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Predictors of Functional and Anatomic Outcomes in Patients with Diabetic Macular Edema Treated with Ranibizumab

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Objective: To investigate baseline predictors of month 24 best-corrected visual acuity (BCVA) and central foveal thickness (CFT) in patients with diabetic macular edema (DME) treated monthly with ranibizumab or sham.

Design: Post hoc analysis of DME patients in 2 identical phase 3 studies.

Participants: Patients randomized to ranibizumab (n = 502) or sham (n = 257).

Methods: Multivariate regression on predictors with $P < 0.20$ in univariate logistic regression using backward selection to retain predictors with $P < 0.05$.

Main Outcome Measures: Patient characteristics correlating with month 24 BCVA in Early Treatment Diabetic Retinopathy Study letter score ≥70 (20/40) or ≤50 (20/100), gain or loss from baseline BCVA of ≥15, or CFT ≤250 μm.

Results: Baseline predictors of BCVA ≥20/40 in ranibizumab-treated patients were good BCVA, submacular fluid, no cardiovascular disease, no scatter photocoagulation, and male gender, whereas in sham-treated patients, they were mild increase in CFT, presence of hard exudates in center subfield, and absence of renal disease. Predictors of improvement in BCVA letter score ≥15 in ranibizumab-treated patients were poor BCVA, submacular fluid, young age, and short diabetes duration, and those in sham-treated patients were poor BCVA, young age, and mild increase in CFT. Predictors of resolution of edema (CFT ≤250 μm) in ranibizumab-treated patients were mild foveal thickening and prominent subfoveal fluid, and those in sham-treated patients were poor BCVA, mild foveal thickening, and statin usage. Month 24 BCVA ≤20/100 was predicted by poor baseline BCVA in ranibizumab-treated patients, and by poor baseline BCVA, large intraretinal cystoid spaces, renal disease, and absence of hypercholesterolemia in sham-treated patients. Loss of BCVA ≥15 letters was predicted in sham-treated patients by submacular fluid, intraretinal cystoid spaces, and renal disease.

Conclusions: Patients with DME and submacular fluid, intraretinal cysts, severe thickening, or renal disease respond poorly when untreated and respond well to ranibizumab treatment. Elimination of submacular fluid, intraretinal cysts, and severe thickening are important goals of DME treatment, and in patients with renal disease, treatment should be very aggressive, with a goal of eliminating all macular fluid. *Ophthalmology 2015;122:1395-1401 © 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/4.0/).*

Supplemental material is available at www.aaojournal.org.

Diabetic macular edema (DME) is a prevalent cause of vision loss.[1] Although multiple propermeability factors are likely to be involved, vascular endothelial growth factor (VEGF) plays a critical role in the excessive leakage from retinal vessels, and neutralization of VEGF by intraocular injections of ranibizumab leads to substantial reduction in DME.[2,3] This was confirmed in the RISE and RIDE trials, 2 parallel, phase 3, multicenter, double-masked, sham injection–controlled, randomized studies conducted in the United States and South America.[4] Patients received monthly injections of 0.3 or 0.5 mg ranibizumab or sham injections for 24 months. Macular laser was allowed at the discretion of the investigator starting at month 3. At the 24-month primary end point, 39.2%, 42.5%, and 15.2% of patients in the 0.3-mg, 0.5-mg, and sham groups had an improvement in best-corrected visual acuity (BCVA) letter score of 15 or more. Thus, monthly injections of ranibizumab provided an excellent outcome in a large percentage of patients with DME, but whereas some patients improve to near-normal levels, others are left with substantial visual disability. In this study, we sought to determine why visual outcomes vary in patients with DME treated with ranibizumab. Unlike other studies of this type, a major advantage is the presence of a sham-treated control group for comparison to identify characteristics of DME patients that predict a good or poor prognosis in untreated patients, allowing us to determine how that is changed by ranibizumab treatment. Patients with BCVA of 20/40 or better can read and drive, whereas those with BCVA worse than 20/40 are restricted in driving and reading. This is the primary goal in treating patients with DME—to help them achieve this high-functioning level of activity—so our first questions are,

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Are there baseline characteristics that predict this outcome in ranibizumab-treated patients? Are there any characteristics that are so important that they predict this outcome even in the absence of ranibizumab treatment? The second major goal of treatment in patients with DME is to prevent severe visual disability. Previously, BCVA of 20/200 or worse was considered a cutoff for this, but given new criteria for legal blindness when using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (available at: www.lighthouse.org/about-low-vision-blindness/definition-legal-blindness/), patients with BCVA of 20/100 or worse were considered to have a poor visual outcome; they not only cannot read or drive, they also have difficulty performing many simple tasks of daily life. Another goal of treatment that indicates to clinicians that they are doing everything possible to maximize visual outcome not just for 2 years of treatment, but for the remainder of a patient's life, is resolution of macular edema. With time-domain optical coherence tomography (OCT), central subfield thickness (CST) of 250 μm or less provides an anatomic cutoff for clinically significant macular edema, and for trials that used time-domain OCT, CST of 250 μm or more was an eligibility criterion to identify patients with clinically significant macular edema and an end point to identify patients who had edema resolution versus those with residual edema. We sought to determine which baseline characteristics could predict these functionally relevant outcome measures.

