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ARTICLE

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Intraocular pressure decreases in eyes with glaucoma-related diagnoses after conversion to aflibercept for treatment-resistant age-related macular degeneration

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OBJECTIVE: To understand intraocular pressure (IOP) response after switching from intravitreal bevacizumab (IVB) and/or ranibizumab (IVR) to intravitreal aflibercept (IVA) for treatment-resistant neovascular age-related macular degeneration (nAMD) in patients with and without coexisting glaucoma-related diagnoses.

METHODS: Retrospective, cross-sectional comparative case series of 62 eyes of 58 patients treated with intravitreal injection for nAMD from March 2010 to April 2018. Patients with glaucoma-related diagnoses, defined here as open-angle glaucoma or suspicion of open-angle glaucoma, ocular hypertension, and/or narrow-angle glaucoma, were compared to those without glaucoma. IOP data were collected at baseline, at the three visits where patients received loading doses of IVB/IVR, and at all of the visits following the switch to IVA through the end of follow-up.

RESULTS: 19 eyes with pre-existing glaucoma-related diagnoses were compared to 43 eyes without such diagnoses. Baseline IOP was similar for glaucoma and non-glaucoma patients. The loading doses of IVB/IVR did not impact IOP; however, a small, sustained rise in IOP was noted among patients with glaucoma-related diagnoses by the final IVB/IVR injections before the switch to IVA (ΔIOP 1.61 ± 0.52 mmHg, $P < 0.002$). After conversion to IVA, pre-injection IOP declined in eyes both with (−1.59 ± 0.54 mmHg, $P < 0.001$) and without (−0.99 ± 0.28 mmHg, $P < 0.001$) glaucoma-related diagnoses.

CONCLUSIONS: IOP in patients with glaucoma-related diagnoses appears to be more sensitive to intravitreal injections than it is in patients without glaucoma-related diagnoses. It rises with IVB/IVR and declines after the switch to IVA. Switching patients with nAMD to IVA may present an opportunity to lower IOP in patients with glaucoma.

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INTRODUCTION

Age-related macular degeneration (AMD) remains the leading cause of irreversible central visual loss among individuals 60 years of age and older in Western industrialized countries, despite access to anti–vascular endothelial growth factor (anti-VEGF) therapy [1]. Anti-VEGF therapy has revolutionized the treatment of the neovascular form of the disease to prevent central visual loss [1] and is extremely well-tolerated, although repeated intraocular injections risk ocular and systemic side effects [2, 3].

One of the most common side effects following the intravitreal injection of a small volume of medication is a rise in intraocular pressure (IOP). In most cases, IOP normalizes within 30–60 min post injection [4, 5]. However, a small number of patients experience significant post-injection spikes in IOP [6–20]. Although intravitreal bevacizumab (IVB), ranibizumab (IVR), and aflibercept (IVA) have no effect on average IOP, as assessed by monthly pre-injection measurements in multiyear randomized clinical trials [4, 21–23], fewer total patients treated with IVA had increases in IOP reported over the course of the VIEW 1 and 2 studies [23]. As AMD is a chronic condition that often requires patients to receive treatment over many years, long-term changes in IOP in patients receiving repeated intravitreal injections may contribute to glaucoma progression. However, only a few studies have included groups of patients with the neovascular form of AMD (nAMD) and coexisting glaucoma [24, 25], and fewer still have analyzed the fellow (untreated) eyes of patients receiving unilateral intravitreal injections [7]. Some studies have even excluded patients with known glaucoma [5, 26, 27].

In the current study, we present the results of a retrospective analysis of eye pressure changes in patients with and without coexisting glaucoma-related diagnoses who were switched from IVB and/or IVR to IVA for treatment-resistant nAMD. We examine the period immediately following the initiation of intravitreal injections with IVB and/or IVR, as well as the period before and after the switch to IVA, to understand the impact of this transition on IOP. We also assessed the influence of injection frequency and number of IVA injections on IOP, and used the untreated fellow eyes of these patients, when available, as controls. Our work has identified a small, yet significant, sustained rise in IOP in the subset of eyes that also have coexisting glaucoma. Remarkably, all

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eyes converted from IVB/IVR to IVA experienced a sudden, sustained decline in IOP in the period after the switch—a decline which was more pronounced in the cohort of patients with glaucoma-related diagnoses. Finally, we present evidence that at least some of this drop in IOP is related to the agent administered rather than to the injection procedure. These results indicate that IVA might be a better agent for the management of nAMD in some patients with glaucoma who develop IOP elevation after treatment with IVB and/or IVR.

