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The Real-World Effect of Intravitreous Anti–Vascular Endothelial Growth Factor Drugs on Intraocular Pressure

An Analysis Using the IRIS Registry

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Purpose: To identify sustained differences in intraocular pressure (IOP) after intravitreous injections of anti–vascular endothelial growth factor (VEGF) drugs.

Design: Database study.

Participants: Patients seeing an ophthalmic provider who contributes to the database.

Methods: We identified a total of 23 776 unique patients who received only a single type of anti-VEGF medication (bevacizumab, aflibercept, or ranibizumab) by injection in the right eye in the American Academy of Ophthalmology Intelligent Research in Sight Registry. Subgroups included patients with age-related macular degeneration only and patients who had not received an anti-VEGF injection for at least 1 year before the study. We examined those with at least 12, 18, and 25 injections for each of these 3 medications. For all groups, we used fellow, untreated eyes for comparison.

Main Outcome Measures: The mean change in IOP from baseline at a minimum of 1 year of follow-up and the proportion of eyes with a clinically significant IOP increase (defined as sustained rise of at least 6 mmHg to an IOP of more than 21 mmHg).

Results: All patients in all groups receiving all drugs showed a decrease in IOP from baseline, with a mean of 0.9 mmHg in treated eyes compared with an average decrease of 0.2 mmHg in fellow untreated eyes, a statistically significant difference. A generalized linear model accounting for confounders associated bevacizumab with slightly less lowering of IOP than aflibercept and ranibizumab in most subgroups. A clinically significant IOP increase was seen in 2.6% of eyes receiving injections compared with 1.5% in the associated untreated fellow eyes. Clinically significant IOP increases occurred at a rate of 1.9%, 2.8%, and 2.8% for aflibercept, ranibizumab, and bevacizumab, respectively, which was significantly higher than untreated fellow eyes for bevacizumab and ranibizumab, but not for aflibercept.

Conclusions: These analyses from real-world data indicate that anti-VEGF intravitreous injections are associated with a small but statistically significant decrease in IOP over time. A proportion of patients, on average 2.6%, experienced a sustained clinically significant IOP rise with these drugs overall compared with 1.5% in the fellow untreated eyes. However, such an increase was not seen with aflibercept. *Ophthalmology 2017;■:1–7 © 2017 by the American Academy of Ophthalmology*

Anti–vascular endothelial growth factor (VEGF) intravitreous injections have been proven effective for several retinal pathologic features. Originally developed for oncology, these drugs work by preventing VEGF from binding to VEGF receptors, which stimulate neovascularization and vascular permeability. This class of drugs was used in the eye first for exudative age-related macular degeneration (AMD). Since then, multiple large trials, including ANCHOR, MARINA, VIEW, PIER, HORIZON, CATT, IVAN, and HARBOR, have shown the usefulness of anti-VEGF injections for improving vision in AMD.[1–9] Subsequently, anti-VEGF injections have been shown to be effective for macular edema after retinal vein occlusions (the BRAVO, CRUISE, GALILEO, COPERNICUS, and VIBRANT studies) and diabetic macular edema (DME; BOLT and the Diabetic Retinopathy Clinical Research Network [DRCRnet] trials).[10–16] Intravitreous injection has become one of the most common procedures in medicine. The American Academy of Ophthalmology Intelligent Research in Sight (IRIS) Registry includes 524 485 patients who received 2 419 931 anti-VEGF injections in 2016 alone.

With the delivery of such a large number of injections, it is important to consider the side effects. It is known that immediately after injection, there is a transient spike in intraocular pressure (IOP) to a mean of 44 mmHg that

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quickly decreases to less than 30 mmHg in the first 15 minutes for most patients after injection.[17,18] However, there has been ongoing debate about the degree to which anti-VEGF agents cause sustained increases in IOP. In 2 large trials using ranibizumab to treat exudative AMD, 6% of eyes showed an IOP increase of 8 mmHg or more in the injected group, compared with 4% of fellow eyes after 2 years.[19] A study of 582 eyes found that those eyes receiving ranibizumab for DME were almost 3 times more likely to show an IOP increase of at least 6 mmHg, resulting in an absolute IOP of at least 22 mmHg after 2 years.[1] Two relatively large trials using ranibizumab or aflibercept every 4 weeks to treat neovascular AMD found 19.7% and 14.1% eyes, respectively, demonstrated a sustained IOP increase of at least 5 mmHg at 96 weeks compared with baseline.[20] However, all of these studies examined a much smaller sample than the IRIS Registry and are limited by not being real-world data, because the data were gathered in the somewhat artificial environment of a clinical trial or from a single practice. Our study aimed to address this question using a much larger dataset that is more representative of most clinical practices.

Methods

This was a post hoc analysis of patients included in the IRIS Registry, an observational longitudinal dataset that started collecting records in January 2013. Analysis included patients who received an intravitreous injection with aflibercept, bevacizumab, or ranibizumab in the right eye for a diagnosis of AMD, macular edema resulting from branch or central retinal vein occlusion, or DME between January 1, 2013, and December 31, 2015. Exclusion criteria were receiving more than 1 type of anti-VEGF drug or an intravitreous corticosteroid injection in the treated right eye or receiving any intravitreous drug in the untreated fellow eye during the study period. Eyes lacking at least 1 year of follow-up, at least 1 baseline (preinjection) and postinjection IOP measurement, or indication of poor data quality from the site also were excluded.

