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Efficacy and Safety of Ranibizumab 0.5 mg for the Treatment of Macular Edema Resulting from Uncommon Causes

Twelve-Month Findings from PROMETHEUS

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Purpose: To evaluate the efficacy and safety of ranibizumab 0.5 mg in adult patients with macular edema (ME) resulting from any cause other than diabetes, retinal vein occlusion, or neovascular age-related macular degeneration.

Design: A phase 3, 12-month, double-masked, randomized, sham-controlled, multicenter study.

Participants: One hundred seventy-eight eligible patients aged ≥18 years.

Methods: Patients were randomized 2:1 to receive either ranibizumab 0.5 mg (n = 118) or sham (n = 60) at baseline and month 1. From month 2, patients in both arms received open-label individualized ranibizumab treatment based on disease activity. A preplanned subgroup analysis was conducted on the primary end point on 5 predefined baseline ME etiologies (inflammatory/post-uveitis, pseudophakic or aphakic, central serous chorioretinopathy, idiopathic, and miscellaneous).

Main Outcome Measures: Changes in best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study letters) from baseline to month 2 (primary end point) and month 12 and safety over 12 months.

Results: Overall, 156 patients (87.6%) completed the study. The baseline characteristics were well balanced between the treatment arms. Overall, ranibizumab showed superior efficacy versus sham from baseline to month 2 (least squares mean BCVA, +5.7 letters vs. +2.9 letters; 1-sided $P = 0.0111$), that is, a treatment effect (TE) of +2.8 letters. The mean BCVA gain from baseline to month 12 was 9.6 letters with ranibizumab. The TE at month 2 was variable in the 5 predefined etiology subgroups, ranging from >5-letter gain to 0.5-letter loss. The safety findings were consistent with the well-established safety profile of ranibizumab.

Conclusions: The primary end point was met and ranibizumab showed superiority in BCVA gain over sham in treating ME due to uncommon causes, with a TE of +2.8 letters versus sham at month 2. At month 12, the mean BCVA gain was high (9.6 letters) in the ranibizumab arm; however, the TE was observed to be variable across the different etiology subgroups, reaching a >1-line TE in BCVA in patients with ME resulting from inflammatory conditions/post-uveitis or after cataract surgery. Overall, ranibizumab was well tolerated with no new safety findings up to month 12. *Ophthalmology 2017;■:1–13 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

Macular edema (ME) is characterized by vascular leakage and accumulation of fluid resulting from pathologic changes in the retinal vasculature and may result in irreversible structural damage and permanent loss of vision.[1] The underlying pathophysiology of ME is multifactorial, complex, and poorly understood.[1–3] Thus, ME remains one of the major therapeutic challenges in ophthalmology. In many cases, ME involves abnormally increased vascular endothelial growth factor (VEGF) levels in the retina that cause disruption of the blood–retinal barrier, followed by increased accumulation of fluid within the intraretinal layers of the macula.[1]

The most common causes for ME in the working-age population are diabetic retinopathy and retinal vein occlusion (RVO).[2,3] These ocular conditions can lead to severe and irreversible vision loss if left untreated.[1–6] Less frequent retinal vascular disorders, inflammatory disorders, choroidal vascular diseases, inherited retinal dystrophies, intraocular tumors, and optic nerve abnormalities also cause ME and their prevalence varies worldwide.[2,3] Currently, there is no health authority–approved therapy for treating ME caused by conditions other than diabetic retinopathy, RVO, or neovascular age-related macular degeneration (nAMD). Different available treatment options for ME

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resulting from less common causes include topical nonsteroidal anti-inflammatory drugs, topical corticosteroids, verteporfin photodynamic therapy (vPDT), laser photocoagulation, and intravitreal corticosteroids along with the off-label use of anti-VEGF agents.[3,7–12] Considering the well-established efficacy and safety of ranibizumab for the treatment of visual impairment resulting from diabetic ME (DME) and ME after RVO,[13–24] ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland, and Genentech, Inc, South San Francisco, CA) as an anti-VEGF agent could be beneficial also for the treatment of ME secondary to uncommon ocular conditions.

Previously published reports assessed the potential of anti-VEGF agents like bevacizumab and ranibizumab in the treatment of ME resulting from uncommon causes like uveitis, pseudophakia or aphakia, central serous chorioretinopathy (CSC), radiation retinopathy, and others.[9,25–36] The treatment effect observed with anti-VEGF agents was variable[7,25–29,32,36]; hence, there was need for a long-term randomized clinical trial to establish the efficacy and safety of anti-VEGF in these uncommon conditions.

