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Impact of Cataract Surgery during Treatment with Ranibizumab in Patients with Diabetic Macular Edema

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Purpose: To determine how best-corrected visual acuity (BCVA) was affected by cataract surgery in patients with diabetic macular edema (DME) who were treated with ranibizumab during the RIDE/RISE phase III trials.

Design: Post hoc analysis of data from RIDE and RISE, 2 phase III, parallel, randomized, multicenter, double-masked trials (clinicaltrials.gov identifiers, NCT00473382 and NCT00473330).

Participants: Patients with DME (N = 759) who were randomized 1:1:1 to monthly intravitreal ranibizumab 0.3 mg or 0.5 mg, or sham injections for 24 months.

Methods: Patient records in the electronic HARBOR study database were examined for cataract surgeries using the terms "cataract extraction," "cataract removal," "cataract surgery," "lens implant," and "lensectomy." The last study visit immediately before cataract surgery served as the redefined baseline to examine subsequent BCVA changes. The *t* test was performed to compare times to cataract surgery for the sham and pooled ranibizumab groups.

Main Outcome Measures: Mean change in BCVA from redefined baseline to 1, 2, and 3 months (±15 days) after surgery.

Results: Among study eyes that underwent cataract surgery, mean BCVA at original study baseline was 54.6 letters in the pooled ranibizumab arms and 56.6 letters in the sham arm (approximate Snellen equivalent 20/80). At the redefined presurgery baseline, mean BCVA was 54.2 letters for the pooled ranibizumab group and 46.6 letters for the sham-treated study eyes. Compared with the redefined baseline, at 1 month after surgery, mean BCVA changes were +10.6 letters for ranibizumab-treated patients and +10.3 letters for sham-treated patients. Compared with the original baseline, at 1 month after surgery, on average, ranibizumab-treated study eyes experienced mean BCVA improvement (+11.3 letters), whereas sham-treated eyes (−0.5 letters) and fellow eyes (+1.8 and +1.7 letters for ranibizumab and sham, respectively) had a mean BCVA similar to the original baseline.

Conclusions: In patients undergoing ranibizumab treatment for DME and who had cataract surgery, an average of 2 lines of vision were gained from the last visit before surgery to 1 month after surgery. *Ophthalmology Retina 2017;■:1–5 © 2017 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/).*

Patients with diabetes have a higher risk of developing visually significant cataracts compared with phakic age-matched control patients without diabetes,[1,2] with an associated odds ratio of 1.97 (95% confidence interval, 1.45–2.67; $P < 0.001$).[2] One concern with performing cataract surgery in patients with diabetic macular edema (DME) is the potential risk of a transient worsening of the edema after surgery.[3] Increased inflammation and breakdown of the blood–retinal barrier may play a role in the development of macular edema after cataract extraction.[4] In support of this, it has been noted that there are increased levels of vascular endothelial growth factor (VEGF) within 1 month after cataract surgery.[3,5] Angiogenic and inflammatory mediators released after cataract surgery may increase the vascular permeability of retinal capillaries and cause exacerbated macular edema.[6] Therefore, the likelihood that this would develop in eyes that already have a compromised blood–retinal barrier due to preexisting diabetic retinopathy may be even higher.

Ranibizumab binds and inhibits all isoforms of VEGF-A and thereby works to reduce vascular hyperpermeability and to inhibit pathologic ocular neovascularization.[7] In the eyes of patients with DME, intravitreal ranibizumab treatment results in improvements in vision and normalization of retinal thickness.[8,9] In RIDE and RISE (clinicaltrials.gov identifiers: NCT00473382; NCT00473330),[8,9] 2 pivotal, multicenter, randomized, sham-controlled, phase III trials

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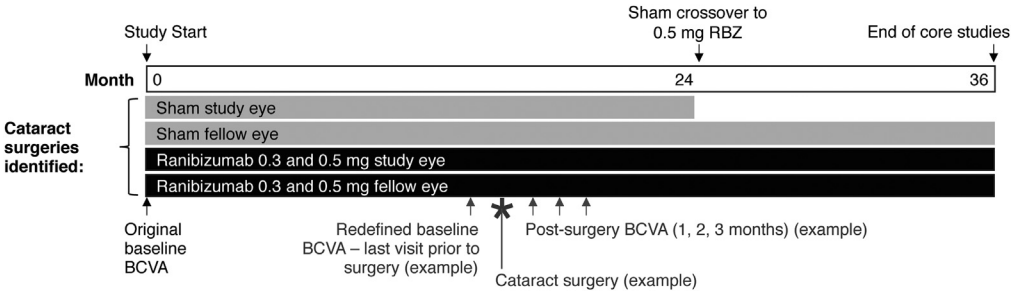

Figure 1. Study design. BCVA = best-corrected visual acuity; RBZ = ranibizumab.

that evaluated ranibizumab for DME, visual acuity and anatomic improvements were generally seen at the first follow-up visit (as early as 7 days after the first injection) and maintained throughout the 36-month core studies. We sought to determine what impact, if any, cataract surgical intervention had on the visual acuity of patients undergoing intraocular ranibizumab therapy for DME. In this analysis, we examined the vision outcomes immediately before and after cataract surgery in patients treated with ranibizumab for DME in the RIDE and RISE trials.

