

Sustained Increased Intraocular Pressure Related to Intravitreal Antivascular Endothelial Growth Factor Therapy for Neovascular Age-related Macular Degeneration

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Purpose: To describe a series of previously normotensive eyes experiencing sustained elevated intraocular pressure (IOP) associated with long-term intravitreal antivascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (AMD).

Patients and Methods: Clinical data were reviewed for 25 eyes of 23 patients with neovascular AMD who had increased IOP while receiving interval doses of intravitreal ranibizumab and/or bevacizumab. All eyes had tolerated multiple anti-VEGF injections in the past without IOP elevations.

Results: After a mean of 20.0 anti-VEGF injections (range, 8-40 injections), the mean IOP was 29.8 mm Hg (range, 22-58 mm Hg), compared with a baseline of 16.9 mm Hg (range, 14-21 mm Hg). The mean highest IOP while receiving intravitreal anti-VEGF therapy was 35.8 mm Hg (range, 23-58 mm Hg). Overall, 23 of 25 cases required IOP management. In the remaining 2 cases, anti-VEGF dosing was switched from regular interval dosing to an optical coherence tomography-guided variable regimen, with subsequent improvement in IOP without antiglaucoma treatment.

Conclusions: Serial injections of anti-VEGF agents may lead to persistent IOP elevations that require glaucoma therapy. The clinician should recognize this phenomenon, as it can occur even if the patient has tolerated multiple prior injections without IOP elevation. Further exploration of the relationship between anti-VEGF therapy and IOP is needed.

Key Words: anti-VEGF, ranibizumab, bevacizumab, ocular hypertension, neovascular age-related macular degeneration

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Intravitreal antivascular endothelial growth factor (VEGF) therapy has emerged as the standard of care in the management of neovascular age-related macular degeneration (AMD). The well-established safety and efficacy of ranibizumab (Lucentis, Genentech Inc, South San Francisco,

CA), a recombinant, humanized monoclonal antibody Fab targeting VEGF-A, has led to its approval by the United States Food and Drug Administration (FDA) for the treatment of neovascular AMD and, more recently, retinal vein occlusion. Bevacizumab (Avastin, Genentech, Inc), a full-size humanized monoclonal antibody to VEGF-A, is approved by the FDA for the treatment of various cancers, but "off-label" intraocular administration for neovascular AMD, retinal vein occlusion, and diabetic retinopathy has also gained widespread acceptance.

The introduction of additional fluid into the vitreous cavity by intravitreal therapy would be expected to cause an immediate rise in the intraocular pressure (IOP). This transient, short-term IOP elevation after intravitreal anti-VEGF therapy has been well described.¹⁻⁵ However, anti-VEGF therapy may also cause long-term, sustained IOP elevation.⁶⁻⁹

We herein report 25 eyes with persistent IOP elevation after repeated injections of intravitreal anti-VEGF agents for neovascular AMD.

PATIENTS AND METHODS

All patients were seen in a single group vitreoretinal practice by 4 physicians (K.B.F., J.A.S., M.J.C., or J.M.K.) and were being treated with the "treat-and-extend" dosing regimen described previously.¹⁰ In total, we evaluated 25 eyes of 23 previously ocular normotensive neovascular AMD patients who developed sustained increased IOP after multiple injections of intravitreal ranibizumab (0.5 mg/0.05 mL) and/or intravitreal bevacizumab (1.25 mg/0.05 mL). Ocular normotension was defined as IOP less than 21 mm Hg on all earlier evaluations within 12 months. Sustained increased IOP was defined as an IOP > 21 mm Hg detected during at least 2 consecutive office visits and/or an elevation in IOP requiring treatment. In most cases, IOP elevations were managed by glaucoma subspecialists.

All IOPs were measured by applanation tonometry. Measurements were performed before injection at office visits during which patients received anti-VEGF treatment. As is customary in this practice, no eyes received IOP-lowering medications or anterior chamber paracentesis before or after intravitreal injection. IOP measurements were not recorded after injection; rather, central retinal artery perfusion was evaluated by documentation of at least hand-motion visual acuity.

Patient records were reviewed for the following: demographic data, total number of intravitreal ranibizumab and/or bevacizumab injections, past or family history of

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glaucoma, baseline IOP (defined as the median IOP of the last 3 visits before the first episode of ocular hypertension), previous use of intravitreal corticosteroids, previous ocular history and surgeries, number of injections before developing ocular hypertension, frequency of intravitreal anti-VEGF injections, clinical examination details, subsequent glaucoma management, and duration of follow-up.

