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Vision-Related Function after Ranibizumab Treatment for Diabetic Macular Edema

Results from RIDE and RISE

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Objective: To examine the effects of intravitreal ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA) treatment on patient-reported vision-related function, as assessed by 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) scores, in patients with visual impairment secondary to center-involved diabetic macular edema (DME).

Design: Within 2 randomized, double-masked, phase 3 clinical trials (RIDE [A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema {ME} With Center Involvement Secondary to Diabetes Mellitus; NCT00473382] and RISE [A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema {ME} With Center Involvement Secondary to Diabetes Mellitus; NCT00473330]), the NEI VFQ-25 was administered at baseline and at the 6-, 12-, 18-, and 24-month follow-up visits.

Participants: Three hundred eighty-two (100%) RIDE patients and 377 (100%) RISE patients.

Intervention: Patients were randomized 1:1:1 to monthly injections of intravitreal ranibizumab 0.3 or 0.5 mg or sham. Study participants could receive macular laser for DME from month 3 onward if specific criteria were met.

Main Outcome Measures: Exploratory post hoc analysis of mean change from baseline in NEI VFQ-25 scores at 12 and 24 months.

Results: Across all treatment arms, 13% to 28% of enrolled eyes were the better-seeing eye. For all eyes in RIDE and RISE, the mean change in NEI VFQ-25 composite score improved more in ranibizumab-treated eyes at both the 12- and 24-month visits compared with sham treatment. For the better-seeing eyes at baseline, the mean change in composite score with 0.3 mg ranibizumab at the 24-month visit was 10.9 more (95% confidence interval [CI], 2.5−19.2) than sham for RIDE patients and 1.3 more (95% CI, −10.5 to 13.0) than sham for RISE patients. For the worse-seeing eyes at baseline, the mean change in composite score with 0.3 mg ranibizumab at the 24-month visit was 1.0 more (95% CI, −4.7 to 6.7) than sham for RIDE patients and 1.8 more (95% CI, −2.7 to 6.2) than sham for RISE patients. Similar results for most of these outcomes were seen with 0.5 mg ranibizumab.

Conclusions: These phase 3 trials demonstrated that ranibizumab treatment for DME likely improves patient-reported vision-related function outcomes compared with sham, further supporting treatment of DME with ranibizumab. *Ophthalmology 2014;121:2461-2472 © 2014 by the American Academy of Ophthalmology.*

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

Several phase 3 randomized clinical trials evaluating treatments for diabetic macular edema (DME) have reported significant visual acuity benefits of ranibizumab, an anti−vascular endothelial growth factor treatment, compared with prompt focal/grid laser[1−3] or sham treatment, with laser permitted as early as 3 months after initiating anti−vascular endothelial growth factor treatment.[4] A secondary outcome evaluated in some of these studies included patient-reported vision-related function using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25).[5,6] This study examined the effect of ranibizumab on patient-reported outcomes in 2 phase 3 randomized clinical trials, RIDE and RISE, including outcomes according to whether the study eye was the better- or worse-seeing eye at baseline.

Methods

As described elsewhere,[4] the trials adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act, and protocols were approved by institutional review boards, ethics committees, or as applicable. All participating patients provided written, informed consent. Both

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RIDE and RISE are registered on www.clinicaltrials.gov (RIDE identifier, NCT00473382; RISE identifier, NCT00473330).

Synopsis of the Protocol

The eligibility requirements for patients and eyes, clinical evaluation procedures, and clinical data collection methods and schedules for RIDE and RISE are described in detail elsewhere.[4] All patients were scheduled for follow-up NEI VFQ-25 interviews 6, 12, 18, and 24 months after the initial interview and treatment and for best-corrected visual acuity measurements every month. In this report, the study eye was categorized as the better- or worse-seeing eye or neither the better- nor worse-seeing eye (i.e., same as the fellow eye) based on definitions described previously.[7] These definitions of better- and worse-seeing eyes, as used by the Age-Related Eye Disease Study Group,[8] were based on the reliability of best-corrected visual acuity measurements using Early Treatment Diabetic Retinopathy Study charts.[9,10]

Eyes were excluded from analyses by better- or worse-seeing eye in cases where the study and fellow eyes were categorized as the same, that is, neither the better- nor worse-seeing eye, or when baseline visual acuity was not assessed in both eyes. Eyes were excluded from analyses of NEI VFQ-25 when baseline interview responses were not available.

