Repeated Intravitreous Ranibizumab Injections for Diabetic Macular Edema and the Risk of Sustained Elevation of Intraocular Pressure or the Need for Ocular Hypotensive Treatment

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**IMPORTANCE** For the management of retinal disease, the use of intravitreous injections of anti–vascular endothelial growth factor has increased. Recent reports have suggested that this therapy may cause sustained elevation of intraocular pressure (IOP) and may potentially increase the risk of glaucoma for patients with retinal disease.

**OBJECTIVE** To assess the risk of sustained IOP elevation or the need for IOP-lowering treatments for eyes with diabetic macular edema following repeated intravitreous injections of ranibizumab.

**DESIGN, SETTING, AND PARTICIPANTS** An exploratory analysis was conducted within a Diabetic Retinopathy Clinical Research Network randomized clinical trial. Study enrollment dates were from March 20, 2007, to December 17, 2008. Of 582 eyes (of 486 participants) with center-involved diabetic macular edema and no preexisting open-angle glaucoma, 260 were randomly assigned to receive a sham injection plus focal/grid laser treatment, and 322 were randomly assigned to receive ranibizumab plus deferred or prompt focal/grid laser treatment.

**MAIN OUTCOMES AND MEASURES** The cumulative probability of sustained IOP elevation, defined as IOP of at least 22 mm Hg and an increase of at least 6 mm Hg from baseline at 2 consecutive visits, or the initiation or augmentation of ocular hypotensive therapy, through 3 years of follow-up.

**RESULTS** The mean (SD) baseline IOP in both treatment groups was 16 (3) mm Hg (range, 5-24 mm Hg). The cumulative probability of sustained IOP elevation or of initiation or augmentation of ocular hypotensive therapy by 3 years, after repeated ranibizumab injections, was 9.5% for the participants who received ranibizumab plus prompt or deferred focal/grid laser treatment vs 3.4% for the participants who received a sham injection plus focal/grid laser treatment (difference, 6.1% [99% CI, –0.2% to 12.3%]; hazard ratio, 2.9 [99% CI, 1.0-7.9]; P = .01). The distribution of IOP and the change in IOP from baseline at each visit through 3 years were similar in each group.

**CONCLUSIONS AND RELEVANCE** In eyes with center-involved diabetic macular edema and no prior open-angle glaucoma, repeated intravitreous injections of ranibizumab may increase the risk of sustained IOP elevation or the need for ocular hypotensive treatment. Clinicians should be aware of this risk and should consider this information when following up with patients who have received intravitreous injections of anti–vascular endothelial growth factor for the treatment of diabetic macular edema.
intravitreal injections of any agent may transiently increase the volume of the eye, which may also increase intraocular pressure (IOP). To our knowledge, the sustained elevation of IOP following repeated intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) in eyes with diabetic macular edema (DME) has not been previously reported. However, recent reports have suggested a potential association between repeated intravitreal anti-VEGF injections and sustained IOP elevation in eyes with age-related macular degeneration (AMD). Considering that sustained IOP elevation may increase the risk of developing glaucoma, further evaluation of a possible association between repeated intravitreal anti-VEGF injections and sustained IOP elevation in eyes with age-related macular degeneration (AMD). An exploratory ad hoc analysis that assesses whether repeated intravitreal injections of ranibizumab increase the risk of sustained elevation of IOP or of initiation or augmentation of IOP-lowering treatment in eyes with DME compared with eyes receiving focal/grid laser treatment through 3 years is reported herein.