Methods

Details of the study design and methods for the RISE and RIDE trials (ClinicalTrials.gov identifiers NCT00473330 and NCT00473382, respectively) have been reported previously.[4] In the 2 trials, 759 patients with DME were randomized 1:1:1 to monthly injections of 0.3 mg or 0.5 mg ranibizumab or to sham injections. These trials complied with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki. Institutional review board or ethics committee approval was obtained for each participating institution, and written informed consent from each subject was obtained.

Study Participants

The inclusion criteria included (1) age 18 years or older; (2) type 1 or 2 diabetes mellitus; (3) DME causing visual loss, with study eye BCVA measured by ETDRS protocol[5] of a letter score between 73 and 23 (Snellen equivalent, 20/40−20/320); and (4) macular edema with CST of 275 μm or more measured by time-domain OCT. Key exclusion criteria were (1) prior vitreoretinal surgery, (2) panretinal or macular laser photocoagulation in the study eye within the previous 3 months, (3) intraocular corticosteroids or antiangiogenic drugs within the previous 3 months, (4) uncontrolled hypertension, (5) uncontrolled diabetes with glycosylated hemoglobin of more than 12%, and (6) cerebrovascular accident or myocardial infarction within 3 months.

Study Procedures

During the initial visit, it was determined whether patients had a history of hypertension, hypercholesterolemia or hyperlipidemia, cardiovascular disease, renal disease, cerebrovascular disease, and smoking. Baseline blood pressure and glycosylated hemoglobin were used in this analysis. Baseline and subsequent OCT scans, fundus photographs, and fluorescein angiograms were graded at the University of Wisconsin Fundus Photograph Reading Center.

Data Analysis

Analysis was carried out for all randomized patients. Patients were categorized as having received either monthly ranibizumab injections (0.5- or 0.3-mg groups combined) or monthly sham injections. Univariate logistic regression was run on the following outcome variables at month 24 for ranibizumab- and sham-treated patients: (1) final BCVA of 20/40 or better (≥70 ETDRS letter score), (2) improvement from baseline ETDRS letter score of 15 or more, (3) final BCVA of 20/100 or worse (≤50 ETDRS letter score), (4) reduction from baseline ETDRS letter score of 15 or more, and (5) final CST of 250 μm or less. Predictors with a P value less than 0.2 in the univariate analysis were included in a multivariate logistic regression model. The final multivariate model was created by applying a backward selection procedure that retained only those predictors with $P < 0.05$. The final multivariate logistic model was used to calculate odds ratios (ORs) and their 95% confidence intervals, with a change of 5 letters, 50 μm, and 5 years considered as standard units of change. All data analyses were performed using SAS software version 9.2 (SAS, Inc, Cary, NC).

Results

Baseline Characteristics of Study Patients

A total of 502 patients in the ranibizumab group and 257 patients in the sham group were randomized. Patient and study eye characteristics assessed at baseline were comparable between the 2 groups and are summarized in Tables 1 and 2 (available at www.aaojournal.org).

Predictors of an Excellent Visual Outcome

In ranibizumab-treated patients, final BCVA of 20/40 or better correlated with good baseline BCVA (OR, 1.59; $P < 0.0001$), submacular fluid at baseline (OR, 2.88; $P = 0.0002$), and male gender (OR, 1.85; $P = 0.005$; Fig 1A). Final BCVA of 20/40 or better was less likely in patients who had history of cardiovascular disease (OR, 0.52; $P = 0.006$) or who had received panretinal photocoagulation (OR, 0.44; $P = 0.0012$; Fig 1A). In sham control patients, final BCVA of 20/40 or better correlated with good BCVA at baseline (OR, 1.81; $P < 0.0001$), mild foveal thickening (OR, 0.81; $P = 0.0004$), and hard exudates within 2 disc areas of the fovea (OR, 2.54; $P = 0.03$) and was less likely in patients who had a history of renal disease (OR, 0.16; $P = 0.01$; Fig 1B).

Predictors of a Large Improvement in Visual Acuity

In ranibizumab-treated patients, improvement from baseline BCVA letter score of 15 or more correlated with poor baseline BCVA (OR, 0.73; $P < 0.0001$), submacular fluid at baseline (OR, 2.43; $P = 0.004$), shorter duration of diabetes (OR, 0.89; $P = 0.03$), and young age (OR, 0.88; $P = 0.02$; Fig 2A). In sham-treated control patients, improvement from baseline BCVA letter score of 15 or more correlated with poor baseline BCVA (OR, 0.67; $P < 0.0001$), mild foveal thickening at baseline (OR, 0.83; $P = 0.006$; Fig 2B), and young age (OR, 0.76; $P = 0.004$).