SUBJECTS AND METHODS

The study comprised a retrospective, cross-sectional comparative case series. The research followed the tenets of the Declaration of Helsinki and was approved by the institutional review board of Lahey Hospital & Medical Center (Burlington, Massachusetts, USA). Using billing records, we identified patients who received 0.05 mL IVA injection for nAMD between March and April 2018. We excluded patients with retinal vein occlusions, myopic choroidal neovascularization, or diabetic retinopathy with macular edema or proliferative retinopathy. Criteria for inclusion included having received at least three IVA injections and at least three IVB or IVR injections prior to the switch to IVA. We also excluded individuals who received injections at other institutions or who had ocular or laser surgery within three months of the initiation of anti-VEGF treatment.

For the study, a glaucoma and retina sub-specialist reviewed the charts and extracted demographic and clinical data related to ocular health, AMD, and glaucoma diagnosis, severity, and treatment. The analysis divided patients into those with and without glaucoma-related diagnoses by ICD-10-CM codes. We collected IOP data prior to treatment with IVB/IVR (baseline), at the three visits when patients received loading doses of IVB/IVR, at the three visits before the switch to IVA, and for all of the visits during the IVA treatment period through the end of follow-up (EOF). Unless otherwise noted, IOP is presented as the average of the three visits in each period. To calculate the change in IOP (ΔIOP) at specific time points after switching to IVA, we used the IOP from the injection visit closest to the desired time point. If the date was not within 14 days of the desired time point, the average to the IOP of the preceding and succeeding injections was used. In order to control for variations in clinical IOP measurements, we first averaged IOP by patient within each period before calculating the average IOP for each group.

A majority of IOPs were measured by Goldmann applanation tonometry by certified ophthalmic technicians; fewer than 10% of clinical values were obtained by Tonopen-XL (Medtronic Solan, Jacksonville, FL). We adjusted EOF for eyes that had an event that could be expected to impact IOP, such as the addition of an IOP-lowering medication, cataract extraction, laser surgery or iridotomy during the study period. No eyes underwent trabeculectomy or tube shunt procedures before or during the study.

We collected clinical data for the fellow eye of each patient, including any history of injections. A clinically significant IOP increase was defined as a rise of ≥6 mmHg from baseline or a rise of >2 mmHg with an IOP of >21 mmHg [19, 20, 26].

Data are presented as mean (±SD) for continuous variables and IOP mean (±SE). We used Student's *t* test (*t* test), paired and unpaired, analysis of variance (ANOVA), and analysis of covariance (ANCOVA) to compare continuous variables and used logistic regression to analyze categorical variables (SPSS® Statistics version 22.0, IBM Corp., Armonk, NY). Kaplan–Meier Survival curves and the Wilcoxon log-rank test provided assessment of the time-to-conversion to IVA. All tests are 2-sided, and we consider *P* values below 0.05 as statistically significant.

RESULTS

Clinical characteristics

Of 228 patients who received IVA, 62 eyes of 58 patients with nAMD were included in the study. The majority of eyes ($n = 52$) received IVB before conversion to IVA. Based upon a chart review, 19 eyes had glaucoma-related diagnoses, and 43 eyes were categorized as non-glaucoma. Of the eyes with glaucoma-related diagnoses, seven had a diagnosis of primary open-angle glaucoma, six were glaucoma suspects with open angles, four had ocular hypertension with open angles, one had a history of a narrow-angle and prior laser peripheral iridotomy, and one had ocular hypertension and a narrow angle without a history of laser peripheral iridotomy. The rate of glaucoma-related diagnoses in our study population is similar to that reported in a review of US claims-based data in a large Medicare population ($\chi^2 = 1.133$, $P = 0.287$) [28]. No patient had a change of glaucoma diagnosis or surgery during the study. One patient stopped topical glaucoma medication several months after the switch to IVA; two patients with glaucoma had EOF defined by the addition of a new topical glaucoma medication; no patient was on oral glaucoma therapy. Additional study population characteristics are presented in Table 1.