Methods

Detailed methods of RIDE and RISE have been published.[8,9] These trials were compliant with the Health Insurance Portability and Accountability Act and Declaration of Helsinki. Protocols were approved by institutional review boards or ethics committees at individual participating centers. All patients provided written informed consent before enrolling in the study. Patients received ranibizumab 0.3 or 0.5 mg or sham injections monthly for 24 months; then through month 36, monthly treatment continued for the ranibizumab arms, and patients in the sham arm crossed over to receive ranibizumab 0.5 mg.[8,9]

Per protocol, cataract surgery could be performed in the study eye if clinically indicated. Surgery was to occur 7 or more days after the last study injection, and the next injection was withheld for 28 or more days after the surgery. In the present retrospective analysis, data from the 2 studies were pooled. Patient records in the electronic HARBOR study database were examined post hoc to determine whether cataract surgery was performed during the study period by searching for the following terms: "cataract extraction," "cataract removal," "cataract surgery," "lens implant," and "lensectomy." Cataract surgeries were identified during the 36-month study period for study and fellow (nonstudy) eyes of ranibizumab-treated patients and fellow eyes of sham-treated patients (Fig 1). As a result of sham study eye cohort crossover to active treatment with ranibizumab 0.5 mg after month 24, study eyes of sham-treated patients were only assessed for cataract surgery during the first 24 study months.

The last study visit immediately before or on the date of scheduled cataract surgery was used as the redefined baseline to examine changes in best-corrected visual acuity (BCVA) after cataract surgery. Months after cataract surgery were defined as 30±15 days to account for variability in when surgery was performed relative to prespecified monthly study visits. The main outcome measure was the mean change in visual acuity from redefined baseline to months 1, 2, and 3 after cataract surgery, and was summarized with descriptive statistics. Baseline variables were compared between the sham and pooled ranibizumab groups using the *t* test for numeric variables and Pearson chi-square test for categoric variables. The *t* test was performed to compare time to cataract surgery between the sham and pooled ranibizumab groups and between the 0.3 and 0.5 mg ranibizumab arms. All analyses were conducted using the SAS software system (version 9.2; SAS Institute Inc, Cary, NC).

Results

Study Population

Of the pooled RIDE/RISE patients (N = 759), 69.4% (527) had study eyes that were phakic at baseline; 71.8% (544/758) of fellow eyes were phakic at baseline. A similar proportion of patients underwent

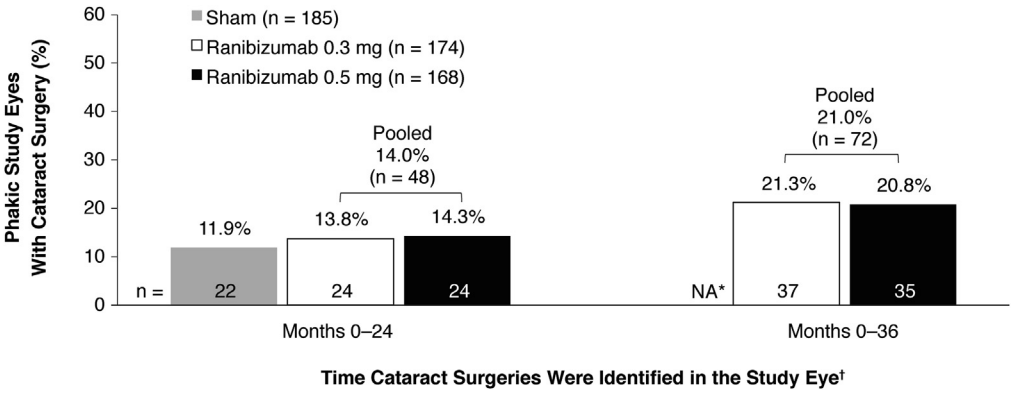

Figure 2. Percentage of phakic study eyes that underwent cataract surgery. *Surgeries that occurred in the sham arm between months 25 and 36 were not included in analyses because of crossover to ranibizumab 0.5 mg after month 24. †Excludes eyes that were pseudophakic at baseline. NA = not applicable.

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