RESULTS

Study data are summarized in Table 1. Twenty-five eyes of 23 patients (11 male, 12 female) were evaluated. The mean age of the patients was 81.8 years (range, 59-99 y) and the mean follow-up time, defined as the period between the first detection of elevated IOP and the last recorded visit, was 47.9 weeks (range, 9-159 wk). Overall, 24 of 25 eyes received injections of intravitreal ranibizumab or bevacizumab at each visit every 5 to 8 weeks (based on a "treat-and-extend" dosing regimen) before the noted IOP elevation; the remaining eye (case 10) received ranibizumab every 12 weeks based on "treat-and-extend" dosing. All eyes had undergone gonioscopy showing open angles without neovascularization, inflammatory deposits, or silicone oil droplets. Anterior chamber inflammation had not been detected in any of the study eyes. At the time of the IOP elevation, 15 eyes (60.0%) were phakic and 10 eyes (40.0%) were pseudophakic, all with posterior chamber intraocular lens implants. Of the 10 pseudophakic eyes, 3 had undergone YAG laser capsulotomy. None of the remaining 15 eyes in the series had a history of prior intraocular surgery.

For the 25 eyes in this series, the mean IOP before initiating intravitreal anti-VEGF therapy was 16.9 mm Hg (range, 14-21 mm Hg). Eyes had received a mean of 20.0 and a median of 17.0 intravitreal injections of anti-VEGF medication before elevated IOP was first detected (range, 8-40 injections). All 25 eyes had received at least 8 or more injections of intravitreal ranibizumab. In all, 11 eyes had received intravitreal ranibizumab alone; the remaining 14 had also received injections of intravitreal bevacizumab, although typically at a lower frequency. In the 14 eyes that had received both agents, the mean and median number of prior bevacizumab injections was 3.3 and 3.0, respectively (range, 1-8 injections). The mean IOP at the first-noted elevation was 29.8 mm Hg (range, 22-58 mm Hg); the mean highest IOP while on ranibizumab was 35.8 mm Hg (range, 23-58 mm Hg).

Prevalence

Of the 25 eyes in this series, 21 eyes of 19 patients were treated by 1 physician (K.B.F.), and comprise all cases of sustained elevated IOP after intravitreal anti-VEGF therapy seen by this physician. These 19 patients represent 3.4% (19/555) of the total number of patients treated by this physician with intravitreal ranibizumab or bevacizumab for the diagnosis of neovascular AMD over the preceding 62 months. Of 425 patients treated by this physician with intravitreal anti-VEGF agents over the previous 6 months, 4.5% (19/425) of patients had sustained elevated IOP.

Glaucoma History

Of the 25 eyes, 23 had no prior history of glaucoma. One eye had a history of primary open-angle glaucoma (POAG) that had been controlled with topical timolol maleate (0.5%), dorzolamide hydrochloride (2%), and latanoprost (0.005%) (case 11). Although 3 eyes of 3 patients (cases 5, 9, and 14) had been followed for clinical

suspicion of glaucoma based on optic nerve appearance, each previously had normal IOP. In addition, none of these 3 eyes had visual field loss by perimetry or prior treatment with ocular hypotensive therapy. Only 1 patient in this series had a family history of glaucoma. One patient (case 1) had a history of adult-onset diabetes mellitus with no evidence of diabetic retinopathy.

Clinical Examination

On clinical examination, no eyes had evidence of neovascular glaucoma or pseudoexfoliation. On the basis of the absence of cell and flare, no eyes had evidence of anterior segment inflammation. Droplets of silicone oil were not detected in the aqueous of any eyes. Gonioscopy revealed open angles in all eyes. No eyes had evidence of peripheral anterior synechiae (PAS) or trabeculitis. Silicone droplets were not detected in the angle of any eyes in this series.

