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Evaluation of Sustained Intraocular Pressure Elevations Across Antivascular Endothelial Growth Factor Agents

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Abstract

Purpose: To evaluate the effect of antivascular endothelial growth factor (anti-VEGF) agents on the development of sustained intraocular pressure (IOP) elevations. **Methods:** This single-center retrospective cohort study included eyes receiving anti-VEGF injections for various indications along with nontreated fellow eyes from 2012 to 2022. Patients were grouped according to treatment with bevacizumab, ranibizumab, or aflibercept. Trends in IOP were recorded after treatment initiation for 1 year. The development of sustained IOP elevations (defined as an increase of 5 mm Hg or greater than baseline for 4 or more weeks) and glaucoma manifestations were recorded. **Results:** The analysis included 1604 eyes (injection cohort, 907; control cohort, 697). The mean age of the injection cohort was 83.3 years; 56.9% were women and 82.0% were White. Injections were for neovascular age-related macular degeneration (498 [54.9%]), diabetic retinopathy (219 [24.1%]), retinal vein occlusion (161 [17.8%]), and other indications (29 [3.2%)]. Bevacizumab was used in 521 eyes (57.4%), ranibizumab in 129 eyes (14.2%), and aflibercept in 257 eyes (28.3%). The mean age in the control cohort was 81.6 years; 56.1% were women and 84.1% were White. Sustained IOP elevations developed in 97 (6.0%) of 1604 eyes throughout the study. Compared with controls, treated eyes overall did not have an increased rate of sustained IOP elevations ($P = .38$) or glaucoma progression ($P = .51$), although patients treated with bevacizumab had a significantly greater incidence of IOP elevation than controls (relative risk, 1.81; 95% CI, 1.18-2.78). The mean number of injections to sustained IOP elevation was 5.4 and did not differ between agents ($P > .05$). **Conclusions:** Although not all anti-VEGF agents are associated with IOP-related adverse effects, bevacizumab carries an increased risk for sustained IOP elevation. Further investigation into the long-term effects of bevacizumab on IOP and glaucoma and a comparison with other anti-VEGF agents may be warranted.

Keywords

anti-VEGF agent, wet (neovascular) AMD, diabetic retinopathy, branch retinal vein occlusion, electronic medical record, retina

Introduction

Diabetic retinopathy (DR), age-related macular degeneration (AMD), and retinal vein occlusion (RVO) are major contributors to visual impairment.[1] Intravitreal (IVT) antivascular endothelial growth factor (anti-VEGF) agents are the standard of care for managing neovascularization (NV) and complications associated with late stages of these conditions, with bevacizumab, ranibizumab, and aflibercept the 3 most commonly used agents that have been shown to improve visual outcomes.[2–4]

There are few adverse effects associated with treatment with IVT anti-VEGF agents.[5] A transient increase in intraocular pressure (IOP) is a known side effect immediately after injection as a result of the acute volumetric expansion of the eye and often subsides within 1 to 2 hours.[6,7] In 2011, however, Good et al[8] reported that IVT injection with bevacizumab or ranibizumab may be associated with chronic IOP elevation in patients with neovascular AMD (nAMD). Further post hoc analysis of randomized controlled trials showed that treatment with anti-VEGF agents may significantly increase the risk for sustained IOP elevations compared with panretinal photocoagulation or laser treatment.[9] Contradicting these findings, Kähkönen et al[10] recently evaluated patients treated with bevacizumab and aflibercept and found no significant increase in sustained IOP

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changes compared with untreated fellow eyes, necessitating more studies to draw further conclusions.

Multiple variables may be related to sustained elevations in IOP, such as the injection agent, frequency of injection, and underlying indication for the injection.[9] Sustained IOP elevations have been reported after injection with anti-VEGF agents; however, to our knowledge no study to date has compared all 3 commonly used injection agents, nor has a proper control cohort of untreated fellow eyes been used. This study comprised a large cohort of patients treated with anti-VEGF agents to assess how the injection agent affects the likelihood of developing sustained IOP elevations.

Methods

This study was conducted after receiving approval from the Cleveland Clinic Institutional Review Board. Study-related procedures were performed in accordance with good clinical practice (International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use E6), applicable US Food and Drug Administration regulations, the US Health Insurance Portability and Accountability Act of 1996, and the Declaration of Helsinki. Individual informed consent was not needed for this study because no patient-level identifying information was used.

