VEGF injections at 1 year

http://dx.doi.org/10.1016/j.ophtha.2014.07.043
ISSN 0161-6420/14

after stereotactic radiotherapy (SRT).[13] The trial recruited 230 participants with previously treated neovascular AMD who had already received at least 3 anti-VEGF injections in the preceding year and had an ongoing need for anti-VEGF therapy at enrollment. Stereotactic radiotherapy is a nonsurgical procedure undertaken in an office setting, using a robotically controlled device that delivers 3 beams of radiation through the inferior sclera to overlap at the macula (Fig 1, available at www.aaojournal.org).[14] The eye was held in position using a suction-coupled contact lens; eye tracking software suspended treatment if the eye moved out of alignment. Typical total procedure time was less than 20 minutes, with less than 4 minutes of X-ray delivery. In participants whose AMD lesions were ≤4 mm (the size of the treatment zone), and who had notable fluid leakage at the time of treatment, there was a highly significant 55% reduction in anti-VEGF retreatment and visual acuity (VA) that was significantly superior (5.3-letter difference) to sham.[15] No significant safety concerns were identified.[13]

Although the year 1 results of INTREPID were encouraging, they were not sufficient to establish the safety of SRT. In particular, radiation retinopathy may occur after 1 year, thus necessitating longer surveillance. In the CABERNET study of EMB, 10 cases (3%) developed radiation retinopathy, and 8 of these occurred in the second year.[9,12] In another study of 53 participants treated with EMB, no cases of radiation retinopathy were observed in the first year, but 1 case (2%) emerged in the second year.[8,10,11] Therefore, the second year results of INTREPID provide valuable information regarding the longer-term effects of SRT, because there is a higher likelihood of detecting microvascular abnormalities (MVAs) than in year 1. Furthermore, year 2 results help establish the durability of the treatment effect. This article details the 2-year outcome of the INTREPID study, presented on behalf of the INTREPID study group (Appendix 1, available at www.aaojournal.org).

Methods

Study Design

Details of the INTREPID study have been reported.[13] Briefly, 230 participants with neovascular AMD already receiving anti-VEGF therapy were recruited into a randomized, double-masked, sham-controlled clinical trial, across 21 European sites (Clinical Trial Registration at www.clinicaltrials.gov, identifier: NCT01016873; accessed October 17, 2013). To be eligible, participants had to have neovascular AMD that was treated with at least 3 intravitreal anti-VEGF injections in the year before enrollment and to have required additional anti-VEGF treatment at the time of enrollment. The choroidal neovascularization (CNV) complex was limited to <12 disc areas, with the greatest linear dimension ≤6 mm, and the distance from the center of the fovea to the farthest point on the CNV lesion perimeter ≤3 mm. Full inclusion and exclusion criteria are listed in Appendix 2 (available at www.aaojournal.org). Institutional review board/research ethics committee approval was received for all sites, all participants provided written informed consent, and the trial complied with the tenets of the Declaration of Helsinki.

Study Treatment

Participants were randomized to 16 Gray (n = 75) or 24 Gray (n = 75) SRT, or sham SRT (n = 80), using a CE-marked, low-voltage, X-ray–based system (Oraya Therapeutics, Newark, CA). They received a baseline injection of ranibizumab alongside SRT, and thereafter attended every 4 weeks for 1 year for Early Treatment of Diabetic Retinopathy Study (ETDRS) refraction and determination of best-corrected VA (BCVA), slit-lamp biomicroscopy, dilated fundus examination, and time-domain optical coherence tomography (Stratus OCT, Carl Zeiss Meditec, Dublin, CA). Participants were retreated with monthly pro re nata (PRN) intravitreal 0.5 mg ranibizumab (Lucentis, Genentech, South San Francisco, CA) if they met predefined retreatment criteria, including any of the following: a 100-μm increase in central subfield thickness from the lowest previous OCT measurement; new or increased macular hemorrhage documented by fundus photographs; or a >5 letter decrease in BCVA since the last visit or the baseline BCVA, with disease activity such as persistent or increased fluid on OCT or leakage on fluorescein angiography (FA). After the first year of protocol-mandated follow-up and treatment, participants reverted to their standard care, with the criteria for retreatment determined by the attending clinician. Participants returned for mandated study safety visits at 18 and 24 months (with a further safety visit planned for 36 months). At the month 24 visit, participants underwent full ophthalmic examination, ETDRS BCVA, OCT, fundus photography, and FA using trial-certified equipment and staff. Images were assessed by the same independent reading center.

Outcome Measures

The primary outcome was the number of PRN ranibizumab injections administered over 52 weeks. Year 1 secondary outcomes included the change in mean BCVA; the proportion of participants losing <15 letters, gaining ≥0 letters, and gaining ≥15 letters; and the change in mean total lesion area and mean CNV area based on fundus photographs and FA, assessed by a masked, independent reading center.[13] These outcomes were also assessed at year 2. In addition, the reading center assessed the change in OCT central subfield thickness at 1 and 2 years. Safety outcomes included adverse events (AEs) and serious AEs. The reading center specifically examined for any MVAs that might be due to radiation. To increase the likelihood of detecting radiation-induced changes, the graders reported all MVAs even if these were within the area occupied by the neovascular lesion and therefore might be due to AMD rather than radiation. Graders were masked to study arm and timing (before or after baseline treatment/sham).

Subgroup Analysis

An exploratory subgroup analysis was conducted to determine which baseline variables influence the response to SRT. A prior analysis of the year 1 data showed that lesions that could fit within the 4-mm treatment zone responded better than lesions extending beyond the zone, as were lesions with significant macular fluid at the time of treatment.[15] These analyses were repeated at year 2. Group definitions were lesions ≤4 mm in greatest linear dimension versus those >4 mm, and lesions with an OCT macular volume greater than the median value of 7.4 mm^3 versus lesions ≤7.4 mm^3. The greatest linear dimension and macular volume were determined by the reading center. Several other subgroup analyses were undertaken to determine which variables influence the response to SRT, as undertaken at year 1.[15]