Prior Intravitreal Corticosteroid Therapy

Five eyes of 4 patients had a remote history of prior intraocular steroids, either intravitreal triamcinolone acetonide (IVTA) (4 mg/0.1 mL) or dexamethasone in combination with bevacizumab (1.25 mg bevacizumab with 240 µg dexamethasone/0.08 mL). One eye (case 11) received a bevacizumab/dexamethasone injection 23 months before the detection of sustained IOP elevation on intravitreal anti-VEGF therapy. This patient, as noted above, had a history of well-controlled POAG but ultimately required a trabeculectomy after sustained IOP elevation on anti-VEGF therapy. The remaining steroid-injected eyes (cases 1, 3, and 10) received IVTA a mean of 42.5 months (range, 13-55 mo) before the first IOP elevation on anti-VEGF therapy. One of these eyes (case 3) required a short-term course of topical antihypertensive medications for steroid-induced ocular hypertension after IVTA, after which the IOP remained normal for 13 months. After 8 injections of intravitreal ranibizumab, IOP again became elevated. This eye also required surgical IOP management with a combined cataract extraction and trabeculectomy after failed argon laser trabeculoplasty. At the last follow-up, 5 months after trabeculectomy, IOP was 13 mm Hg on brimonidine tartrate (0.1%) and timolol maleate (0.5%).

Laser Trabeculoplasty and/or Filtration Procedures

There were 2 additional eyes that required filtration surgery in which there was no history of intravitreal corticosteroids: cases 6 and 13 (highlighted below). Case 6 had a final IOP of 17 mm Hg on brimonidine tartrate (0.15%) and timolol maleate (0.5%) 3 months after combined cataract extraction and trabeculectomy. In addition, another patient (case 12) had selective laser trabeculoplasty (SLT), after which IOP was controlled with the addition of brimonidine tartrate (0.15%) and timolol maleate (0.5%).

Bilateral Injections

Six of the 23 patients in this series received bilateral anti-VEGF therapy. Two of these patients had elevated IOP in both eyes (cases 1 and 22), whereas the remaining 4 experienced elevated IOP in only 1 eye (cases 3, 8, 13, and 19). In 3 of these patients (cases 3, 8, and 13), the unaffected fellow eye received far fewer injections than the study eye (mean 11 vs. 28 injections). Case 19 received an equal number of injections in each eye but experienced an elevation of IOP in only the right eye.

TABLE 1. Summary of Patients With Ocular Hypertension After Multiple Intravitreal Ranibizumab Injections for Neovascular Age-related Macular Degeneration

Case	Sex	Age	Eye	Glaucoma History	Prior Ocular Surgery	Baseline IOP*	First Elevated IOP	Highest IOP	Final IOP	RZB Interval (wk)	No. RZB Injections	No. Prior RZB Injections	No. Prior BZB Injections	No. Prior Steroid Injections	Glaucoma Treatment	Follow-up (wk)
1	M	78	OD	—	—	18	22	32	16	5	27	27	2	1 (IVTA)	Brimonidine, latanoprost	37
			OS	—	—	18	27	31	22	5	25	25	6	1 (IVTA)	Brimonidine, latanoprost	37
2	F	76	OD	—	—	18	22	28	14	6	10	10	0	0	Travoprost	132
3	M	81	OD	Steroid-induced glaucoma	—	15	23	38	13	5	8	8	2	1 (IVTA)	ALT, latanoprost, timolol, brimonidine, pilocarpine, acetazolamide, phaco/traab	159
4	M	84	OD	—	—	14	24	29	13	5	28	28	2	0	Levobunolol	34
5	F	59	OS	Suspect (+) FHx	—	15	25	33	32	5	22	22	0	0	Brimonidine, brinzolamide, latanoprost, timolol	52
6	M	78	OD	—	CE/IOL	14	34	46	16	5	25	25	4	0	Bimatoprost, timolol, brimonidine, phaco/traab	38
7	M	86	OD	—	CE/IOL	16	30	30	19	8	8	8	0	0	Latanoprost, brimonidine	32
8	F	74	OS	—	—	16	38	53	42	5	32	32	8	0	Brimonidine, timolol, travoprost, acetazolamide, phaco/traab†	33
9	F	87	OD	Suspect	CE/IOL	18	26	40	35	8	22	22	2	0	Brimonidine, timolol, travoprost	37
10	F	99	OS	—	CE/IOL	15	58	58	22	12	16	16	1	1 (IVTA)	Timolol, brimonidine bimatoprost, acetazolamide	30
11	F	90	OD	Primary open angle glaucoma	CE/IOL	20	42	42	16	5	22	22	1	1 (BZB/dexamethasone)	Pilocarpine, timolol, dorzolamide, latanoprost, trabeculectomy	19
12	M	83	OD	—	CE/IOL	14	34	35	13	5	24	24	0	0	Brimonidine, timolol, travoprost	20
13	M	78	OS	—	CE/IOL	15	38	38	24	5	32	32	3	0	SLT	20
14	F	81	OD	Suspect	—	21	29	29	24	6	18	18	0	0	Brimonidine, latanoprost, timolol	27
15	F	85	OD	—	CE/IOL	20	34	34	22	6	12	12	0	0	SLT, trabeculectomy†	88
16	F	83	OD	—	—	17	28	35	24	6	13	13	4	0	Travoprost, brimonidine	34
17	F	77	OD	—	—	18	23	30	20	7	15	15	0	0	Latanoprost	20
18	F	86	OD	—	CE/IOL	14	28	28	20	6	15	15	0	0	—	9
19	F	87	OD	—	—	17	41	41	24	8	17	17	0	0	Travoprost	10
20	M	71	OS	—	—	16	30	30	18	5	13	13	3	0	Travoprost	15
21	M	81	OS	—	CE/IOL	17	22	38	8	6	10	10	4	0	Brimonidine, timolol, travoprost, acetazolamide	134
22	M	85	OD	—	—	19	23	24	18	8	16	16	0	0	Travoprost	25
			OS	—	—	18	23	23	15	8	11	11	0	0	Travoprost	25
23	M	92	OD	—	—	20	22	50	20	5	12	12	4	0	Brimonidine, brinzolamide, timolol	96