25-Item National Eye Institute Visual Function Questionnaire Methods

The interview instrument selected for the RIDE and RISE trials, the NEI VFQ-25, was developed to measure a patient's subjective assessment of vision-related function and included a 25-item base set of questions as well as 6 additional items to enhance the reliability of both the near and distance visual subscales.[5,11,12] The NEI VFQ-25 comprises 11 vision-related subscales and 1 general health question.[5] The scores were calculated using the recommendations of the developers and according to published guidelines for the NEI VFQ-25.[5] The composite score is calculated by averaging the vision-related subscales' scores and does not include the general health rating question.[5]

Although no minimum important difference has been established for the NEI VFQ-25, several studies have now shown that at least a 10-point difference in NEI VFQ-25 scores is deemed clinically important in age-related macular degeneration (AMD), and recent psychometric analyses showed a 4- to 7-point difference was considered a clinically relevant difference in AMD.[13–15] Thus, in the current study, a 10-point or more change in the NEI VFQ-25 overall composite or subscale scores was used to estimate a clinically meaningful change in DME. The NEI VFQ-25 interview was administered before visual acuity measurements at a study visit by trained study site personnel who were masked to treatment assignment.

Data Analysis and Statistical Methods

Outcome measures included mean change from baseline in the best-corrected visual acuity score over time (up to 12 months and at 24 months) and mean change from baseline in NEI VFQ-25 scores for the near activities, distance activities, and vision-specific dependency subscales over time (up to 12 months and at 24 months). These subscales were given special attention because they seemed to be responsive to changes in visual acuity in previous trials of neovascular AMD patients.[16,17] The mean change from baseline at 24 months in overall composite score and the remaining 12 subscales of the NEI VFQ-25 were prespecified as exploratory efficacy outcomes in the RIDE and RISE statistical analysis plans. The analysis by better-seeing or worse-seeing eye was undertaken post hoc, after the planned NEI VFQ-25 analysis was completed. To maximize sample size for these post hoc analyses, data from both studies were pooled to examine results according to better-, same-, and worse-seeing study eye. Pooling the data for these exploratory analyses was judged reasonable because the protocol inclusion criteria, exclusion criteria, and methodologies were the same for RIDE and RISE, the baseline characteristics judged relevant to the main outcomes were similar across both studies, and the main outcomes judged relevant to these exploratory analyses seemed similar across both studies for most results.

All efficacy analyses presented herein were performed on a subset of the intent-to-treat patient population defined by better eye, neither the better nor worse eye, or worse eye; patients with missing visual acuity values in 1 or both eyes or baseline NEI VFQ-25 were excluded. Missing values were imputed using the last observation carried forward method. Sensitivity analyses based on observed data, with no imputation of missing data, also were performed. The NEI VFQ-25 results were similar regardless of whether missing data were imputed (data not shown).

Mean changes in study eye visual acuity from baseline to 12 and 24 months were compared between treatment groups using 95% confidence intervals (CIs) and t tests from analysis of variance stratified by baseline visual acuity (letter score >55 [approximate Snellen equivalent, 20/80 or better], letter score ≤ 55 [approximate Snellen equivalent, worse than 20/80]), baseline glycated hemoglobin value ($\leq 8\%$, $>8\%$), and prior therapy for DME (no, yes). Mean changes in NEI VFQ-25 subscale scores from baseline to follow-up interviews at 12 and 24 months were compared between treatment groups using 95% CIs and t tests from analysis of covariance stratified as described above for analysis of variance plus a covariate, the baseline value of the respective NEI VFQ-25 composite or subscale score. Patients achieving at least a 10-point gain on NEI VFQ-25 subscales at 12 or 24 months were compared using descriptive statistics (percentages and corresponding 95% CIs). Times for first achieving a 10-point gain or more in NEI VFQ-25 composite score (and confirmed to be sustained at the next qualifying visit or at the last visit by an observed, not an imputed, score) over 24 months also were compared descriptively with Kaplan-Meier time-to-event curves. Data from all interviews were analyzed using SAS software (SAS, Inc., Cary, NC).

Results

Demographic and Clinical Characteristics

Of the 382 patients enrolled in RIDE, 380 had baseline responses on the NEI VFQ-25. Of these patients, 128 were randomized to sham injections, 125 to 0.3 mg ranibizumab every 4 weeks, and 127 to 0.5 mg ranibizumab every 4 weeks. Of the 377 patients enrolled in RISE, 374 had baseline responses on the NEI VFQ-25. Of these patients, 125 were randomized to sham injections, 125 to 0.3 mg ranibizumab every 4 weeks, and 124 to 0.5 mg ranibizumab every 4 weeks.

In RIDE, 3 of 382 patients (0.79%) were excluded from this analysis because either their baseline visual acuity was evaluated in only 1 eye ($n = 1$) or no portion of the NEI VFQ-25 was completed at baseline ($n = 2$). In RISE, 4 of 377 patients (1.06%) were excluded because either their baseline visual acuity was evaluated in only 1 eye ($n = 1$) or no portion of the NEI VFQ-25 was completed at baseline ($n = 3$).

Baseline characteristics of interest for all eyes and by better-seeing eye and worse-seeing eye in each trial are shown in Table 1 (available at www.aaojournal.org). Data for eyes that were neither