The electronic medical records were queried for all patients aged 18 years or older being treated with bevacizumab, ranibizumab, or aflibercept for the management of ocular disease between January 1, 2012, and May 30, 2022. Treatment-naïve patients being treated for AMD, RVO, or DR with follow-up IOP data were included. The vast majority of patients in the study received bevacizumab (Avastin, Genentech) compounded at our hospital system; however, in the last year of the study, some patients received externally compounded bevacizumab. If both eyes were treated, 1 eye per patient was included at random using a random number generator. If the fellow eye was not treated during the study period, IOP data were collected as part of a control cohort.

Exclusion criteria included any of the following: ocular surgery 90 days before the initial injection, a history of ocular or cranial trauma, a history of neovascular glaucoma (NVG), administration of multiple forms of anti-VEGF treatment, and previous anti-VEGF treatment. If a patient had ocular surgery at any time throughout the study period, data were collected up to that timepoint.

Baseline clinical information was collected, including sex, age, race, and smoking status. Patients were then classified by treatment with anti-VEGF (injection cohort) vs no treatment (fellow eyes [control cohort]). Patients in the injection cohort were further classified according to the anti-VEGF agent used and the indication for treatment throughout the 12-month study period. Additional variables collected included the IOP at follow-up visits, the incidence of sustained elevations in IOP, the number of repeat injections given, and new clinical diagnoses of glaucoma or evidence of worsening glaucoma (including a new glaucoma medication prescription, new selective laser trabeculoplasty or glaucoma surgery, or other documented evidence of worsening). At each visit, if repeat measures of IOP were taken, the highest IOP measurement was used. As in previous studies, an increase of 5 mm Hg or greater from baseline for at least 4 weeks was indicative of a sustained IOP elevation.[9] If an IOP elevation was found, the time from treatment initiation to the increase in IOP was noted. IOP was measured with a Tonopen or a Goldmann tonometer; however, given the retrospective nature of the study, there was no universal protocol.

Data are reported as the frequency (percentage) or the mean ± SD. Independent samples *t* tests and analysis of variance testing were used to compare mean differences between groups with respect to continuous variables. The relative risk (RR) was calculated to compare the incidence of sustained IOP elevation between the injection groups and the control group as well as between the injection groups themselves. The RR was also calculated for the incidence of new or worsening glaucoma between the control group and the treatment groups. Statistical analysis was performed using Excel software (Microsoft Inc). Statistical significance was set at $P < .05$.

Table 1. Demographic Information.

Characteristic	Cohort		*P* Value
	Treated Eyes (n = 907)	Control Eyes (n = 697)	
Age (y)	83.3	81.6	<.01
Sex, n (%)			.75
Male	391 (43.1)	306 (43.9)	
Female	516 (56.9)	391 (56.1)	
Race, n (%)			.59
White	744 (82.0)	585 (83.9)	
Black	122 (13.5)	85 (12.2)	
Other	41 (4.5)	27 (3.9)	
Mean IOP ± SD	15.63 ± 3.5	15.66 ± 3.6	.87
Glaucoma, preglaucoma, or ocular hypertension at baseline, n (%)	54 (6.0)	54 (7.7)	.16

Abbreviation: IOP, intraocular pressure.

Results

Demographics

A total of 2204 eyes were analyzed for potential inclusion in the study, with 1604 eyes included in the final analysis. Of these, 907 eyes were in the injection cohort and 697 in the control cohort. In the injection cohort, 56.9% were women and 82.0% were White; the mean age was 83.3 ± 13.1 years and the mean IOP, 15.63 ± 3.5 mm Hg. In the control cohort, 56.1% were women and 83.9% were White; the mean age was 81.6 ± 11.8 years and the mean IOP, 15.66 ± 3.6 mm Hg. Table 1 shows the complete demographic information. The difference in characteristics

Table 2. Breakdown of Injection Agent Subgroups by Treatment Indication and Race.