*Defined as the median of the 3 recorded IOPs prior to the first episode of ocular hypertension.

†Scheduled.

ALT indicates argon laser trabeculoplasty; BZB, bevacizumab; CE/IOL, cataract extraction with posterior chamber intraocular lens implant; FHx, family history; IOP, intraocular pressure; IVTA, intravitreal triamcinolone acetonide; OD, right eye; OS, left eye; phaco/trabeculectomy, combined cataract extraction and trabeculectomy; RZB, ranibizumab; SLT, selective laser trabeculectomy.

Bimatoprost, bimatoprost (0.03%); Brimonidine, brimonidine tartrate (0.15%); Brinzolamide, brinzolamide (1%); Dorzolamide, dorzolamide hydrochloride (2%); Latanoprost, latanoprost (0.005%); Levobunolol, levobunolol hydrochloride; Pilocarpine, pilocarpine hydrochloride (2%); Timolol, timolol maleate (0.5%); Travoprost, travoprost (0.004%).

Eyes Switched to Optical Coherence Tomography-guided Dosing (Data Summarized in Table 2)

Overall, 23 of the 25 eyes underwent pharmacologic IOP reduction. In the 2 remaining eyes (cases 16 and 18), both of which had quiescent subfoveal fibrosis and preserved central vision in the fellow eye, the treating physician, upon detection of elevated IOP, elected to change the anti-VEGF dosing regimen from a “treat-and-extend”¹⁰ strategy to an optical coherence tomography (OCT)-guided variable regimen^{11,12} and observe the IOP. Neither eye required additional injections of anti-VEGF therapy over 4 to 8 weeks of follow-up. Both eyes experienced a reduction in IOP while anti-VEGF therapy was held, but neither returned to baseline. In addition, 4 of the remaining 23 eyes that had been started on topical ocular hypotensive agents were also changed to OCT-guided dosing (cases 9, 14, 19, and 20). Two of these cases had quiescent peripapillary choroidal neovascularization that was not viewed to be an imminent threat to the fovea. The third had already lost foveal function with preserved central vision in the fellow eye, and the fourth was switched to an OCT-guided regimen owing to patient preference. Only 1 of these patients (case 14) received a single further ranibizumab injection with IOP remaining stable. With short-term follow-up (3 to 16 wk), the IOP was noted to decrease in 3 of these 4 cases (cases 9, 19, and 20).

Transient IOP Lowering After Ranibizumab

In 2 cases, a transient lowering of IOP was noted 1 to 2 weeks after intravitreal injection with ranibizumab. In 1 patient (case 1), both eyes were noted to be hypertensive immediately before injection but became normotensive 1 week after ranibizumab therapy without any intervention. The IOP in both the eyes eventually became persistently elevated and responded to pressure-lowering medications. A second patient (case 2) also initially experienced normalization of IOP after ranibizumab without glaucoma medications, but IOP eventually became persistently elevated after 12 more monthly injections.