Methods

Study Design

The Diabetic Retinopathy Clinical Research Network (DR-CR.net) study “Intravitreal Ranibizumab or Triamcinolone Acetonide in Combination With Laser Photocoagulation for Diabetic Macular Edema Trial” (NCT00444600) was a multicenter randomized clinical trial that compared patients who received focal/grid laser treatment with patients who received 0.5 mg of intravitreal ranibizumab with prompt or deferred (≥24 weeks) laser treatment and patients who received 4 mg of intravitreal triamcinolone plus prompt laser treatment, for the treatment of center-involved DME causing vision impairment. Only eyes randomly assigned to the sham injection plus prompt laser treatment, to the ranibizumab injection plus prompt laser treatment, or to the ranibizumab injection plus deferred laser treatment were included in this report. Data from the ranibizumab groups were similar (data not shown) and are therefore combined in our report. The complete protocol is available online (http://www.drcr.net), and the trial methods, treatment algorithm, and efficacy and safety results have been published elsewhere. Our study adhered to the tenets of the Declaration of Helsinki. The patients provided written informed consent. The consent forms were compliant with the protocol and the Health Insurance Portability and Accountability Act, and they and the study were approved by multiple institutional review boards. Study enrollment dates were from March 20, 2007, to December 17, 2008.

We note that, relevant to our report, patients with a history of open-angle glaucoma or steroid-induced IOP elevation that required IOP-lowering treatment, patients with neovascular glaucoma, or patients with IOP of 25 mm Hg or higher at baseline were ineligible for the trial. However, having a history of angle-closure glaucoma was not an exclusion criterion. Eyes were permitted to have ocular hypertension if IOP was less than 25 mm Hg with use of up to 1 topical glaucoma medication. Gonioscopy was not performed at baseline. Both eyes from the same participant could be enrolled if they both were eligible, with one eye randomly assigned to the sham injection plus prompt laser treatment and the other assigned to 1 of the 3 remaining treatments.

Although not required, it was recommended that the IOP measurements occur before pupillary dilation. Of the 645 eyes randomly assigned to the sham group or the ranibizumab group, 63 (10%) (8.5% in the sham group and 11% in the ranibizumab group) in the original study cohort with a baseline IOP measurement obtained after dilation were excluded from the analysis cohort. Follow-up IOP measurements obtained after dilation also were excluded from analyses. The method used to obtain the IOP measurement was at the discretion of the investigator. Measurements obtained with a Goldmann applanation tonometer were combined with those obtained from the use of Tono-Pen (Reichert Technologies) or some other similar device.

Study Outcome

The primary outcome was defined as sustained IOP elevation (IOP of at least 22 mm Hg, with an increase of at least 6 mm Hg from baseline occurring at 2 consecutive visits at least 1 month apart) or initiation or augmentation of IOP-lowering treatments, including ocular hypotensive medications, laser trabeculoplasty, or surgery. These thresholds were selected because the majority of the general population has IOP measurements below 22 mm Hg and IOP variability of less than 6 mm Hg between visits. Intraocular pressure of 30 mm Hg or higher and an increase in IOP of 10 mm Hg or more also were reported because these were prespecified safety outcomes for this protocol.

Protocol visits occurred every 4 weeks during the first year of follow-up. After 1 year, the frequency between visits differed according to treatment group; therefore, only data collected at visits that occurred at 16-week intervals, which were common to all treatment groups, were included in the sustained IOP definition after 52 weeks.

Statistical Analysis

The hazard ratio for the composite study outcome over the 3 years of follow-up and the corresponding 99% CI were estimated with the Cox proportional hazards model, with adjustment for correlation between study eyes from the same participant. The cumulative probabilities of outcome and standard errors from this model were used to estimate the cumulative outcome rate at 3 years by treatment group and construct a 99% CI on the difference using a z score method. The association between the number of injections and the primary outcome was evaluated by including the number of injections as a time-dependent covariate in a proportional hazards model. Table reports the reasons for data censoring in the primary outcome analysis. The results for the treatment groups were similar from a sensitivity analysis of censoring data at the time of cataract surgery during study participation for 126 of 582 eyes (22%) (data not shown). All analyses were conducted using SAS version 9.3 (SAS Institute Inc.).
Results