Intravitreal injections

Patients received either IVB, IVR, or both during the period before IVA. Of glaucoma-related patients, 84% received IVB ($n = 16$) and 16% received IVR ($n = 3$). For non-glaucoma patients, 81% of patients received IVB ($n = 35$), 14% received IVR ($n = 6$), and 5% received both IVB and IVR ($n = 2$). Both groups received similar numbers of both pre- and post-switch injections (Supplementary Table S1). The average number of IVB/IVR injections was 12.0 ± 1.34 for the glaucoma group compared to 10.0 ± 0.85 for the non-glaucoma group ($P = 0.204$, *t*-test). The number of IVA injections was 18.3 ± 2.3 for the glaucoma group compared to 23.9 ± 2.2 for the non-glaucoma group ($P = 0.124$). Using the Kaplan–Meier method, we found no difference in the time-to-switch to IVA between the groups (Supplementary Fig. S1).

Changes in intraocular pressure

Baseline IOP was similar in eyes with glaucoma-related diagnoses and those without glaucoma (15.63 ± 0.72 mmHg versus 15.07 ± 0.39 mmHg, $P = 0.465$). There was no change in IOP following the three loading doses of IVB/IVR for both the glaucoma and non-glaucoma groups (0.07 ± 0.30 mmHg versus −0.22 ± 0.52 mmHg, $p = 0.605$, Fig. 1). The presence of a glaucoma-related diagnosis was associated with a small but significant rise in IOP of 9.8 ± 2.8% (1.61 ± 0.52 mmHg, $P = 0.006$, paired *t*-test) by the time of the final IVB/IVR injections before the switch to IVA. By comparison, there was no change in IOP relative to baseline observed in eyes without glaucoma before the switch to IVA (0.19 ± 0.33 mmHg, $P = 0.579$). Although several previous studies have shown that the proportion of patients with a sustained IOP rise increases in proportion to the number of injections [13, 19, 29], we found no association between ΔIOP and the number of IVB/IVR injections ($P = 0.103$), including among the subset of eyes with glaucoma-related diagnoses ($P = 0.090$).

Next, we ascertained the proportion of eyes that experienced a significant IOP increase during the study. We did so by using the criteria reported in multiyear randomized clinical trials of these agents as the basis for comparison [4, 21–23, 30, 31]. All but one eye in the glaucoma group ($n = 18$) and all the eyes in the non-glaucoma group ($n = 43$) had a baseline IOP of 21 mmHg or less. At the switch, three eyes with glaucoma had an IOP ≥21 mmHg and a rise in IOP of >2 mmHg, compared to two eyes in the non-glaucoma group. No eyes in the study had an IOP ≥21 mmHg by EOF. During the IVA treatment period, 16% of glaucoma eyes ($n = 3$) experienced two or more pre-injection IOPs of ≥6 mmHg from baseline, while no change in pre-injection IOP from baseline of that magnitude was observed in eyes without glaucoma. This rate is not statistically different from the rate of such IOP increases reported in large randomized clinical trials [30, 31]. Furthermore, 26% of eyes with glaucoma-related diagnoses ($n = 5$) experienced pre-injection IOPs of 22 mmHg or more during the IVA period while none of the eyes without glaucoma experienced any pre-injection IOPs of that magnitude. One eye with glaucoma had both a pre-injection IOP of 22 mmHg or greater and a pre-injection IOP change from baseline of ≥6 mmHg.

Both glaucoma and non-glaucoma groups experienced a drop in IOP after switching to IVA. Patients in the glaucoma group

Table 1. Demographic and clinical characteristics.