The PROMETHEUS study (a complete listing of the members of the study group is available in Appendix 1, available at www.aaojournal.org) was designed to evaluate the efficacy and safety of an individualized ranibizumab 0.5-mg dosing regimen, based on disease activity, in adult patients with visual impairment resulting from ME associated with uncommon causes other than DME, nAMD, and RVO.

Methods

Study Design

The PROMETHEUS study was a 12-month, phase 3, randomized, double-masked, sham-controlled multicenter study conducted across 19 countries (Appendix 2, available at www.aaojournal.org). The study was initiated in October 2013 and was completed in September 2015. The study protocol was reviewed and approved by an independent ethics committee or institutional review board for each center and the study was conducted in accordance with the tenets of the Declaration of Helsinki. Patients provided written informed consent at screening and a re-consent after the implementation of the first protocol amendment. The study is registered with Clinicaltrials.gov (identifier, NCT01846299).

Patients

The study population consisted of patients 18 years of age or older with visual impairment due to active ME secondary to causes other than diabetic retinopathy, nAMD, or RVO. The inclusion criteria were diagnosis of active chronic ME (>3 months) confirmed by the presence of 1 of the following 3 criteria: (1) posterior pole changes compatible with active ME observed by fundus ophthalmoscopy, biomicroscopy, and fundus photography; (2) leakage from ME documented by fluorescein angiography (FA); and (3) intraretinal fluid or cysts seen by OCT and best-corrected visual acuity (BCVA) between 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters or more and 83 ETDRS letters or fewer.

Patients were excluded if they demonstrated ME associated with diabetic retinopathy, nAMD, or RVO; retinal angiomatous proliferation lesions in patients 50 years of age or older; any type of systemic advanced, severe, or unstable disease or its treatment that could interfere with primary or secondary outcome evaluations, or both; uncontrolled systemic inflammation or infection related directly to the underlying causal disease of ME; active diabetic retinopathy and active ocular or periocular infectious disease or active severe intraocular inflammation (intraocular pressure ≥25 mmHg); history of laser photocoagulation with involvement of the macular area, vPDT, and vitreoretinal surgery and intravitreal implants at any time; and use of anti-VEGF agents and intravitreal steroids within 6 months of the baseline visit (inclusion and exclusion criteria are listed in detail in Appendix 3, available at www.aaojournal.org).

Randomization and Treatment

Eligible patients were randomized in a 2:1 ratio to either of 2 treatment arms (ranibizumab 0.5 mg or sham) at baseline using interactive response technology. Although patients received open-label therapy from month 2 onward, the examiners who assessed the efficacy outcomes were masked and not allowed to perform any other tasks that would unmask them to the treatment received by the patients through the entire study period of 12 months.

Patients in the ranibizumab arm received ranibizumab 0.5 mg at baseline followed by an individualized pro re nata (PRN) treatment regimen based on evidence of disease activity (judged clinically or based on morphologic features or imaging) as judged and assessed by the investigator at each individual follow-up visit (Fig S1, available at www.aaojournal.org). All the patients were monitored for disease activity by the masked investigator (details of masking are available in Appendix 4, available at www.aaojournal.org) at each monthly visit.

Patients in the sham arm received a sham injection at baseline and another sham injection PRN at month 1. From month 2, sham patients could be switched to open-label treatment with PRN ranibizumab 0.5 mg based on the evidence of disease activity (with no mandatory ranibizumab injection at month 2 in case of no disease activity). Thus, as of month 2, patients in both treatment arms could receive open-label PRN ranibizumab.

Rescue Medication

Patients could receive rescue treatment, as per routine clinical practice, only at month 1, and patients could be treated with laser photocoagulation or periocular treatments (e.g., sub-Tenon's, retrobulbar, or subconjunctival corticosteroid) at the discretion of the masked investigator if the patient had a visual acuity (VA) loss of more than 5 letters from baseline to month 1 because of disease activity. Further details are provided in Appendix 5 (available at www.aaojournal.org).

Objectives

The primary objective was to demonstrate that individualized ranibizumab 0.5 mg had superior efficacy compared with sham treatment in adult patients with visual impairment due to ME with respect to the change in BCVA from baseline to month 2. Preplanned subgroup analyses were conducted on the primary end point for the following predefined baseline ME etiologies inflammatory or post-uveitis, pseudophakic or aphakic, CSC, idiopathic retinopathy or retinochoroidopathy, and miscellaneous (causes that did not fit into the other ME etiology subgroups and were insufficiently frequent to form a separate subgroup). The secondary objectives were to evaluate (1) mean change in BCVA from baseline to month 12, (2) mean change in central subfield thickness (CSFT) and central subfield volume (CSFV) from baseline to month 12 and from baseline to months 2 and 12 by baseline ME cause subgroups, (3) overall treatment exposure of