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Ranibizumab 0.5 mg for Diabetic Macular Edema with Bimonthly Monitoring after a Phase of Initial Treatment

18-Month, Multicenter, Phase IIIB RELIGHT Study

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Purpose: To evaluate ranibizumab 0.5 mg using bimonthly monitoring and individualized re-treatment after monthly follow-up for 6 months in patients with visual impairment due to diabetic macular edema (DME).

Design: A phase IIIb, 18-month, prospective, open-label, multicenter, single-arm study in the United Kingdom.

Participants: Participants (N = 109) with visual impairment due to DME.

Methods: Participants received 3 initial monthly ranibizumab 0.5 mg injections (day 0 to month 2), followed by individualized best-corrected visual acuity (BCVA) and optical coherence tomography–guided re-treatment with monthly (months 3–5) and subsequent bimonthly follow-up (months 6–18). Laser was allowed after month 6.

Main Outcome Measures: Mean change in BCVA from baseline to month 12 (primary end point), mean change in BCVA and central retinal thickness (CRT) from baseline to month 18, gain of ≥10 and ≥15 letters, treatment exposure, and incidence of adverse events over 18 months.

Results: Of 109 participants, 100 (91.7%) and 99 (90.8%) completed the 12 and 18 months of the study, respectively. The mean age was 63.7 years, the mean duration of DME was 40 months, and 77.1% of the participants had received prior laser treatment (study eye). At baseline, mean BCVA was 62.9 letters, 20% of patients had a baseline BCVA of >73 letters, and mean baseline CRT was 418.1 μm, with 32% of patients having a baseline CRT <300 μm. The mean change in BCVA from baseline to month 6 was +6.6 letters (95% confidence interval [CI], 4.9–8.3), and after institution of bimonthly treatment the mean change in BCVA at month 12 was +4.8 letters (95% CI, 2.9–6.7; $P < 0.001$) and +6.5 letters (95% CI, 4.2–8.8) at month 18. The proportion of participants gaining ≥10 and ≥15 letters was 24.8% and 13.8% at month 12 and 34.9% and 19.3% at month 18, respectively. Participants received a mean of 6.8 and 8.5 injections over 12 and 18 months, respectively. No new ocular or nonocular safety findings were observed during the study.

Conclusions: The BCVA gain achieved in the initial 6-month treatment period was maintained with an additional 12 months of bimonthly ranibizumab PRN treatment. *Ophthalmology 2015;■:1–9 © 2015 by the American Academy of Ophthalmology.*

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

Diabetic macular edema (DME) is the leading cause of blindness among the working-age population in many developed countries.[1–3] Although macular laser photocoagulation has been shown to stabilize vision, it does not lead to visual acuity (VA) improvement in the majority of patients.[3] The advent of anti–vascular endothelial growth factor (VEGF) therapy revolutionized the management of DME, with patients with DME experiencing not just stabilization but improvement in vision for the first time.[3–7] However, challenges in optimization of treatment regimen remain.

Ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland; and Genentech Inc., South San Francisco, CA) is a humanized monoclonal antibody Fab fragment specifically designed for ocular use. It binds to VEGF-A with high affinity, inhibiting multiple isoforms of VEGF-A, and has minimal systemic exposure after intravitreal injection.[8,9] Ranibizumab was the first anti-VEGF agent approved for

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DME in the European Union (ranibizumab 0.5 mg pro re nata [PRN]) in 2010 based on the RESOLVE and RESTORE studies.[4,5] It was approved in the United States (ranibizumab 0.3 mg monthly) in 2012 based on the Ranibizumab Injection in Subjects with clinically significant macular Edema with center involvement secondary to diabetes mellitus (RISE) and Ranibizumab Injection in subjects with clinically significant macular Edema with center involvement secondary to Diabetes mellitus (RIDE) studies.[10]

The RISE and RIDE studies showed that the VA gained in the first year was maintained over 3 years (+14.2/+11.0 letters and +10.5/+11.4 letters with ranibizumab 0.3 mg/0.5 mg in RISE and RIDE, respectively) with continued monthly ranibizumab treatment (mean of 28−30 injections over 3 years).[10]