Continuous variables				
Age (years)	Mean (SD)	Median	Range	*P*
Glaucoma-related ($n = 19$)	85.1 (5.2)	84	75–94	
Non-glaucoma ($n = 43$)	84.9 (7.5)	84	60–95	0.949
Visual acuity at baseline	Snellen	Average Visual Acuity[b] (SD)		*P*
Glaucoma-related	20/25-20/80	0.29 (0.14)		
Non-glaucoma	20/20-20/200	0.42 (0.25)		0.0386[a]
Visual acuity at EOF	Snellen	Average Visual Acuity[b] (SD)		*P*
Glaucoma-related	20/20-20/200	0.33 (0.25)		
Non-glaucoma	20/20-20/600	0.43 (0.32)		0.221
Optic nerve	CDR (SD)	Range		*P*
Glaucoma-related	0.47 (0.19)	0.20–0.85		
Non-glaucoma	0.35 (0.16)	0.10–0.70		0.009[a]
Categorical variables				
Gender	Female	Male	*P*	
Glaucoma-related	68%	31%		
Non-glaucoma	49%	51%	0.451	
Race	White	Other	*P*	
Glaucoma-related	95%	5%		
Non-glaucoma	98%	2%	0.938	
Lens status	Pseudophakic	*P*		
Glaucoma-related	63%			
Non-glaucoma	56%	0.783		
Topical glaucoma medications		*P*		
Glaucoma-related	53%			
Non-glaucoma	0%	0.001[a]		

[a]$P < 0.05$, statistically significant.
[b]Visual acuity presented in LogMAR.

normalized back to their baseline IOP (0.02 ± 0.53, $P = 0.974$), and patients without glaucoma had a small, but statistically significant decline in IOP relative to their baseline IOP (-0.80 ± 0.28, $P = 0.007$). No eyes had a change in glaucoma treatment during this pre-IVA period or within the period of the switch. This change in IOP relative to baseline for patients without glaucoma remained statistically significant at EOF (-0.67 ± 0.32, $P = 0.046$). However, when measured relative to the average IOP in the pre-switch period, a sustained decline in IOP was noted for both groups after the switch to IVA; this decline persisted through EOF. When measured relative to the IOP in the pre-IVA period, IOP immediately after the switch fell by $-8.8 \pm 2.0\%$ (-1.59 ± 0.54 mmHg, $P = 0.007$) and $-5.7 \pm 1.7\%$ (-0.99 ± 0.28 mmHg, $P = 0.004$) for patients with and without glaucoma-related diagnoses, respectively. This drop in IOP persisted through EOF for both the glaucoma group (-1.40 ± 0.31 mmHg, $P = 0.002$) and non-glaucoma group (-0.88 ± 0.31 mmHg, $P = 0.010$). The decrease in IOP after the switch to IVA was not associated with age, gender, or lens status. We also examined the impact of the switch to IVA at specific time points beyond the initial 3 injections of IVA (Supplementary Fig. S2 and Table S2). Interestingly, the decline in IOP measured relative to the IOP in the pre-IVA period was associated with the total number of IVB/IVR injections received before the switch to IVA ($R^2 = 0.20$, $P < 0.001$), though for the subset of eyes with glaucoma, this finding did not reach statistical significance ($P = 0.080$).

In order to determine the potential impact of the intervals between injections and the number of injections on ΔIOP, we analyzed pre-injection IOP data for the entire IVA period. A continuous ΔIOP ($^{\Delta}$ΔIOP) was calculated as the change between successive IVA injections relative to the pre-IVA IOP for each of the first 14 injections of IVA (Fig. 2). This number of injections would represent the maximum number of IVA injections in one year if given at four-week intervals. After switching to IVA, patients with glaucoma experienced a decrease in IOP (-1.81 ± 0.14 mmHg) that continued to fall with successive injections ($F_{1,13} = 7.11$, $P = 0.020$). By contrast, although patients without glaucoma demonstrated a sustained drop in IOP (-0.92 ± 0.06 mmHg), there was no further decline in IOP beyond the loading doses of IVA ($F_{1,13} = 0.88$, $P = 0.360$). The slope of IOP change following the initiation of IVA between the groups differed significantly (ANCOVA, $F_{1,26} = 5.89$, $P = 0.023$).