A total of 486 participants contributed 582 study eyes, among which 260 were randomly assigned to receive a sham injection plus focal/grid laser treatment and 322 were randomly assigned to receive ranibizumab plus deferred or prompt focal/grid laser treatment. The baseline characteristics were similar in each group (Table 2). Three percent of study eyes in each group had a history of glaucoma or were treated with IOP-lowering medications at baseline. Primary and secondary forms of open-angle glaucoma were exclusion criteria; therefore, eyes with a reported history of glaucoma at baseline (5 eyes that received a sham injection plus focal/grid laser treatment and 3 eyes that received ranibizumab plus deferred or prompt focal/grid laser treatment) were presumed to have had previous angle-closure glaucoma or were misreported. The majority (82%) of baseline measurements were obtained with Goldmann tonometry. Through the 3-year visit, 59% and 63% of all IOP measurements in sham and ranibizumab groups, respectively, were obtained with Goldmann tonometry, and 72% and 79% of eyes in sham and ranibizumab groups, respectively, had IOP measurements consistently obtained with the same method (with the Goldmann applanation tonometer or Tono-Pen).

The cumulative probability of the primary outcome of sustained IOP elevation or the need for IOP-lowering therapy through the first year was 2.0% and 5.7% in the sham and ranibizumab groups, respectively. Throughout the first year of the study, the patients in both the sham and ranibizumab groups had an average of 13 visits. Among eyes that were still at risk of meeting the outcome at 1 year (ie, those without the outcome and not censored before the 1-year visit), the mean (SD) number of injections received was 10 (4) in the sham group and 8 (3) in the ranibizumab group.

During the 3-year study period, 6 eyes in the sham group and 22 eyes in the ranibizumab groups met the composite outcome for a 3-year cumulative probability of 3.4% and 9.5% in the sham and ranibizumab groups, respectively, for a difference of 6.1% (99% CI, −0.2% to 12.3%) (hazard ratio for ranibizumab group vs sham group, 2.9 [99% CI, 1.0–7.9]; P = .01) (Figure 1). One eye in the sham group and 2 eyes in the ranibizumab groups that met the study outcome had a history of (presumed angle-closure) glaucoma or were treated with IOP-lowering medication prior to study entry.

During the 3-year follow-up period, among the 6 eyes in the sham group and the 22 eyes in the ranibizumab groups that met the primary outcome, the mean IOP at the time of the event was 23 and 28 mm Hg, respectively; the mean change in IOP from baseline was 7 and 9 mm Hg, respectively. Intraocular pressure measurements were not available at the time of the primary outcome in 3 and 2 eyes from the sham and ranibizumab groups, respectively, because initiation of IOP medication did not coincide with a study visit.

At any single visit, an increase in IOP of 10 mm Hg or higher from baseline occurred in 5% and 4% of eyes in the sham and ranibizumab groups, respectively, through year 1 and in 9% and 6% of eyes through the 3-year visit, respectively. Intraocular pressure of 30 mm Hg or higher at any single visit was reported in 1% and 2% of eyes in the sham and ranibizumab groups, respectively, through year 1 and in 3% and 2% of eyes through year 3, respectively. There were no eyes at risk for the study outcome that required an IOP-lowering procedure (laser or intraocular surgery) throughout the 3-year period (Table 3).
Among the 22 eyes in the ranibizumab group that met the primary outcome during the 3 years of follow-up, the mean (SD) cumulative number of ranibizumab injections received through 3 years in eyes that completed the 3-year visit (n = 116), without meeting the composite outcome, was 15 (8). The number of injections received was not associated with the primary outcome when it was included in the proportional hazards model as a time-dependent covariate (hazard ratio, 0.95 [95% CI, 0.83-1.10]; P = .50). The distribution of IOP and IOP change from baseline through 3 years at each visit was similar across treatment groups (Figure 2).

Discussion
In this ad hoc analysis of phase 3 clinical trial data evaluating repeated ranibizumab injections in eyes with DME, the cumulative number of ranibizumab injections at the time of meeting the outcome was 7 (4). The mean (SD) cumulative number of injections in patients with outcomes was 15 (8). The number of injections received was not associated with the primary outcome when it was included in the proportional hazards model as a time-dependent covariate (hazard ratio, 0.95 [95% CI, 0.83-1.10]; P = .50). The distribution of IOP and IOP change from baseline through 3 years at each visit was similar across treatment groups (Figure 2).

