Original Investigation

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.

JAMA Ophthalmol. 2015;133(5):589-597. doi:10.1001/jamaophthalmol.2015.186
Published online February 26, 2015.

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Intravitreous injections of any agent may transiently increase the volume of the eye, which may also increase intraocular pressure (IOP).[1-4] To our knowledge, the sustained elevation of IOP following repeated intravitreous injections of anti-vascular endothelial growth factor (anti-VEGF) in eyes with diabetic macular edema (DME) has not been previously reported. However, recent reports[5-9] have suggested a potential association between repeated intravitreous 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 intravitreous anti-VEGF injections and sustained IOP elevation is indicated.[5,6,10-13] An exploratory ad hoc analysis that assesses whether repeated intravitreous 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 (DRCR.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 intravitreous ranibizumab with prompt or deferred (≥24 weeks) laser treatment and patients who received 4 mg of intravitreous 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.[14-16] 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.[14]

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 2 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 1** 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).

Table 1. Participant Disposition and Data Censoring During 3-Year Follow-up

Disposition	Sham Group (n = 260)	Ranibizumab Group (n = 322)	Total (n = 582)
Met primary outcome,[a] No. of eyes	6	22	28
Did not meet primary outcome, No. of eyes	254	300	554
Censored prior to 3 y,[b] No. (%) of eyes	201 (79)	184 (61)	385 (69)
Reason for censoring			
Lost to follow-up	7 (3)	9 (3)	16 (3)
Withdrew from study	13 (5)	18 (6)	31 (6)
Death	15 (6)	16 (5)	31 (6)
Exposure to corticosteroids[c]	65 (26)	92 (31)	157 (28)
Sham group eyes receiving anti-VEGF	64 (25)	0 (0)	64 (12)
Too many consecutively missed visits or only postdilation IOP[d]	27 (11)	38 (13)	65 (12)
Vitrectomy	9 (4)	7 (2)	16 (3)
Neovascular or ghost-cell glaucoma or endophthalmitis	1 (0.4)	4 (1)	5 (0.9)
Completed 3-y visit, No. (%) of eyes	53 (21)	116 (39)	169 (31)

Abbreviations: Anti-VEGF, anti–vascular endothelial growth factor; IOP, intraocular pressure.

[a] Persistent IOP elevation (IOP ≥ 22 mm Hg at 2 consecutive visits ≥4 weeks apart with ≥6–mm Hg increase in IOP from baseline) or initiation or augmentation of IOP-lowering medicine or surgery.

[b] Data censored on date of exposure.

[c] Oral, nasal, intra-articular, intramuscular, inhaler, topical cutaneous, intravenous, subcutaneous, topical ocular, intradermal, or transdermal.

[d] Data from eyes with 4 or more IOP measurements missing during year 1 and data from eyes missing any 16-week IOP measurement after year 1 were censored, as were data from eyes with IOP exclusively measured after dilation.

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**).

Table 2. Baseline Characteristics of Analysis Cohort

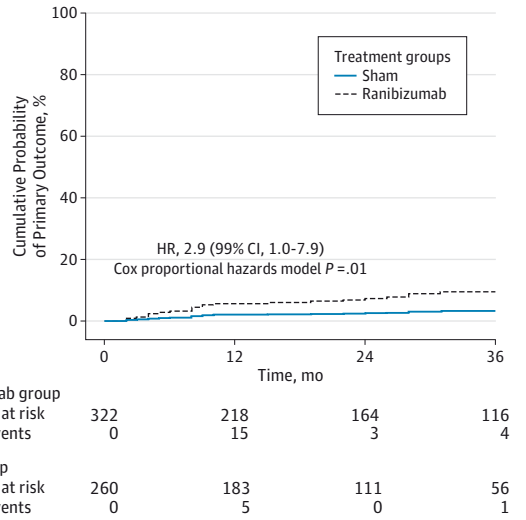
Characteristic	No. (%) of Eyes	
	Sham Group (n = 260)	Ranibizumab Group (n = 322)
Age at randomization, mean (SD), y	63 (10)	63 (10)
Female sex	113 (43)	138 (43)
Race/ethnicity		
White	188 (72)	237 (74)
Black or African American	48 (18)	53 (16)
Hispanic or Latino	19 (7)	24 (7)
Other	5 (2)	8 (2)
Bilateral study eyes	96 (37)	96 (30)
Baseline IOP, mm Hg		
Mean (SD)	16 (3)	16 (3)
Range	8-24	5-24
IOP of 22-24 mm Hg	10 (4)	16 (5)
Device used for IOP measurement		
Goldmann applanation tonometer	213 (82)	263 (82)
Tono-Pen (Reichart Technologies)[a]	47 (18)	59 (18)
History of glaucoma[b]	5 (2)	3 (0.9)
IOP-lowering treatment at baseline with history of glaucoma	2 (0.8)	1 (0.3)
IOP-lowering treatment at baseline without history of glaucoma	3 (1)	7 (2)

Abbreviation: IOP, intraocular pressure.