Selected Patient Cases

Case 8

A 75-year-old woman with no history of glaucoma or earlier ocular surgery received repeated intravitreal anti-VEGF treatment in both eyes for neovascular AMD. To date, the right eye has remained normotensive after 21 ranibizumab and 1 bevacizumab injections. After 32 ranibizumab and 8 bevacizumab injections, the left eye had its first episode of ocular hypertension with a pressure

of 38 mm Hg. Examination revealed no evidence of anterior chamber inflammation or rubeosis in either eyes, and angles were open without PAS by gonioscopy. The optic nerves appeared healthy with no evidence of glaucomatous cupping. Intravitreal injection was deferred, and the patient was referred to a glaucoma specialist, who began treatment with timolol maleate 0.5%. Two days later, the IOP in this eye was noted to be 18 mm Hg, after which 2 subsequent intravitreal ranibizumab injections were given 5 weeks apart. On routine follow-up, while remaining on timolol maleate (0.5%) in the left eye, IOPs were measured at 17 and 53 mm Hg in the right and left eye, respectively. Addition of oral acetazolamide, topical brimonidine tartrate (0.15%), and travoprost ophthalmic (0.004%) was unsuccessful in normalizing IOP. At the last evaluation by the glaucoma specialist, the left eye had an IOP of 42 mm Hg despite maximally tolerated medical therapy, and trabeculectomy was planned.

Case 13

A 78-year-old man was started on intravitreal ranibizumab for neovascular AMD in the left eye. After 32 ranibizumab and 3 bevacizumab injections, the IOP was found to be 38 mm Hg. On the same day, the right eye, which had received 4 ranibizumab injections for neovascular AMD, had an IOP of 14 mm Hg. Gonioscopy showed 4+ open angles with no evidence of neovascularization, trabeculitis, or PAS. The optic nerves appeared healthy with no evidence of glaucomatous cupping. The patient was initially started on latanoprost (0.005%), which failed to establish IOP control. After SLT, IOP was controlled for 1 month but later became elevated again (35 mm Hg, compared with 12 mm Hg in the fellow eye). At the last visit, the IOP was 24 mm Hg on latanoprost (0.005%), brimonidine tartrate (0.15%), and timolol maleate (0.5%) (compared with 14 mm Hg in the fellow right eye, which had received a total of 9 injections). This eye is now scheduled for trabeculectomy.

DISCUSSION

Short-term transient ocular hypertension immediately after intravitreal ranibizumab and bevacizumab therapy is a well-described phenomenon,^{1–5} but recent reports suggest that sustained ocular hypertension after intravitreal anti-VEGF treatment is also possible.^{6–9}

In our series, we identified 25 previously normotensive eyes that developed sustained ocular hypertension after a mean of 20.0 injections (range, 8–40 injections) of intravitreal ranibizumab and/or bevacizumab for neovascular AMD. Of the 25 eyes, only 3 had been suspected of glaucoma based upon optic nerve appearance, and a single eye had a history of POAG. The majority of the intravitreal injections administered were of ranibizumab (453 of 499, 90.8%), and 11 of 25 eyes had been treated with ranibizumab alone. As ranibizumab has been used far more often than

TABLE 2. Summary of Patients With Ocular Hypertension After Multiple Intravitreal Ranibizumab Injections for Neovascular Age-Related Macular Degeneration Who Were Subsequently Changed From “Treat-and-Extend” Dosing to Optical Coherence Tomography-Guided Variable Dosing

Case	Eye	Final IOP on	Final IOP on OCT-guided	Glaucoma Treatment	Follow-up*(wk)
		Treat-and-Extend Dosing	PRN Dosing		
9	OD	30	35	Travoprost, brimonidine, timolol	3
14	OD	24	24	Travoprost, brimonidine	14
16	OD	32	24	—	4
18	OD	28	20	—	8
19	OD	41	24	Travoprost	10
20	OS	30	18	Travoprost	16

*After change to OCT-guided PRN dosing regimen.