To determine whether there was a relationship between injection interval and change in IOP, we examined the impact of time between injections on $^{\Delta}$ΔIOP (Fig. 3). No relationship was found between the drop in IOP and the intra-injection interval for the eyes in the glaucoma ($F_{1,219} = 0$, $P = 0.998$) or non-glaucoma groups ($F_{1,606} = 0.011$, $P = 0.915$) during the first 14 injections after the switch to IVA. Similarly, examining only the subset of injections performed at intervals of eight weeks or greater, a common dosing interval for IVA after three monthly doses [30], found no difference in $^{\Delta}$ΔIOP for the glaucoma ($F_{1,86} = 0.035$, $P = 0.852$) or non-glaucoma eyes ($F_{1,251} = 0.622$, $P = 0.431$). Importantly, there was no difference in the average injection interval in the pre-IVA period (40 ± 12 days) compared with the period following the switch to IVA (38 ± 10 days, $P = 0.170$), or for either subgroup of eyes.

Finally, we compared the study eyes to their untreated, fellow eyes. Ten of the 19 eyes with glaucoma-related diagnoses and 22

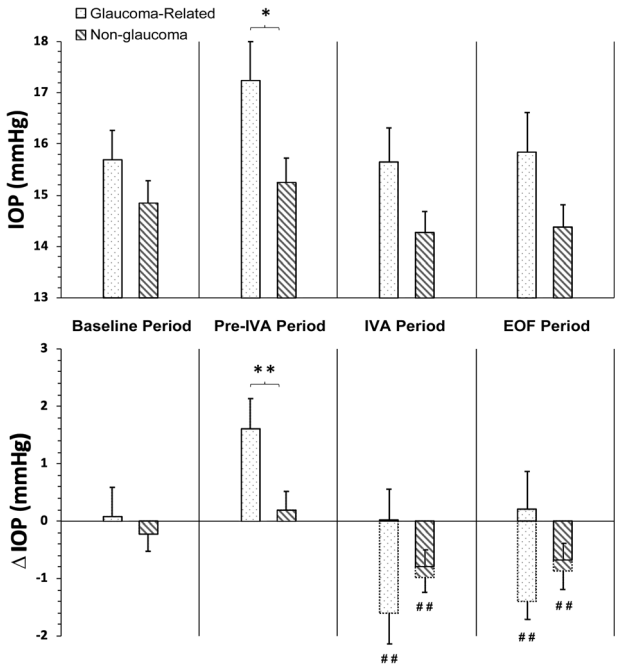

Fig. 1 Intraocular pressure changes in eyes with treatment-resistant age-related macular degeneration. Average IOP and ΔIOP relative to baseline IOP (solid-outline bars) and relative to pre-IVA IOP (dotted-outline bars). Although IOP did not rise following three loading doses of IVB/IVR (baseline period), average IOP was higher for the final IVB/IVR injection visits in patients with glaucoma-related diagnoses. This rise in IOP reversed toward baseline after switching to IVA. Eyes without glaucoma had no underlying increase in IOP following IVB/IVR injections but experienced a drop in IOP similar in magnitude to their glaucoma counterparts ($P = 0.194$). Decreased IOP persisted through EOF for all patients. Data are presented as the mean ± standard error of mean (SEM). The dotted-outline bars reflect the IOP relative to the pre-IVA period and before any exposure to IVA. (*$P < 0.05$, **$P < 0.01$, $^{\#\#}P < 0.01$).