Parameter	Total (N = 907)	Injection Agent Subgroup			*P* Value
		Bevacizumab (n = 521)	Ranibizumab (n = 129)	Aflibercept (n = 257)	
Treatment indication, n (%)					
Neovascular AMD	498 (54.9)	262 (50.3)	78 (60.5)	158 (61.5)	.093
Diabetic retinopathy	219 (24.1)	147 (28.2)	12 (9.3)	60 (23.3)	<.001[a]
Retinal vein occlusion	161 (17.8)	93 (17.9)	33 (25.6)	35 (13.6)	.037[a]
Other	29 (3.2)	19 (3.6)	6 (4.7)	4 (1.6)	.198
Race, n (%)					
White	744 (82.0)	407 (78.1)	112 (86.8)	225 (87.5)	.332
Black	122 (13.5)	88 (16.8)	12 (9.3)	22 (8.6)	.004[a]
Other	41 (4.5)	26 (5.0)	5 (3.9)	10 (3.9)	.640

Abbreviation: AMD, age-related macular degeneration.
[a]Statistically significant.

between the cohorts was statistically significant for age only ($P < .01$).

Table 2 shows a breakdown of treatment indication and race by injection agent. Of all eyes, 498 (54.9%) received injections for nAMD, 219 (24.1%) for DR, 161 (17.8%) for RVO, and 29 (3.2%) for other indications. Of the 907 eyes in the injection cohort, 521 (57.4%) received bevacizumab injection(s), 129 (14.2%) received ranibizumab injection(s), and 257 (28.3%) received aflibercept injections. Notably, ranibizumab was used significantly less often than the other anti-VEGF agents for DR ($P < .001$) and more often for RVO ($P = .037$). Bevacizumab was used in 78.1% of White patients, ranibizumab in 86.8% of White patients, and aflibercept in 87.5% of White patients. Black patients were significantly more likely to receive bevacizumab than the other anti-VEGF agents ($P = .004$).

Table 3. Characteristics of Treatment and Control Eyes With Sustained IOP Elevation.

Parameter	Eyes With Sustained IOP Elevation		*P* Value
	Treated Eyes (n = 63)	Control Eyes (n = 34)	
Mean age (y)	80.3	81.8	.61
Sex, n (%)			.76
Male	35 (55.6)	20 (58.8)	
Female	28 (44.4)	14 (41.2)	
Race, n (%)			.06
White	51 (81.0)	27 (79.4)	
Black	9 (14.3)	5 (14.7)	
Other	3 (4.8)	2 (5.9)	

Abbreviation: IOP, intraocular pressure.

Development of Sustained IOP Elevation

Of the 1604 eyes, 97 had sustained IOP elevations of 5 mm Hg or greater for at least 4 weeks, for a total frequency of 6.0%. All 97 cases represented an elevation of 20% or more from the baseline IOP. Sixty-three cases (6.9%) of sustained IOP elevation occurred in the injection cohort and 34 (4.9%) in the control cohort. The RR for IOP elevation between the 2 groups was not significant (RR, 1.42; 95% CI, 0.95-2.14).

Table 3 shows the characteristics of treatment eyes and control eyes with sustained IOP elevation. Of the 63 eyes in the injection cohort with a sustained IOP elevation, 44.4% were of female patients and 81.0% were of White patients with a mean age of 80.3 ± 14.0 years. Of the 34 control eyes with a sustained IOP elevation, 41.2% were of female patients and 79.4% were of White patients with a mean age was 81.8 ± 12.2 years. These characteristics did not differ significantly between the cohorts. The most frequent indication in the injection cohort with a sustained IOP elevation was nAMD (57.1%) followed by diabetic eye disease (23.8%), RVO (14.3%), and other indications (4.8%).

Comparison of Individual Anti-VEGF Agent Groups and the Control Group

Table 4 shows a summary of the incidence of sustained IOP elevations, with subcohorts of eyes treated with bevacizumab, ranibizumab, and aflibercept compared with the control cohort of untreated eyes. Of the 63 cases of sustained IOP elevation in the injection cohort, 46 eyes were treated with bevacizumab (representing 8.8% of all bevacizumab-treated eyes), 8 were treated with aflibercept (1.5% of all aflibercept-treated eyes), and 9 were treated with ranibizumab (7.0% of all ranibizumab-treated eyes). This frequency of sustained IOP elevation for bevacizumab patients was significantly higher than that for control patients (RR, 1.81; 95% CI, 1.18-2.78). No significant differences in frequency were observed for ranibizumab (RR, 1.43;

Table 4. Incidence of Sustained IOP Elevation in the Cohorts.