The phase II RESOLVE and phase III RESTORE and Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I (year 1) studies using a monthly PRN dosing regimen of ranibizumab, after a loading phase of 3 or 4 monthly injections, have demonstrated that best-corrected VA (BCVA) gains can be maintained with a PRN dosing regimen and that monthly dosing is not a requisite for optimum management.[4,11,12] In the RESTORE (N = 345) ranibizumab monotherapy arm, there was a mean average gain of 6.1 letters with a mean of 7.0 injections over 12 months.[5] The data from the RESTORE 24-month extension study (N = 240) and DRCR.net Protocol I (N = 691; years 2 to 5) demonstrated that the mean VA gained in the first year (+6.8 and +9.0 letters in the RESTORE ranibizumab monotherapy arm and DRCR.net Protocol I ranibizumab plus deferred laser arm, respectively) was maintained through subsequent years (+8.0 and +9.7 letters in the RESTORE 24-month extension and DRCR.net Protocol I, respectively), with a markedly reduced number of injections beyond year 1 of treatment.[5,6,11] In years 2 to 5 of the DRCR.net Protocol I study, patients with stable VA could have their monitoring visits extended to a maximum of 16 weeks.[6]

In the Ranibizumab for Edema of the macula in Diabetes-2 (READ-2) study, initial monthly doses at months 0, 1, 3, and 5 were followed by bimonthly follow-up and PRN treatment; this resulted in a mean BCVA gain of +6.61 and +7.70 letters at months 12 and 24, respectively, in the ranibizumab monotherapy group.[13]

Although PRN treatment with monthly monitoring has been successful in delivering visual gains that are maintained for up to 3 years, the burden of monthly monitoring visits is huge and often impractical and not achievable in routine clinical practice. Therefore, it is valuable to explore alternative management pathways that permit and reduced visits.

Ranibizumab Treatment of Diabetic Macular Oedema with bimonthly Monitoring after a Phase of Initial treatment (RELIGHT) study was an 18-month study designed to assess the outcome of a bimonthly follow-up and individualized re-treatment schedule on the efficacy and safety of ranibizumab in DME. In RELIGHT, we instituted bimonthly monitoring after month 6, thus combining the benefits of less frequent follow-up in later stages while ensuring sufficient treatment opportunities for more intense management in the first 6 months. This allowed us to address the need for reduction of the overall health care burden that is associated with monthly monitoring of patients.

The data from RELIGHT will aid physicians in refining their clinical management of DME with individualized ranibizumab treatment guided by both VA and high-resolution spectral-domain optical coherence tomography (SD OCT) criteria.

Methods

Study Design

RELIGHT was an 18-month, prospective, open-label, multicenter, single-arm, phase III study of patients in the United Kingdom with visual impairment due to DME using a bimonthly follow-up and treatment protocol after a 6-month period of monthly monitoring. The study was conducted between January 2011 and April 2013 in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by a multicenter research ethics committee for each contributing center. Patients provided written informed consent before entering the study. The study is registered with clinicaltrials.gov as NCT01257815.

Patients

The study population consisted of both male and female patients aged >18 years with type 1 or type 2 diabetes mellitus and visual impairment due to focal or diffuse DME. The key inclusion criteria were (1) BCVA between 78 and 24 letters in the study eye using Early Treatment Diabetic Retinopathy Study (ETDRS) VA charts at a testing distance of 4 m (approximate Snellen equivalent of 20/32−20/320) at screening and (2) increased central retinal thickness (CRT) due to DME in the opinion of the investigator. The exclusion criteria and the complete list of inclusion criteria are provided online in Appendix 2 (available at www.aaojournal.org).

Treatment

This was a single-arm study, and thus all the enrolled patients received an open-label treatment. When both eyes fitted eligibility criteria, the eye with worse VA was selected unless the investigator deemed that the fellow eye was more appropriate. The study consisted of 3 treatment periods (Fig 1). The dose of ranibizumab used in the RELIGHT study is that approved in Europe (ranibizumab 0.5 mg) and differs from the approved dose in the United States (ranibizumab 0.3 mg) for the treatment of patients with DME.

Loading Phase. Participants received 3 consecutive ranibizumab 0.5 mg injections at the first 3 visits from baseline (day 0) to month 2.

Maintenance Phase 1. During this phase, months 3 to 5, there was monthly follow-up with ranibizumab 0.5 mg PRN treatment based on predefined re-treatment criteria.

Maintenance Phase 2. During this phase, months 6 to 11 and 12 to 17, there was bimonthly follow-up with ranibizumab 0.5 mg PRN treatment based on predefined re-treatment criteria. After month 17, participants were assessed for final efficacy and safety assessments at the end of month 18.

Re-treatment. Subsequent to the 3 initial doses, ranibizumab 0.5 mg was given if there was an SD OCT reading ≥225 μm, or there was an increase in central subfield retinal edema by >10% or 25 μm from the lowest in-study reading, or there was no residual central subfield retinal edema, but there was a total decrease of ≥5 ETDRS letters from the in-study BCVA. Treatment with