of the 43 eyes without glaucoma could be compared with untreated fellow eyes. Baseline IOP was similar for these fellow eyes in the glaucoma and non-glaucoma groups (14.30 ± 1.37 mmHg versus 15.42 ± 0.51 mmHg, $P = 0.347$), and there was no difference in IOP between the fellow eyes in these groups in the period after the three loading doses of IVB/IVR (15.17 ± 0.69 mmHg versus 14.35 ± 1.28 mmHg, $P = 0.400$). However, in the period before the switch to IVA, the subset of eyes with glaucoma-related diagnoses treated with IVB/IVR showed a significant rise in IOP (1.9 ± 0.79 mmHg, $P = 0.039$), whereas their fellow eyes did not (0.10 ± 0.45 mmHg, $P = 0.828$). After the switch to IVA, the treated eyes of patients with and without glaucoma experienced a drop in IOP relative to the pre-IVA period (−2.43 ± 0.51 mmHg, $P < 0.001$, and −0.75 ± 0.39 mmHg, $P = 0.068$, respectively), whereas their fellow eyes had no appreciable change in IOP (−0.28 ± 0.41 mmHg, $P = 0.515$, and −0.24 ± 0.41 mmHg, $P = 0.571$, respectively). Lastly, the difference in IOP increased between the treated and fellow eyes for patients with glaucoma-related diagnoses before the switch to IVA compared to the difference at baseline (2.7 ± 0.77 mmHg); this increase was not seen in the eyes without glaucoma (−0.02 ± 0.01, $P < 0.0001$). After the switch to IVA, the difference in IOP between the treated and fellow glaucoma eyes resolved (0.55 ± 0.69 mmHg). In addition, before the switch to IVA, the IOP in treated eyes was higher 60% of the time compared to their untreated counterparts, while after the switch to IVA, the direction of the asymmetry reversed, and the IOP in untreated eyes was now higher 66.3% of the time ($P = 0.006$).

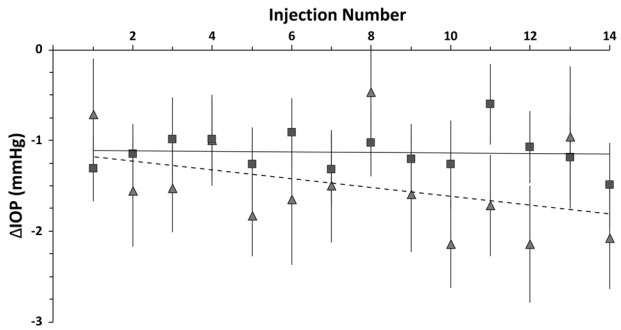

Fig. 2 Effect of number of IVA injections on ΔIOP. ΔIOP for the first 14 injections following the switch to IVA in eyes with glaucoma-related diagnoses (blue triangles) and without glaucoma (purple squares). The IOP continued to decline over time in eyes with glaucoma-related diagnoses (dashed line, ANCOVA, $F_{1,26} = 5.89$, $P = 0.023$); these eyes had a greater pre-switch increase in IOP from IVB/IVR. In contrast, the slope is nearly zero for the non-glaucoma group (solid line), indicating that additional injections had no further impact on IOP. Data are presented as the mean ± SEM for the average IOP at each injection.

DISCUSSION

Our study identified a significant and sustained drop in IOP immediately after the switch from IVB and/or IVR to IVA in eyes with treatment-resistant nAMD, which was greater for the subset of eyes with glaucoma-related diagnoses. As a percentage, the decrease in IOP after switching to IVA amounted to −5.7% among eyes without glaucoma-related diagnoses but was an average of −8.8% in patients with co-existing glaucoma-related diagnoses. This drop in IOP is approximately half of the decrease in IOP known to occur after cataract surgery, an effect which is also more pronounced in patients with glaucoma [32].

Interestingly, in the subset of eyes with glaucoma and related diagnoses, we identified a small rise in IOP occurring by the time of the switch from IVB/IVR to IVA. This was not seen in eyes without glaucoma or in the untreated fellow eyes of our nAMD patients. Whereas injection frequency did not impact the decline in IOP, our study shows that over the first 14 injections after the switch to IVA, IOP continues to decline further for eyes in the glaucoma group. This decline is long after any direct effect from IVB/IVR would still be expected, as both molecules have an estimated half-life of seven to ten days [3]. This evidence suggests that aflibercept, or its excipient, is at least partially responsible for the decline in IOP.