	Number (%)					
Sustained IOP Increase	Bevacizumab Injection (n = 521)	Ranibizumab Injection (n = 129)	Aflibercept Injection (n = 257)	Total Treated Eyes (n = 907)	Untreated Control Eyes (n = 697)	Total Sample (N = 1604)
Yes	46 (8.8)	9 (7.0)	8 (1.5)	63 (6.9)	34 (4.9)	97 (6.0)
No	475 (91.2)	120 (93.0)	249 (98.5)	844 (93.1)	663 (95.1)	1507 (94.0)

Abbreviation: IOP, intraocular pressure.

95% CI, 0.70-2.91) or aflibercept (RR, 0.64; 95% CI, 0.30-1.36) compared with the control cohort.

Comparison of Anti-VEGF Agents

There was a significant difference in the incidence of IOP elevation between eyes treated with bevacizumab and eyes treated with aflibercept (RR, 2.84; 95% CI, 1.26-5.92). There was no significant difference in the incidence of IOP elevation between eyes treated with bevacizumab and eyes treated with ranibizumab (RR, 1.27; 95% CI, 0.64-2.52) or between eyes treated with ranibizumab and eyes treated with aflibercept (RR, 2.24; 95% CI, 0.89-5.68).

Comparison of Overall Injection Group and the Control Group

Forty-four eyes of 36 patients developed a new diagnosis of glaucoma or had evidence of disease progression, including a new glaucoma medication prescription, new selective laser trabeculoplasty or glaucoma surgery, or other documented evidence of worsening. Of these 44 eyes, 16 (10 treated; 6 control) were categorized as having worsening primary open-angle glaucoma. No eye was categorized as having NVG because these eyes were excluded from the study. Fifteen eyes had a new diagnosis of glaucoma (9 primary open-angle glaucoma, 2 low-tension, 4 other), and the other 13 eyes had worsening of a secondary glaucoma (eg, phacolytic, uveitic).

Table 5 shows the characteristics of treated eyes and control eyes with glaucoma progression. Twenty-seven of the 44 eyes with the development or worsening of glaucoma were in the injection cohort and 17 were in the control cohort. This difference was not significant (RR, 1.22; 95% CI, 0.67-2.22). Of the 27 eyes with glaucoma progression in the injection cohort, 59.3% were of female patients and 70.4% were of White patients with a mean age of 84.9 ± 11.4 years. Of the 17 control eyes with glaucoma progression, 74.9% were of female patients and 79.4% were of White patients with a mean age of 85.7 ± 8.2 years. These characteristics did not differ significantly between cohorts. Of the 27 eyes in the treatment cohort, the underlying condition for injections was nAMD (8 eyes [29.6%]), diabetic eye disease (7 eyes [25.9%]), RVO (10 eyes [37.0%]), and other conditions (2 eyes [7.4%]).

Table 5. Characteristics of Treatment and Control Eyes With Glaucoma Progression.

	Eyes With Glaucoma Progression		
Parameter	Treated Eyes (n = 27)	Control Eyes (n = 17)	*P* Value
Mean age (y)	84.9	85.7	.79
Sex, n (%)			.72
Male	11 (40.7)	6 (35.3)	
Female	16 (59.3)	11 (74.9)	
Race, n (%)			.17
White	19 (70.4)	15 (88.2)	
Black	8 (29.6)	2 (11.8)	
Other	0	0	

Comparison of Individual Anti-VEGF Agent Groups and the Control Group

Each individual anti-VEGF agent was compared with the pool of all control eyes. Table 6 shows a summary of the incidence of glaucoma progression. Eighteen bevacizumab-treated eyes (3.6%) had evidence of new or worsening glaucoma that was not significant compared with control eyes (RR, 1.420; 95% CI, 0.74-2.72). Four aflibercept-treated eyes (1.6%) had evidence of new or worsening glaucoma that was also not significant (RR, 0.64; 95% CI, 0.22-1.88). Finally, 5 ranibizumab-treated eyes (3.9%) had evidence of new or worsening glaucoma that was not significant (RR, 1.59; 95% CI, 0.60-4.23).

Number of Injections to Sustained IOP Elevations

Table 7 shows the number of injections before sustained IOP elevation. Among the entire treatment cohort, sustained IOP elevations occurred in 6.9% of eyes after a mean of 5.4 injections. However, the remaining 93.1% of treated eyes never developed these IOP elevations even after a mean of 5.1 injections. For the individual anti-VEGF agents, the mean number of injections to sustained IOP elevation was 5.3 in the bevacizumab group, 6.5 in the aflibercept group, and 5.4 in the ranibizumab group. The difference by agent was not significant ($P = .46$).