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Primary outcome was defined as sustained intracocular pressure (IOP) elevation (IOP of ≥22 mm Hg, with an increase of ≥6 mm Hg from baseline occurring at 2 consecutive visits ≥1 month apart) or initiation or augmentation of IOP-lowering treatments, including ocular hypotensive medications, laser trabeculoplasty, or surgery. The number of eyes at risk are the eyes at the start of the interval that did not meet the definition of sustained IOP or that did not receive IOP-lowering therapy prior to the start of the interval. The number of events are those events in which the eyes met the definition of sustained IOP or received IOP-lowering therapy in the prior interval. Eyes with ocular hypertension at study entry are not included in the composite study outcome unless they fulfilled the criteria for the study outcome during the study follow-up. HR indicates hazard ratio.

Intravitreous injections of therapeutic agents may transiently elevate IOP or lead to a sustained elevation of IOP. Elevated IOP is an important risk factor for glaucoma, which raises concerns about the long-term safety of administering intravitreous injections. Theories potentially explaining the relationship between repeated intravitreous injections and elevated IOP include increased inflammation, and mechanical or functional alteration of the trabecular meshwork. Several studies of patients with neovascular AMD receiving repeated injections of anti-VEGF agents have reported rates of sustained IOP elevations varying from 3% to 13%. Definitions of “sustained” IOP differed across these studies, which may account for the variability. Some of these studies were retrospective, some did not have standardized procedures for measuring IOP, and some lacked a control arm for comparison. In large randomized trials for neovascular AMD, the frequency of IOP-related serious ocular adverse events and the mean IOP measurements over time were similar between eyes managed with repeated intravitreous injections (at least 24) and...
Table 3. Cumulative Percentage With Sustained IOP Elevation or Ocular Hypotensive Treatment, by Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Through Year 1a</th>
<th>Through Year 3b</th>
<th>Only Bilateral Study Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (n=260)</td>
<td>Ranibizumab (n=322)</td>
<td>Sham (n=96)</td>
</tr>
<tr>
<td>Composite outcomea</td>
<td>2.0</td>
<td>5.7</td>
<td>3.4</td>
</tr>
<tr>
<td>No. of eyes meeting</td>
<td>5</td>
<td>15</td>
<td>6</td>
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<tr>
<td>Cumulative probability, %</td>
<td>2.0</td>
<td>5.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Sustained IOP elevation component of study outcome only</td>
<td>2.0</td>
<td>5.7</td>
<td>3.4</td>
</tr>
<tr>
<td>No. of eyes meeting outcome</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Cumulative probability, %</td>
<td>0.7</td>
<td>2.4</td>
<td>1.1</td>
</tr>
<tr>
<td>IOP medication component of study outcome only</td>
<td>2.0</td>
<td>5.7</td>
<td>3.4</td>
</tr>
<tr>
<td>No. of eyes meeting outcome</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Cumulative probability, %</td>
<td>0.9</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Both sustained IOP elevation and medication component of study outcome met</td>
<td>2.0</td>
<td>5.7</td>
<td>3.4</td>
</tr>
<tr>
<td>No. of eyes meeting outcome</td>
<td>1</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Cumulative probability, %</td>
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<td>1.9</td>
<td>0.5</td>
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<td>Any glaucoma procedure</td>
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<td>0</td>
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<tr>
<td>No. of eyes meeting outcome</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cumulative probability, %</td>
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<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Abbreviation: IOP, intraocular pressure.

a Eyes with ocular hypertension at study entry are not included in the composite study outcome unless they fulfilled the criteria for the study outcome during the study follow-up.

b Study visits every 4 weeks through 1 year, then every 16 weeks thereafter.

c Study visits every 4 weeks through 1 year, then every 16 weeks thereafter.

The majority of eyes that met the study outcome did so within the first year of treatment when the requirement for monthly study visits facilitated detection of sustained IOP elevation relative to later follow-up, when visits were less frequent. This is the interval in which we have the greatest confidence in our data, given an identical visit schedule for all treatment arms that limits potential ascertainment bias.