Although several case series have reported an increase in IOP after treatment with IVB/IVR [11, 24], a recent analysis of data from the Intelligent Research in Sight (IRIS) Registry found that although the vast majority of patients receiving these agents experience little change in IOP from baseline (at a minimum of one year of follow-up), three times as many patients who experienced a clinically significant IOP rise had a pre-existing diagnosis of glaucoma [19]. Retrospective analysis of data from the Fight Retinal Blindness! registry also found that eyes with glaucoma were more likely to show an IOP elevation at both 12 and 24 months of follow-up [25]. The rate in our study of a (pre-switch) sustained rise in IOP among eyes with glaucoma was greater (26%) than that found in these registries, but similar to the rate (26.1%) in the MARINA and ANCHOR trials [15]. By contrast, no cases of a clinically significant IOP rise while being treated with IVB/IVR were found among eyes in our study without glaucoma.

Our study further differs from the analysis of the IRIS registry [19] in that we specifically examined the impact of switching from IVB/IVR to IVA on IOP in patients with treatment-refractory nAMD. AMD is a multifactorial, heterogenous disease, and the experience of this subset of patients may be different from those in patients without treatment-refractory disease. Few studies have examined

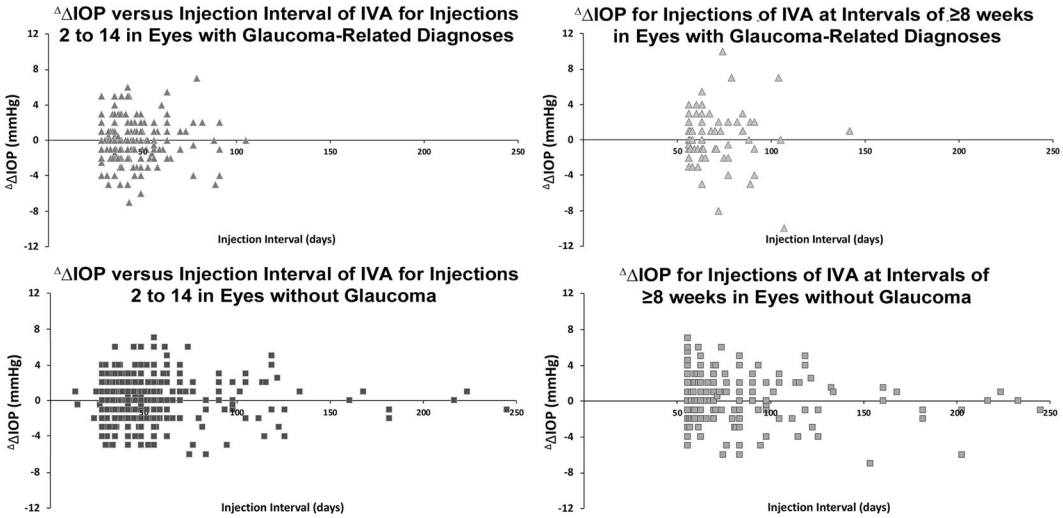

Fig. 3 Effect of IVA injection interval on $^{\Delta}\Delta$IOP. No association was found between injection interval and the continuous ΔIOP ($^{\Delta}\Delta$IOP) between successive IVA injections for the first 14 injections in the eyes with glaucoma-related diagnoses ($F_{1,219} = 0$, $P = 0.998$, top left panel) or in eyes without glaucoma ($F_{1,606} = 0.011$, $P = 0.915$, bottom left panel). No association was also observed for the subset of injections at intervals greater than eight weeks or more for both groups ($F_{1,86} = 0.03504$, $P = 0.852$, and $F_{1,251} = 0.622$, $P = 0.431$, top right and bottom right panels, respectively). By eight weeks, roughly only 1% of aflibercept should remain, since the intravitreal half-life of aflibercept has been estimated to be approximately nine days [3].