Table 6. Glaucoma Progression, Including Development and Worsening, in the Cohorts.

	Number (%)					
Glaucoma Progression	Bevacizumab Injection (n = 521)	Ranibizumab Injection (n = 129)	Aflibercept Injection (n = 257)	Total Treated Eyes (n = 907)	Untreated Control Eyes (n = 697)	Total Sample (N = 1604)
Yes	18 (3.6)	5 (3.9)	4 (1.6)	27 (3.0)	17 (2.4)	44 (2.7)
No	503 (96.5)	124 (96.1)	253 (98.4)	880 (97.0)	680 (97.6)	1560 (97.3)

Table 7. Number of Injections Before Sustained IOP Elevation.

	Treated Eyes With Sustained IOP Increase				
Injections to Sustained IOP Elevation	Bevacizumab (n = 46)	Ranibizumab (n = 9)	Aflibercept (n = 8)	Total (N = 63)	*P* Value
Number	5.3	5.4	6.5	5.4	.46

Abbreviation: IOP, intraocular pressure.

Table 8. Number of Days Between Treatment Initiation and Sustained IOP Elevation.

	Mean Days to IOP Elevation (n)		
Anti-VEGF Agent	Treated Eyes	Control Eyes	*P* Value
All agents	132.4	91.6	$<.02$
Bevacizumab	128.6	91.6	$<.05$
Ranibizumab	138.4	91.6	$<.04$
Aflibercept	147	91.6	$<.07$

Abbreviations: Anti-VEGF, antivascular endothelial growth factor; IOP, intraocular pressure.

Time to Sustained IOP Elevations

Table 8 shows the mean number of days between treatment initiation and sustained IOP elevation. The mean time to a sustained IOP elevation was significantly greater in the pooled anti-VEGF group than in the control group (mean, 132.4 days for injection cohort vs 91.6 days for control cohort; $P < .02$). The difference was still significant when comparing only bevacizumab-treated eyes with control eyes (128.6 days vs 91.6 days; $P < .05$) and aflibercept-treated eyes with control eyes (147.0 days vs 91.6 days; $P < .04$). No significant difference was found between ranibizumab-treated eyes and control eyes (138.4 days vs 91.6 days; $P < .07$).

Conclusions

Although transient increases in IOP are known consequences of IVT anti-VEGF agents, it remains unclear whether there is an association with long-term, sustained IOP elevations.[11] To date, the literature on this topic has reported mixed results, largely because of the variability in study design and inconsistent definitions of sustained IOP elevation, underscoring the need for controlled studies with larger samples.[10]

Our study sought to bridge this gap by analyzing a large controlled cohort and enlisting the lowest threshold commonly used in the literature (ie, sustained IOP increase of 5 mm Hg or greater from baseline for at least 4 weeks).[9] Using these parameters, we found no difference in the risk for sustained IOP elevation among anti-VEGF–treated eyes compared with untreated control eyes (6.9% vs 4.9%; 95% CI, 0.89-5.67). Among the few existing fellow-eye controlled studies examining this relationship, the findings in our study align with those of Wehrli et al,[12] who reported no significant difference in the incidence of sustained IOP elevations between treated eyes and control eyes. In fact, Wehrli et al's definition of sustained IOP (ie, an IOP greater than 22 mm Hg on 2 consecutive visits with a concomitant increase from baseline greater than 6 mm Hg) was more stringent than this study's criteria. Thus, even with a lower threshold for what constitutes a sustained IOP elevation, the current study corroborates Wehrli et al's findings.

In contrast, our findings differ from those of several others, including Hoang et al,[13] who reported a significantly higher rate of sustained IOP elevations in anti-VEGF–treated eyes than in untreated control eyes. This discrepancy may be explained by several factors, such as the larger sample of eyes in our study (1604 vs 449) and the inclusion of patients treated with aflibercept, the newest of the commonly used anti-VEGF agents. However, the follow-up in the current study was only 1 year after treatment initiation compared with up to 5 years in the Hoang et al study.