[a] Or some other similar device.

[b] No study eyes had a history of primary or secondary open-angle glaucoma because these were study exclusion criteria. However, these eyes had a history of glaucoma presumed to be angle-closure glaucoma or were misreported.

Figure 1. Cumulative Probability of the Composite Study Outcome Through 3 Years



Primary outcome was defined as sustained intraocular 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.

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 at the time of meeting the outcome was 7 (4). 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**).

Ninety-six participants had 2 study eyes in the trial, with 1 eye randomly assigned to receive a sham injection plus focal/grid laser treatment and the other to receive ranibizumab plus deferred or prompt focal/grid laser treatment. Within this restricted cohort, the cumulative probability of meeting the study outcome was 8.3% and 15.0% in the sham and ranibizumab groups, respectively, for a differences of 6.6% (99% CI, −8% to 21%) (hazard ratio for ranibizumab group vs sham group, 1.9 [99% CI, 0.7-5.1]; P = .11).

Discussion

In this ad hoc analysis of phase 3 clinical trial data evaluating repeated ranibizumab injections in eyes with DME, the cumulative rate of sustained IOP elevation or initiation or augmentation of therapy for elevated IOP through 3 years of visits was higher in eyes that were randomly assigned to receive ranibizumab injections (with deferred or prompt focal/grid laser treatment) than in eyes that were randomly assigned to receive focal/grid laser treatment alone.

Intravitreous injections of therapeutic agents may transiently elevate IOP or lead to a sustained elevation of IOP.[2,4,9] 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[5-9] 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,[5-9] 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[a]

Outcome	Through Year 1[b]		Through Year 3[c]			
			All Eyes		Only Bilateral Study Eyes	
	Sham (n=260)	Ranibizumab (n=322)	Sham (n=260)	Ranibizumab (n=322)	Sham (n=96)	Ranibizumab (n=96)
Composite outcome[d]						
No. of eyes meeting	5	15	6	22	5	10
Cumulative probability, %	2.0	5.7	3.4	9.5	8.3	15.0
Sustained IOP elevation component of study outcome only						
No. of eyes meeting outcome	2	6	2	9	2	4
Cumulative probability, %	0.7	2.4	1.1	3.8	2.6	5.1
IOP medication component of study outcome only						
No. of eyes meeting outcome	2	4	3	7	2	2
Cumulative probability, %	0.9	1.5	1.9	3.2	4.7	3.7
Both sustained IOP elevation and medication component of study outcome met						
No. of eyes meeting outcome	1	5	1	6	1	4
Cumulative probability, %	0.4	1.9	0.5	2.4	1.6	5.8
Any glaucoma procedure						
No. of eyes meeting outcome	0	0	0	0	0	0
Cumulative probability, %	0.0	0.0	0.0	0.0	0.0	0.0

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.

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

[d] Sustained 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 for glaucoma.

control eyes.[2,9,17,18] More recently, in a post hoc analysis of the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trial and the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA), investigators reported that 11% of ranibizumab-treated eyes had IOP of at least 25 mm Hg and that 5% of control eyes behaved similarly.[9] Also, a combined end point of 6 mm Hg or more in the increase in IOP from baseline with IOP of at least 21 mm Hg was more common for eyes treated with ranibizumab.[9]

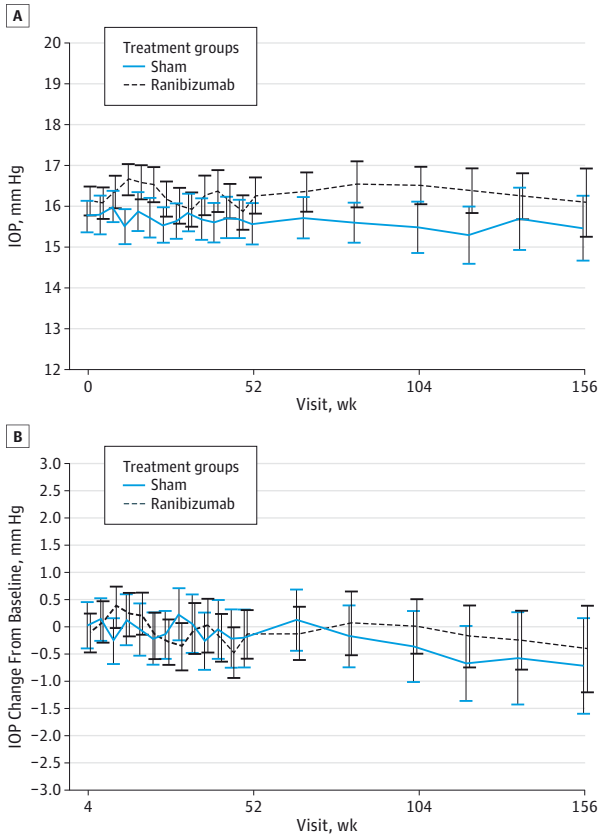
This analysis explored a potential association between repeated intravitreous injections of ranibizumab and an increased risk of sustained IOP elevation or ocular hypotensive therapy for eyes with DME. The cumulative probability of meeting the composite study outcome was approximately 3 times higher for eyes managed with repeated intravitreous injections than for eyes receiving sham injections, with an absolute increase in risk of 6% at 3 years. However, because the total number of events was small, the confidence intervals around the estimates are wide, indicating that ranibizumab-treated eyes may have anywhere from 6 times the risk of this event to no increased risk. It is unknown whether eyes with the outcome had visual field or optic nerve alterations because these glaucoma assessments were not collected. Other risk factors for glaucoma, such as central corneal thickness and family history of glaucoma, were not evaluated in our study. In most cases, these eyes were managed solely with observation or a single medication.