IOP as an outcome after a conversion from IVB/IVR to IVA. Unsal et al. [26] reported a small drop in IOP among a small number of patients with nAMD, but only considered the change in IOP relative to baseline and *excluded* patients with pre-existing glaucoma. Rusu et al. [24] also found that IOP declined following the switch from IVB/IVR to IVA, but performed an analysis limited to a few timepoints and only had five patients with unspecified glaucoma-related diagnoses.

The mechanism by which IVA leads to a decrease in IOP requires further study. Anti-VEGF agents or their excipients may trigger inflammation or an immunological reaction, which appears to be more common with IVA [33]. This could impact aqueous humor production or outflow pathways, such as the trabecular meshwork. Aflibercept is also the only one of these agents that has affinity for placental growth factor [23]. The role that this might play in IOP regulation is unknown. Finally, although it has been hypothesized that physical damage to the trabecular meshwork may result from repeated IOP spikes [5–7] after injections or from disruption of the anterior hyaloid [8], the injection procedure itself does not significantly vary among these agents. Our findings show that not only did the rise in IOP after injections with IVB/IVR reverse after the switch to IVA, but also that IOP decreased while on IVA in patients both with and without glaucoma-related diagnoses. This suggests that the agent (or excipient) itself rather than the injection procedure is responsible for these changes in IOP.

Limitations of the present study include its retrospective nature, small sample size, variations in the number and frequency of injections, IOP measurement timing and methods, and the broad definition of glaucoma used to define the study groups. Relying on the clinical diagnosis of glaucoma and related conditions also means that some patients may have been misclassified, thereby diluting our findings especially if patients with nAMD were underdiagnosed with these conditions [34]. The population in our study is derived from a single center, outpatient clinic that serves as a glaucoma referral center, which likely accounts for the higher-than-expected prevalence of glaucoma-related diagnoses in our study population of patients with nAMD [35, 36]. Lastly, although we controlled for clinical events that could be expected to affect eye pressure, other glaucoma-related, patient-specific factors may not have been taken into account. For example, we had no ability to objectively confirm topical glaucoma drop use.

Glaucoma is the leading cause of irreversible blindness globally [36] and the second leading cause of visual impairment in the United States [37]. Although AMD and glaucoma can be observed together [35], the two diseases are generally managed separately. Given that AMD is a chronic condition often requiring patients to receive treatment over many years, long-term changes in IOP in patients receiving repeated intravitreal injections may be an especially important modifiable risk for glaucoma or its progression. Previous work in the Early Manifest Glaucoma Trial has shown that a sustained IOP reduction of only 1 mmHg during follow-up can result in a 10% decrease in the risk of glaucoma progression [38]. This suggests that the IOP changes found in the present study could be clinically relevant.

In conclusion, clinicians should be aware of the potential reduction in IOP that results from switching from IVB/IVR to IVA for nAMD. Future studies assessing larger numbers of patients and with careful attention to the timing and method of IOP measurement are needed to determine whether IVA is a better treatment for certain patients with nAMD who have coexisting glaucoma.

Summary

What was known before

- Intravitreal injection of aflibercept is associated with fewer intraocular pressure related complications compared with intravitreal bevacizumab and/or ranibizumab.

What this study adds

- Eyes switched from intravitreal bevacizumab and/or ranibizumab to intravitreal aflibercept for the treatment of neovascular AMD have a decrease in intraocular pressure, which is more pronounced in eyes with glaucoma-related diagnoses.

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AUTHOR CONTRIBUTIONS

DJR was responsible for the study hypothesis and design, the development of electronic medical record reporting tools, reviewing and analyzing the data, interpreting the results, and writing of the manuscript. JCM was responsible for the chart review, extracting and analyzing the data, figure development, and writing of the manuscript. EES was responsible for the chart review, extracting and analyzing the data, and writing of the manuscript. YZ was responsible for the chart review, extracting and analyzing the data, figure development, and writing of the manuscript. AMA was responsible for analyzing the data and writing of the manuscript. MLC was responsible for interpreting the data, figure development, and writing of the manuscript. SR was responsible for interpreting the data and writing of the manuscript. PRC was responsible for interpreting the data and writing of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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