Given the discrepancy in the literature despite similar methodologies, we incorporated a parallel analysis of glaucoma progression to evaluate IOP changes from a more clinically relevant standpoint. Correspondingly, the data revealed no increased risk for glaucoma progression with anti-VEGF treatment compared with no treatment (RR, 1.27; 95% CI, 0.70-2.29), despite the broad inclusion criteria used for glaucoma progression (ie, a

new diagnosis of glaucoma and disease worsening evidenced by medication advancement, surgery, or other documented progression). These findings add clinical depth to the quantitative IOP analysis and support our finding of a lack of evidence of sustained IOP elevation with anti-VEGF treatment.

Although the overall results suggest no relationship between treatment with anti-VEGF agents and sustained IOP elevation, this study also compared the risk for sustained IOP elevation between the different anti-VEGF agents. Although neither ranibizumab (RR, 1.43; 95% CI, 0.70-2.91) nor aflibercept (RR, 0.64; 95% CI, 0.30-1.36) was associated with a greater incidence of sustained IOP elevations compared with the control cohort, bevacizumab-treated eyes had a significantly greater incidence of IOP elevation (RR, 1.81; 95% CI, 1.18-2.78). Similarly, direct comparisons of the treatment groups found no significant difference between bevacizumab and ranibizumab or ranibizumab and aflibercept, although bevacizumab-treated eyes were more likely than aflibercept-treated eyes to have a sustained IOP elevation (RR, 2.84; 95% CI, 1.26-5.92). Notably, however, the incidence of glaucoma development or worsening did not differ significantly between any injection subgroup compared with untreated controls. Altogether, these findings are consistent with those in previous reports that bevacizumab promotes slightly higher IOP values while aflibercept is associated with lower IOP values.[10,14–17]

These results may also offer some insight into the theories that have been proposed for the relationship between anti-VEGF agents and sustained IOP elevations. One theory suggests that high-molecular-weight proteins such as anti-VEGF agents can accumulate with repeat injections and obstruct aqueous outflow channels.[18] However, our findings do not support this theory given the significant difference in the risk for sustained IOP elevation between the large bevacizumab (149 kDa) and intermediate-sized aflibercept (115 kDa) but no significant difference in risk between bevacizumab and the small-sized ranibizumab (48 kDa). Moreover, among the treated eyes that experienced sustained IOP elevation, there was no significant difference in the average number of injections to sustained IOP increase between the different agents ($P = .46$), rendering the mechanism of accumulation and obstruction less likely.

Instead, the findings in our study may lend support to an alternate theory that suggests that the different binding targets of aflibercept and bevacizumab may explain their disparate effects on IOP. Specifically, bevacizumab only binds to VEGF-A, whereas aflibercept not only binds VEGF-A with greater affinity but also binds broadly to a variety of other VEGF family members and placenta growth factor.[19] There is growing evidence to suggest that placenta growth factor acts synergistically with VEGF-A in promoting vascular pathology in conditions such as AMD and DR. Therefore, it is feasible that aflibercept's additional binding of placenta growth factor could account for its different influence on IOP than that of bevacizumab.[19] Nevertheless, the role played by ranibizumab in this theory remains unclear because this agent's only target is VEGF-A, although it binds with greater affinity than bevacizumab. Thus, further investigation is needed of the differences in mechanisms between agents and their implications on aqueous outflow and IOP.

Beyond these theories, there are other factors to consider when evaluating bevacizumab's effect on IOP. First, the effect of bevacizumab syringes may be a confounder because the drug is produced for ophthalmologists by compounding pharmacies using off-the-shelf syringes that may have silicone sprayed on instead of baked on, unlike the prefilled syringes for aflibercept and ranibizumab.[20] Second, there was a statistically significant overrepresentation of Black patients in this study's bevacizumab group at baseline compared with the ranibizumab and aflibercept groups ($P = .004$). This may account for the higher risk for sustained IOP elevation in the bevacizumab group because Black patients are known to have higher median IOP values as a result of poorer systemic health and genetic factors[21,22] as well as more rapid progression of glaucoma.[22,23] Thus, our IOP findings in the bevacizumab group may reflect an early manifestation of these known racial differences.

