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Long-term Effects of Therapy with Ranibizumab on Diabetic Retinopathy Severity and Baseline Risk Factors for Worsening Retinopathy

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Purpose: To assess the effects of intravitreal ranibizumab on diabetic retinopathy (DR) severity when administered for up to 3 years, evaluate the effect of delayed initiation of ranibizumab therapy on DR severity, and identify baseline patient characteristics associated with the development of proliferative DR (PDR).

Design: Exploratory analyses of phase III, randomized, double-masked, sham-controlled multicenter clinical trials.

Participants: Adults with diabetic macular edema (DME) (N = 759), baseline best-corrected visual acuity 20/40 to 20/320 Snellen equivalent, and central foveal thickness ≥275 μm.

Methods: Patients were randomized to monthly 0.3 or 0.5 mg ranibizumab or sham injections. Sham participants could switch to 0.5 mg ranibizumab during the third year (sham/0.5 mg crossover). Baseline risk factors were evaluated to explore potential associations with development of PDR. Time to first development of PDR was analyzed by Kaplan–Meier methods to calculate cumulative probabilities by group.

Main Outcome Measures: Study eye change on the Early Treatment Diabetic Retinopathy Study severity scale and a composite clinical outcome evaluating progression to PDR based on photographic changes plus clinically important events defining PDR.

Results: At month 36, a greater proportion of ranibizumab-treated eyes had ≥2- or ≥3-step DR improvement compared with sham/0.5 mg crossover. A ≥3-step improvement was achieved at 36 months by 3.3%, 15.0%, and 13.2% of sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab-treated eyes, respectively ($P < 0.0001$). Through 36 months, 39.1% of eyes in the sham/0.5 mg group developed PDR, as measured by composite outcome, compared with 18.3% and 17.1% of eyes treated with 0.3 or 0.5 mg ranibizumab, respectively. The presence of macular capillary nonperfusion at baseline seems to be associated with progression to PDR in ranibizumab-treated eyes but did not meaningfully influence visual acuity improvement in eyes with DME after ranibizumab therapy.

Conclusions: Ranibizumab, as administered to patients with DME for 12 to 36 months in these studies, can both improve DR severity and prevent worsening. Prolonged delays in initiation of ranibizumab therapy may limit this therapeutic effect. Although uncommon, the development of PDR still occurs in a small percentage of eyes undergoing anti–vascular endothelial growth factor therapy and may be related to the presence of macular nonperfusion. *Ophthalmology 2015;122:367-374 © 2015 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/3.0/).*

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Diabetic retinopathy (DR) is a leading cause of visual loss in the United States, with a prevalence of more than 40% in patients aged >40 years with diabetes.[1] Two general DR subtypes exist: nonproliferative DR (NPDR) and proliferative DR (PDR). Diabetic macular edema (DME) may be present in eyes with either subtype and is frequently the primary cause of vision loss due to DR. Another major cause of vision loss in patients with DR is the development of retinal neovascularization (e.g., PDR) and its accompanying complications. The natural history of NPDR in many patients is a slow, inexorable worsening, with characteristic changes that occur in well-defined and discrete steps. The level of DR severity, as observable on retinal color fundus photographs, is described by the standardized Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity scale.[2] The discrete changes that occur with disease progression leading up to the development of frank neovascularization provide an opportunity to evaluate the effectiveness of new therapies that may arrest the progression of the disease or even reverse it.

In a prior report from our group,[3] we described the effects of monthly intravitreal anti–vascular endothelial growth

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factor (VEGF) therapy with ranibizumab for 24 months on DR severity using data from the RIDE and RISE phase III clinical trials that evaluated the efficacy and safety of ranibizumab for DME. In that exploratory analysis, we showed that monthly ranibizumab for 24 months had profound and beneficial effects on DR severity: treatment with ranibizumab prevented the worsening of DR (i.e., ETDRS severity level progression) and led to DR improvement (i.e., ETDRS severity level reduction). A composite measure evaluating PDR development also was used to demonstrate the benefit of ranibizumab; this composite outcome included not only the described fundus photographic changes, but also clinical measures, such as the need for panretinal laser photocoagulation or vitrectomy as treatment for complications of PDR. We noted that sham-treated patients were 3-fold more likely to develop PDR than patients treated with ranibizumab over 24 months (33.8% vs. 11.2%–11.5%, respectively).[3] Retarding the progression of DR has been reported in analyses from other studies of intravitreal agents (i.e., anti-VEGF therapies, steroids), as well as with systemic therapies, such as candesartan and fenofibrate.[4–8] Compelling preclinical and clinical data suggest that the retinal pathophysiology of DR is mediated in substantial part by VEGF.[9–12] Therefore, based on the biological plausibility that VEGF plays an important role in the clinical course of diabetic eye disease, further studies are needed to evaluate anti-VEGF therapies for the modification of DR progression.

