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Subthreshold Nanosecond Laser Intervention in Intermediate Age-Related Macular Degeneration

Study Design and Baseline Characteristics of the Laser in Early Stages of Age-Related Macular Degeneration Study (Report Number 1)

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Purpose: The Laser Intervention in Early Stages of Age-Related Macular Degeneration (LEAD) study is an investigation of the safety and efficacy of subthreshold nanosecond laser treatment to slow the progression of intermediate age-related macular degeneration (AMD). This report presents the novel study design and baseline characteristics.

Design: Multicenter, double-masked, randomized controlled, medical device feasibility clinical trial.

Participants: Persons with bilateral drusen >125 μm within 1500 μm of the fovea, monocular best-corrected visual acuity (BCVA) ≥20/40, and microperimetric retinal sensitivity of <25 decibels (dB) in at least 1 location within central 6° in 1 eye. Signs of late AMD; choroidal neovascularization or geographic atrophy, or anatomic end points defined on multimodal imaging (MMI) as fundus autofluorescence-defined atrophy, spectral-domain optical coherence tomography (SD-OCT)–defined atrophy, or nascent GA excluded participation.

Methods: Participants were randomized to nanosecond or sham laser treatment. Twelve laser or sham spots are applied to the macular region of the study eye. Participants are reviewed in visits every 6 months with functional testing and MMI for 36 months and are re-treated at each visit (until 30 months) if an end point is not reached in the study eye.

Main Outcome Measures: Progression to late AMD or MMI-defined anatomic end points in the study eye.

Results: A total of 292 participants across 6 centers were enrolled, with 145 participants randomized to arm 1 and 147 participants randomized to arm 2. Population characteristics at baseline were as follows: median age 70 years, 73% female, 90% Anglo-Saxon, and 3% current smokers. Baseline ocular characteristics of the study eyes were BCVA of 83 letters (20/25); low luminance visual acuity (LLVA) of 68 letters (20/50); hyperpigmentation, 33%; reticular pseudodrusen, 23%; square root drusen area (SD-OCT), 0.77 mm; square root drusen area (color photographs), 0.92 mm; cube root drusen volume (SD-OCT), 0.26 mm; average retinal sensitivity, 26 dB; and worst point retinal sensitivity, 20 dB. Only lutein supplement use was significantly different between treatment arms.

Conclusions: The LEAD study uses novel inclusion/exclusion criteria and end points in an attempt to optimize our study design. Risk characteristics for progression to study end points are equally distributed between treatment arms. *Ophthalmology Retina 2016;■:1–13* © *2016 by the American Academy of Ophthalmology*

Supplemental material is available at www.ophthalmologyretina.org.

Vision impairment in late age-related macular degeneration (AMD) results in reduced quality of life; increased rates of depression, falls, and fractures; and increased level of care with its associated direct and indirect costs.[1,2] As such, there is an urgent need for an effective intervention to slow or prevent progression to vision loss in AMD. Apart from lifestyle advice and dietary supplements for subsets of individuals with AMD,[3–5] there is currently no intervention

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that slows or reverses progression to the visually devastating complications of late AMD.

Age-related macular degeneration is characterized clinically by drusen, which are extracellular deposits between the retinal pigment epithelium (RPE) and the Bruch's membrane (BM). The size and extent of drusen observed in a clinical examination have been shown to predict AMD progression.[6] A pathologic hallmark of AMD is a thickened BM, a key component of AMD pathogenesis, where insufficient transport of nutrients and waste across the BM contributes to RPE and photoreceptor degeneration.[7,8] Thus, the reduction of drusen load and BM thickness may be effective in slowing AMD progression.

In 1971, Gass[7] reported the serendipitous observation of drusen regression after thermal (continuous wave) laser photocoagulation to a retinal area remote to the drusen, thus initiating a series of thermal laser intervention studies in AMD. Although several studies found that drusen did disappear, a Cochrane review found no reduction in progression to late AMD.[8] Short-pulse lasers that can be delivered at subthreshold energy levels, below the threshold of visible retinal blanching, recently have been developed in an attempt to harness the positive effects of laser, without inducing photoreceptor damage and inflammation.[9]