In addition to comparing the rates of sustained IOP increase between anti-VEGF–treated eyes and untreated control eyes, this study further analyzed the subcohort of all eyes that ultimately experienced sustained IOP elevation. It was found that eyes treated with anti-VEGF took approximately 31 days longer on average to demonstrate sustained IOP elevations compared with the untreated control eyes ($P < .02$). This relationship remained significant in subcomparisons of bevacizumab-treated eyes with control eyes as well as aflibercept-treated eyes with controls, while compared with control eyes, ranibizumab-treated eyes yielded a P value approaching significance ($P < .07$).

To our knowledge, this difference in time to sustained IOP increase has not been previously reported. Indeed, although much of the research to this point has questioned whether a long-term adverse relationship exists between anti-VEGF agents and IOP, this finding may even suggest that these agents confer some protective effect that delays the onset of sustained IOP elevation in eyes that are already predisposed. Nevertheless, the small sample in this subanalysis necessitates further evaluation. In addition, this study defined a sustained IOP elevation as a 5 mm Hg or greater increase above baseline for a minimum of 4 weeks. However, this definition might lend itself to biased results because patients might not have been reassessed after meeting the criteria of sustained IOP elevation to evaluate the normalization of IOP. Instances of eyes with IOP naturally dropping below the threshold after initially meeting the criteria for sustained IOP elevation were not assessed in this study.

Limitations of this study include the retrospective nature of data collection and analysis. Although the overall cohort was relatively large, data from a single center may not be broadly generalizable. Moreover, there were notable differences in the sizes of the treatment group and control group as a result of some patients receiving treatment bilaterally and thus lacking an untreated fellow eye. Similarly, there were differences in the sizes of the anti-VEGF agent subgroups, with the bevacizumab treatment group being much larger than the ranibizumab and aflibercept groups. This discrepancy in anti-VEGF agent subgroup size is potentially attributable to the more frequent prescription of bevacizumab by clinicians given its affordability. This demand for bevacizumab may be linked to socioeconomic

differences and, correspondingly, to differences in health outcomes between the agent subgroups. Thus, these differences can serve as confounding variables for IOP elevation and ocular health.

Alternatively, the off-label use of bevacizumab in patients with NVG or NV may further confound these data, although these effects may be limited by our exclusion of patients with NVG. In addition, prefilled syringes became the predominant modality for aflibercept injection at our institution in 2020 and some early reports had suggested prefilled syringes were associated with long-term increases in IOP, hence conferring a potentially unaccounted for effect on IOP.[24,25] However, recent studies have disputed this finding, so any effect may be negligible.[26] Finally, the parallel glaucoma analysis in this study is limited because the disease takes time to develop and the cumulative damage to aqueous outflow may not have been sufficient to manifest over the 1-year follow-up.

Overall, the findings in this study highlight the complexity underlying the relationship between anti-VEGF agents and IOP, offering insight into the mechanisms involved. Not all anti-VEGF agents were associated with long-term IOP elevations or glaucoma manifestations; however, treatment with bevacizumab specifically appeared to carry an increased risk for sustained IOP elevation, although with no observable effect on glaucoma in this study's timeframe. Clearly, further research is needed. This study is unique with its investigation of sustained IOP elevation for all 3 commonly used anti-VEGF agents among a large overall cohort and the inclusion of a control cohort of untreated fellow eyes. Moreover, this study approached IOP elevation in a comprehensive manner, evaluating it numerically and with clinical outcomes through glaucoma manifestations. In future studies, it would be worthwhile to perform multicenter prospective controlled studies with longer follow-up periods.

Authors' Note

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Ethical Approval

This study was approved by Cleveland Clinic Institutional Review Board.

Statement of Informed Consent

Informed consent was not obtained from patients because no patient-level identifying information or images were used in this study.

Declaration of Conflicting Interests

Dr. Sharma reports personal consulting fees from Alimera, Abbvie, Bausch + Lomb, Clearside, EyePoint, Genentech/Roche, RegenxBio, and Regeneron and contracted research funding to his institution from Abbvie, Genentech/Roche, Gilead, IONIS, and Santen. Dr. Singh reports personal fees from Alcon/Novartis, Bausch + Lomb, Genentech/Roche, Regeneron Pharmaceuticals Inc, and Zeiss and grants from Apellis and Graybug. Dr. Talcott reports being on the Genentech speaker's bureau, receiving a grant from Zeiss, and being a consultant to Apellis, EyePoint, Genentech, and RegenxBio. None of the other authors declared potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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