Analysis included 3 primary groups: all patients, patients with a diagnosis of AMD, and patients who were treatment naïve for at least 1 year before the start of the study. We examined the untreated, fellow left eyes of these patients. Finally, because of concerns for increased risk of IOP rise with increasing number of injections, we evaluated a subset of patients who received at least 12, 18, and 25 injections during the study period.

For each drug in each group, we calculated mean change from baseline to the last IOP measurement at least 1 year after the first injection. For each group, we calculated the proportion of patients with a baseline IOP $\leq$21 mmHg who showed an IOP rise of at least 6 mmHg that resulted in an IOP of more than 21 mmHg (defined as a clinically significant IOP increase). A generalized linear model (GLM) repeated measures analysis of longitudinal observational data assessed for significant effects of relevant factors. This model controlled for potential confounders including gender, race, age, number of anti-VEGF injections, history of glaucoma, history of vitrectomy, vitrectomy after injection, cataract surgery after injection, pseudophakia after injection, and baseline IOP reading before injection. The level of significance was $P < 0.01$. The data in this manuscript are the product of a new, more precise analysis of the IRIS data for this project than earlier versions, which allowed us to make a direct comparison with fellow untreated eyes.

Results

We identified 972 332 patients for the study with a diagnosis of neovascular AMD, DME, or branch or central retinal vein occlusion. Of these, 118 443 received an injection of bevacizumab, ranibizumab, or aflibercept in the right eye, but none in the left eye, during the study period. We first excluded those who received more than 1 kind of anti-VEGF drug or intravitreous corticosteroid injection in either eye, leaving 95 994 patients. Then, we excluded those without at least 1 baseline pretreatment IOP measurement, those without 1 IOP measurement at least 1 year after the first injection, or those undergoing 75 or more IOP readings during the study period, leaving 25 336 patients. A group of 105 patients lacked data on gender or birth year or were younger than 18 years or older than 100 years at the time of first injection. One thousand four hundred eighty-five patients had an IOP between 0 and 5 mmHg, a possible sign of poor data quality, and thus were removed.

Of the resulting 23 776 patients, 14 333 (60%) were women and 9443 (40%) were men. The average age was 77 years. The proportion of patients by treatment drug was as follows: 13 349 patients (56%) received bevacizumab, 4548 patients (19%) received aflibercept, and 5879 patients (25%) received ranibizumab. The breakdown of patients by diagnosis was as follows: 17 394 patients (73%) had neovascular AMD only, 2873 patients (12%) had DME only, 2658 patients (11%) had a vein occlusion with macular edema, and 851 patients (4%) had a combination of these diagnoses. The numbers of patients by group, drug, and number of injections are shown in Table 1. The mean number of injections by group was 7.9 for all patients, 8.5 for AMD patients, and 7.4 for treatment-naïve patients. By drug among all patients, a mean of 6.9 bevacizumab injections, 9.3 aflibercept injections, and 9.0 ranibizumab injections were administered. At the start of the study, 178 patients (<1%) had a diagnosis of glaucoma. The mean follow-up time was 678 days for all patients, 688 days for the AMD-only group, and 635 days for the treatment-naïve group. This did not differ significantly by drug (Table 2).

Baseline IOP in all patients was 15.3 mmHg for aflibercept, 15.7 mmHg for ranibizumab, and 16.9 mmHg for bevacizumab. Patients receiving all drugs in all subgroups showed a slight decrease in IOP from baseline to last injection ranging from a decrease of 0.3 to 1.2 mmHg compared with a 0.2 to 0.3-mmHg decrease in untreated fellow eyes (Fig 1). This decrease compared with fellow untreated eyes was significant for bevacizumab and aflibercept, but not for ranibizumab.

When controlling for confounders with the GLM (Table 3), there was a trend for bevacizumab to be associated with a lesser decrease in IOP from baseline than aflibercept and ranibizumab, although these differences were small. In the GLM, there were statistically significant trends toward increased IOP over baseline with female gender and cataract surgery after first injection, although again, the differences were small.

When looking at the incidence of IOP rises, the proportion of those having an IOP increase of 6 mmHg or more that caused them to achieve a new IOP of more than 21 mmHg (termed herein as a *clinically significant IOP rise*) was 2.6% overall. For fellow untreated eyes, the rate of clinically significant IOP rise was 1.5% (Fig 2). Among all patients, such a rise occurred in 1.9% of aflibercept injections, 2.8% of ranibizumab injections, and 2.8% of bevacizumab injections. In the fellow untreated eyes, such a rise was seen in 1.6% of those receiving aflibercept, 1.3% of those receiving ranibizumab, and 1.5% of those receiving bevacizumab. These differences between treated and untreated eyes were statistically significant overall and for ranibizumab and bevacizumab, but there was no statistically significant difference