OCT indicates optical coherence tomography; OD, right eye; OS, left eye; IOP, intraocular pressure.

bevacizumab to treat patients with neovascular AMD in this practice, it is not possible to determine from our data which of these agents is more likely to lead to sustained ocular hypertension.

Sustained IOP elevations after intravitreal anti-VEGF therapy have been reported. Bakri et al⁷ found sustained ocular hypertension in 4 eyes of 4 patients after 1 or 2 intravitreal injections of ranibizumab. As all of these eyes had received earlier injections of intravitreal pegaptanib, intravitreal bevacizumab, or intravitreal triamcinolone, it is difficult to conclude that the intravitreal injections of ranibizumab alone were sufficient to produce sustained IOP elevation in these cases. Kahook et al⁸ reported 6 eyes of 6 patients with sustained ocular hypertension after 1 to 10 intravitreal injections of bevacizumab. One eye in this series had been on topical therapy for glaucoma and 2 eyes had prior optic nerve changes suspicious for glaucoma. In the remaining 3 eyes with no history of glaucoma or ocular hypertension, the number of intravitreal bevacizumab injections was 5 to 10. Adelman et al⁹ identified 4 eyes out of 116 (3.45%) patients treated with intravitreal anti-VEGF therapy for neovascular AMD that developed sustained ocular hypertension after a mean of 13.3 (range, 3-19) intravitreal bevacizumab and/or ranibizumab injections. None of these eyes had a prior history of glaucoma, ocular hypertension, or optic nerve changes suspicious for glaucoma. Good et al⁶ found sustained IOP elevations in 13 of 215 eyes (6%) after a median of 9 injections of ranibizumab and/or bevacizumab, noting a higher prevalence in eyes receiving only bevacizumab (9.9%) compared with those receiving only ranibizumab (3.1%). They further noted higher rates in patients with preexisting glaucoma (33% vs 3.1% in eyes without preexisting glaucoma).

In all of these earlier reports, the duration of follow-up after the detection of elevated IOP was limited. Also, in most previously reported cases of sustained ocular hypertension related to intravitreal anti-VEGF therapy, IOP was successfully managed with topical therapy (with the exception of 1 eye treated with laser trabeculoplasty⁶ and another that required a filtration procedure⁸).

The mean follow-up in our series was 47.9 weeks. Typically, IOP continued to increase if intravitreal anti-VEGF therapy was continued. Of the 25 eyes in our series, all 19 in which anti-VEGF treatment was continued eventually required some form of antiglaucoma intervention to control the elevated IOP. In 3 eyes, laser trabeculoplasty with either argon laser trabeculoplasty (case 3) or SLT (cases 12 and 13) was performed, but 2 of these 3 eyes ultimately required glaucoma filtration surgery (cases 3 and 13). Additionally, 3 eyes that had not undergone laser trabeculoplasty also required filtration surgery (cases 6, 8, and 11).

In 2 eyes (cases 16 and 18), IOP treatment was avoided by switching from a "treat-and-extend" dosing regimen, in which continuous maintenance injections of anti-VEGF agents are given at intervals of 5 to 8 weeks, to an OCT-guided *pro re nata* (PRN) dosing strategy. No further intravitreal anti-VEGF injections were needed during the follow-up period in these 2 cases, and IOP in both eyes improved, obviating the need for glaucoma treatment. Similarly, 4 other eyes (cases 9, 14, 19, and 20) that were initiated on topical therapy for IOP elevations were also switched to an OCT-guided PRN dosing regimen. Only 1 of these eyes (case 14) required an additional intravitreal anti-VEGF injection. In the remaining 3 eyes which did not require further anti-VEGF treatment, IOP stabilized or

improved, suggesting at least some reversibility of the treatment-related IOP elevations after the cessation of anti-VEGF therapy.

The manner in which intravitreal anti-VEGF therapy contributes to ocular hypertension is unknown, but several potential mechanisms are possible. The drugs may have a direct pharmacologic effect on aqueous outflow via the trabecular meshwork, uveoscleral pathway, or Schlemm canal. Reports have varied as to whether ranibizumab or bevacizumab is toxic to anterior segment cells at pharmacological doses.^{13,14} The repeated transient IOP rise related to the volume of drug introduced could also alter aqueous outflow pathways. Chronic inflammation or trabeculitis related to repeated intravitreal injections could theoretically contribute to sustained IOP elevation.¹⁵ However, no anterior chamber cell or flare, PAS, or evidence of trabeculitis was noted in any of the eyes in this series, and attempts to control subclinical inflammation and lower IOP with short-term topical corticosteroids in 4 cases were ineffective.