A review of the average number of injections at the time of an event through 3 years and the IOP distribution among eyes across a spectrum of total numbers of injections did not suggest that the number of intravitreous injections was linked to the outcomes of interest. Furthermore, including the number of injections as a time-dependent covariate in the proportional hazards model did not reveal an association with the primary outcome. Past studies evaluating eyes with neovascular AMD have reported an inconsistent relationship between total number of injections and increase in IOP.9,19,20 Although we explored the effect of repeated intravitreous anti-VEGF injections on IOP, we did not explore the potential mechanism(s) by which these injections might influence the IOP.

The study composite outcome was selected to capture eyes believed to be at increased risk of glaucoma for which intervention may be indicated to preserve vision. Thresholds for IOP level and change from baseline were defined to exclude those that were likely within the normal range. The criteria used are similar to previous studies exploring this issue.5,7,24 Our data have limitations in that we chose a conservative outcome that combined sustained elevated IOP and variability of IOP. Given that IOP and variability of IOP are 2 separate risk factors for glaucoma.
primary outcome between treatment groups, we do not know if the difference in our study provides information on risk of sustained IOP elevation or the requirement for ocular hypotensive therapy, which are risk factors for glaucoma.

Additional limitations of our study include the fact that treating physicians were unmasked to treatment assignment, the fact that they generally examined ranibizumab-treated participants more often than participants who received laser treatment only during years 2 and 3 (which increased the probability of capturing an event), and the fact that the protocol did not specify initiation of IOP-lowering therapy at a specific threshold. Study ophthalmologists may have been biased to withhold therapy to eyes receiving a sham injection when IOP fluctuations occurred or to initiate treatment in eyes receiving an intravitreous injection when minimal changes in IOP occurred.

A particular strength of our review is the subgroup analysis of participants with 2 study eyes, one randomly assigned to receive a sham injection and the other randomly assigned to receive ranibizumab. The endogenous factors that would predispose these study eyes to glaucoma should be similar between the sham and ranibizumab groups, affording the opportunity to isolate the effects of the intravitreous injection. In this bilateral subgroup, the eyes of participants who received intravitreous injections appeared to behave similarly to the eyes of the participants in the full cohort. Although more data were censored from the eyes that received sham injections because of the per-protocol switch to anti-VEGF injections, it is unlikely that censoring these data resulted in bias because there is no rationale for why eyes that received sham injections but then received anti-VEGF injections would have increased susceptibility to IOP elevation relative to eyes that received sham injections only. Additional strengths of the full analysis include the large number of eyes evaluated, the prospective data collected, the standardized intervals between IOP assessments during the first year of follow-up, and the censoring of data for intervening factors that could affect IOP, such as corticosteroid use, vitreous hemorrhage, and vitrectomy.

Conclusions

Repeated intravitreous injections of ranibizumab were associated with an increased risk of sustained elevation in IOP or initiation of medications to lower IOP. This exploratory analysis suggests about a 3-fold increased risk of sustained IOP elevation or initiation of IOP-lowering treatment among individuals treated with an average of 15 intravitreous ranibizumab injections over 3 years for DME in the absence of a history of open-angle glaucoma. Although the risk of meeting the outcome appeared higher in the ranibizumab group than it did in the sham group, it is unknown whether this difference is related to intravitreous injections of 0.05 mL of fluid, to the ranibizumab itself, and/or to certain intrinsic factors in eyes that made them more susceptible. Because they were ineligible, our study provides no information of risk of sustained IOP elevation for patients receiving repeated intravitreous ranibi-
zumab injections who have open-angle glaucoma or who have ocular hypertension with IOP of 25 mm Hg or higher that requires treatment with more than 1 medication, or for patients who have had a steroid-associated increase in IOP in the past. The absolute increase in the percentage of people that may be affected appears to be limited, and the magnitude of risk for actual loss of vision remains unknown. These data suggest that IOP should be monitored periodically in eyes receiving repeated injections of anti-VEGF, with consideration of ancillary testing and referral or treatment as needed.
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Sustained IOP Elevation With Repeated Anti-VEGF Injections

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