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.[5,7,21] 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 glau-

Figure 2. Distribution of Intraocular Pressure (IOP) (A) and IOP Change (B) From Baseline at Each Visit Through 3 Years



Error bars represent 95% CIs.

coma, the proportion of participants in our study at risk may be higher than our results suggest. In addition, IOP may have been subject to diurnal fluctuations or variation between the 2 measurement techniques used for IOP determination, and there was no stratification at enrollment for glaucoma risk factors. Eyes that received new IOP-lowering medications were part of the outcome, irrespective of whether they manifested sustained IOP elevation. To what extent the eyes that met our study outcome were truly at risk of glaucoma and its consequences on visual fields is unknown. The mean (SD) level of IOP at the time at which sustained elevation in IOP was met in the ranibizumab groups was 28 (6) mm Hg (range, 22-43 mm Hg), whereas initiation of IOP-lowering therapy was deferred in 9 of these 15 eyes (60%). The mean IOP was 30 mm Hg (range, 23-42 mm Hg) among the ranibizumab-treated eyes that only met the criteria of IOP-lowering medications and for which an IOP measurement was collected at the same visit; however, these data were captured incompletely. Throughout the study, there was no difference identified between eyes in the sham group and eyes in the ranibizumab group for any serious IOP complications, including an IOP increase of at least 30 mm Hg, an increase of at least 10 mm Hg from baseline, or the need for IOP-lowering surgical or laser procedures. Although there was a difference in our primary outcome between treatment groups, we do not know the clinical relevance of this finding. This analysis was not designed to determine incidence of glaucoma but, rather, to determine the incidence 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.

ARTICLE INFORMATION

Submitted for Publication: July 11, 2014; final revision received November 7, 2014; accepted January 12, 2015.

Published Online: February 26, 2015. doi:10.1001/jamaophthalmol.2015.186.

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Obtained funding: Glassman, Jampol.
Administrative, technical, or material support: S. B. Bressler, Almukhtar, Glassman.
Study supervision: S. B. Bressler, Glassman, Jampol, Melia.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and Dr N. M. Bressler reports having received grants from Bayer, Emmes, Genetech, Norvartis Pharma AG, Northwestern University, and Regeneron outside the submitted work; Dr S. B. Bressler reports having received grants from Boehringer Ingelheim Pharma, Emmes, Lumenis, Notal Vision Ltd, Novartis, Regeneron, and ThromboGenics NV and personal fees from GlaxoSmithKline, all outside the submitted work; Dr Jampol reports having received grants from the National Eye Institute during the conduct of the study and other support from Novartis and personal fees from Quintiles/Stem Cell Organization outside the submitted work; Dr Kim reports having received personal fees from Alimera Sciences, personal fees from Allergan, Bayer, Novartis, and ThromboGenics, and other support from Optos, all outside the submitted work; and Ms Melia reports having received grants from the National Eye Institute during the conduct of the study and personal fees from Alimera Sciences outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported by a cooperative agreement from the National Eye Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health, and the US Department of Health and Human Services (grants EY14231, EY14229, and EY18817).

Role of the Funder/Sponsor: The National Institutes of Health participated in oversight of the conduct of the study and review of the manuscript, but had no direct role in the design of the study; collection, management, analysis, or interpretation of the data; preparation or approval of the manuscript; and decision to submit the manuscript for publication.

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Disclaimer: Dr N. M. Bressler is the *JAMA Ophthalmology* editor but was not involved in the review process or the acceptance of the manuscript.

Previous Presentations: This paper was presented at the 31st Annual Meeting of the American Society of Retina Specialists; August 27, 2013; Toronto, Ontario, Canada; the Annual Meeting of the World Ophthalmology Congress; April 5, 2014; Tokyo, Japan; the 37th Annual Meeting of the Macula Society; February 21, 2014; Key Largo, Florida; and the 47th Annual Meeting of the Retina Society; September 14, 2014; Philadelphia, Pennsylvania.

Additional Information: As per the DRCR.net Industry Collaboration Guidelines (available at http://www.drcr.net), the DRCR.net had complete control over the design of the protocol and ownership of the data and all editorial content of presentations and publications related to the protocol. Genentech has provided funds restricted to DRCR.net clinical sites.

Additional Contributions: Genentech provided the ranibizumab for this study.

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