The effect of short-pulse, nanosecond (Retinal Rejuvenation Therapy, 2RT) laser (Ellex Pty Ltd, Adelaide, Australia) at subthreshold energy levels has been investigated in pilot studies involving animal models with thickened BM (ApoE-Null)[10] and patients with intermediate AMD.[11] In ApoE-null mice, nanosecond laser application resulted in a significant reduction in BM thickness and an increased expression of metalloproteinases (MMPs) 2 and 3 back to age-matched control levels.[10] This increase in MMP expression was viewed as a beneficial outcome of nanosecond laser treatment, because MMPs degrade extracellular matrix, including deposits within BM, facilitating improved BM hydraulic conductivity.[12] In a pilot study of patients with intermediate AMD, a single application of nanosecond laser appeared safe and resulted in significant drusen area reduction 12 months post-laser treatment in 44% of treated eyes and an improvement in retinal flicker sensitivity, with its maximal effect 3 and 6 months post-laser treatment.[11] Of note, similar effects on macular appearance and function were observed in the untreated fellow eyes in both animal and human studies.[10,11] These preliminary results warrant further investigation to determine whether this novel intervention can reduce progression to late AMD. It is critical to determine whether drusen resolution with treatment can occur without an increase in geographic atrophy (GA), the usual sequel of natural drusen regression,[13,14] and without an increased risk of choroidal neovascularization (CNV), initially thought to occur with thermal laser treatment.[15]

The Laser Intervention in Early Stages of Age-Related Macular Degeneration (LEAD) study is a 36-month, investigator-initiated, international multicenter, double-masked, randomized controlled, medical device clinical trial. The LEAD study is designed to investigate the safety and efficacy of nanosecond laser (2RT) treatment as a prophylactic intervention for intermediate AMD to slow its progression to late AMD. The effects of 2RT will be investigated in both the treated (study) and the untreated (nonstudy) eyes. This is a randomized feasibility trial of nanosecond laser for intermediate AMD. This report describes the novel study design, which incorporates novel participant inclusion and exclusion criteria, and end points based on multimodal imaging (MMI) signs and functional measures. The study design is an attempt to reduce the sample size, time, and cost required in conducting a randomized controlled trial in the early stages of AMD. These features are desirable, because the current conduct of such trials is significantly challenged by the low conversion rate of intermediate AMD to its late stages. This report also includes the baseline characteristics of the LEAD cohort.

Methods

Study Organization

The coordinating center based at the Centre for Eye Research Australia (CERA) provides ongoing management of the trial including the design and implementation of standardized protocols, and the validation and management of data across 5 Australian and 1 Northern Ireland study centers (Appendix 2). Each site gained ethical approval for the study, which was undertaken in accordance with the Declararion of Helsinki for research on humans. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000704897) and clinicaltrials.gov (NCT01790802). Data collected are entered into a CERA-designed trial database using OpenClinica open source software.[16]

Study Population Participant Eligibility

A full list of the inclusion and exclusion criteria is shown in Table 1 (available at www.ophthalmologyretina.org). Enrollment was restricted to people aged 50 to <95 years with lesion characteristics that met the criteria for intermediate AMD as defined by the Beckman classification.[17] In the Beckman classification, intermediate AMD is defined as large (>125 μm) drusen or any AMD pigmentary abnormalities that are associated with medium (>63 μm) or large drusen within 2 disc diameters (~3000 μm) from the fovea. To select intermediate AMD cases with a greater risk of progression, our inclusion criteria required at least one >125 μm druse to be within 1500 μm from the fovea in both eyes based on color fundus photography (CFP) (Ferris FL, personal communication, November 20, 2012). In addition, participants were required to have a repeatable relative scotoma (<25 decibels [dB], 2 standard deviations from controls[18]) in at least 1 location (same or adjacent) within a central 6° grid of the Macular Integrity Assessment microperimeter in 1 eye. This criterion is consistent with a previous study that reported reduced sensitivity as a risk factor for progression to GA[19] and increases the likelihood of detecting any improvement in macular function. Eligible participants were required to have best-corrected visual acuity (BCVA) of ≥20/40 in both eyes, and no ocular, systemic, or neurologic disease that could compromise retinal assessment.

Individuals with late AMD—CNV and CFP-defined GA—(Table 2 and Fig 1A and B) were excluded. In addition, we excluded anyone without signs of GA on CFP but who had evidence of anatomic changes on MMI that potentially portend