In the RIDE and RISE trials, the active-treatment arms were assigned to monthly ranibizumab therapy for 36 months. Patients randomized to sham for the first 24 months were eligible for crossover to 0.5 mg ranibizumab monthly (sham/0.5 mg) starting at month 25. Thus, in this report we compare the effect of a 2-year delay in the initiation of treatment with ranibizumab on retinopathy severity level between the ranibizumab treatment arms and the sham/0.5 mg crossover arm at month 36. Although in RIDE and RISE ranibizumab therapy significantly reduced the rate of progression to PDR at 24 months versus sham, a small percentage of eyes treated with monthly intravitreal ranibizumab nevertheless experienced a progression from nonproliferative to proliferative disease. Thus, in the current analysis we also sought to determine baseline risk factors associated with the development of PDR. Previously, clinical factors that have been associated with an increased long-term risk of developing PDR included elevated hemoglobin A_{1c} (HbA_{1c}), longer duration of diabetes, other markers of diabetes severity and microvascular damage (i.e., proteinuria, neuropathy), and elevated blood pressure.[13–19] Further exploration of potential risk factors for progression to PDR despite treatment with anti-VEGF therapy is important because identification of eyes at risk may allow for intensified therapy and/or closer monitoring of patients when needed to reduce the likelihood of developing this vision-threatening complication. In addition, identification of subgroups at higher risk of developing PDR even in the setting of anti-VEGF therapy is important because these patients may have unique genetic or other characteristics that could help identify additional target pathways for future therapeutics in retinal vascular disease.

Methods

Clinical Trial Design

RIDE and RISE were methodologically identical, randomized, phase III, double-masked, sham injection–controlled clinical trials of ranibizumab in patients with DME; the design, baseline patient characteristics, and core efficacy and safety outcomes of the trials have been described elsewhere.[3,20] Study protocols were approved by institutional review boards and ethics committees, and participants provided written informed consent. RIDE and RISE are registered on ClinicalTrials.gov with registration identifiers NCT00473382 and NCT00473330, respectively.

Patients and Treatment

Individuals aged 18 years and older with decreased vision due to DME (study eye best-corrected visual acuity [BCVA] of 20/40–20/320 approximate Snellen equivalent) and central foveal thickness ≥275 μm on time-domain optical coherence tomography (OCT) were eligible for enrollment. One eye per patient was randomized to monthly sham injections or intravitreal injections of 0.3 or 0.5 mg ranibizumab through month 24. From months 24 to 36, patients originally randomized to ranibizumab continued with monthly therapy at their assigned dosage. Patients initially randomized to sham were eligible to switch to 0.5 mg ranibizumab monthly starting at month 25. In this report, this is referred to as the "sham/0.5 mg" or "sham/0.5 mg crossover" group.

Grading Protocol and Clinical Assessment of Diabetic Retinopathy Progression

Stereoscopic 7-field color fundus photographs were obtained at each patient's screening visit and at months 3, 6, 12, 18, 24, 30, and 36. Photographs were graded according to the ETDRS severity scale for retinopathy level and were evaluated and defined in the same manner as previously described.[3] To include the clinically important DR progression events occurring between the periodic photographic assessments, we measured DR progression using the same composite outcome as previously described.[3,21]

Statistical Analyses

Baseline distributions of retinopathy severity were assessed and were similar across the RIDE and RISE studies; thus, data were pooled for these analyses. Unless otherwise specified, analyses of the outcomes are based on the assessment of the study eye only. The ETDRS retinopathy severity level was summarized over time. The number of eyes worsening (i.e., ETDRS level progression) or improving (i.e., ETDRS level reduction) by ≥2 or ≥3 steps from baseline were summarized at month 36. Cochran–Mantel–Haenszel chi-square tests stratified for baseline study eye visual acuity (≤55 vs. >55 ETDRS letters), baseline HbA_{1c} level (≤8% vs. >8%), and prior treatment for DME in the study eye (yes vs. no) were used to compare the rates of DR worsening and improvement among patients treated with ranibizumab versus sham/0.5 mg; Pearson chi-square tests were used to compare results between the ranibizumab groups and the sham/0.5 mg crossover group. Missing data were imputed using the last observation carried forward method.

The cumulative probability of developing PDR at month 36 was analyzed in each treatment group using Kaplan–Meier methods. The log-rank test was used to compare the risk of developing PDR among the treatment groups. Univariate and multivariate Cox proportional hazard models were used to evaluate baseline risk factors for progression to PDR for the sham- and ranibizumab-treated patients. As with the assessment of DR improvement/worsening, this