Mechanical obstruction to outflow, either by the anti-VEGF agent or byproducts of pharmacologic compounding or storage, may be implicated. Kahook et al¹⁶ found varying levels of high-molecular weight protein aggregates when comparing different samples of compounded preparations of bevacizumab and hypothesized that this large particulate matter could lead to elevated IOP by obstructing aqueous outflow. Although a similar mechanism may have contributed to the elevation of IOP in some of our cases, there are important distinctions between our eyes and those of other investigators. For example, 11 cases in our series did not receive bevacizumab, and the remaining 14 eyes had discontinued bevacizumab and started ranibizumab a mean of 37.5 months (range, 4-49 mo) before ocular hypertension was detected.

Another potential cause of mechanical obstruction to outflow is retention of intraocular silicone oil droplets, as observed in eyes undergoing frequent intravitreal injections of various pharmacologic agents.¹⁷⁻²⁰ The source of these droplets seems to be the syringe used to inject the drugs, as the barrels, plungers, and needles of these syringes are all lubricated with dimethicone (polymethylsiloxane) to reduce friction. As silicone droplets were not observed in the aqueous or anterior chamber angle in any of our eyes, we do not believe that mechanical obstruction to aqueous outflow owing to retained silicone droplets played a significant role in sustained ocular hypertension in our cases.

One limitation of this study is the inability to prove a direct causal relationship between intravitreal anti-VEGF therapy and sustained ocular hypertension owing to a limited sample size, lack of controls, and the large variation in the number of injections given before the detection of sustained IOP elevations. It is possible that eyes in this series may have had some other unknown predisposition or risk for developing sustained ocular hypertension after intravitreal treatment. Future studies with more frequent monitoring of IOP pre-treatment and post-treatment will help to clarify if a causative mechanism exists. The use of additional measures to study aqueous dynamics, such as ocular tonography to investigate aqueous outflow facility, may help clarify the underlying pathophysiology in these cases.

Interestingly, case 3 had a history of steroid-induced glaucoma after an injection of IVTA. Although this history confounds the potential association of ocular hypertension and anti-VEGF therapy, it may suggest a common pathway for IOP elevation secondary to corticosteroids and

ranibizumab. It should be noted that the IOP in the fellow eye of this patient, which had not received an intravitreal steroid injection, remained normal despite 32 ranibizumab and 3 bevacizumab injections.

We also noted that in 3 eyes (cases 1 and 2), all of which had been normotensive before repeated intravitreal ranibizumab injections, the IOP, which was elevated immediately before anti-VEGF treatment, returned to normal when the patient returned for repeat tonometry approximately 1 week after reinjection, even though no antiglaucoma treatment had been initiated. This finding suggests a possible short-term antihypertensive effect of intravitreal anti-VEGF therapy. Anti-VEGF agents have been studied in neovascular glaucoma²¹ and filtration surgeries²² for their antiangiogenic effects, but perhaps these drugs can transiently lower IOP via effects on the ciliary body, uveoscleral pathway, or trabecular meshwork. Lee et al²³ found a statistically significant reduction in IOP at 1 day and 1 week after intravitreal bevacizumab injection on the order of 1 to 2 mm Hg, and postulated that this might be due to increases in matrix metalloproteinase activity from the increased intraocular volume and subsequent mechanical stretching of trabecular meshwork cells.

As the half-life of intravitreal ranibizumab is approximately 3 days, any antihypertensive effect might be transient. Accordingly, all 3 of these eyes eventually required topical antihypertensive medications, despite the short-term improvement in IOP after reinjection. We speculate that, as the anti-VEGF effect declines, the IOP may increase owing to rebound swelling of cells controlling outflow through trabecular meshwork or uveoscleral pathway, or possibly owing to the return of normal aqueous production by the ciliary body. Why the duration of pharmacologic effect on these tissues appears shorter than that needed to control choroidal neovascularization²⁴ is unclear.

Of the 25 eyes in this series, 24 had been managed using a "treat and extend" dosing regimen in which maintenance injections were given every 5 to 8 weeks before the development of sustained ocular hypertension. This dosing strategy may predispose eyes to a rebound increase in IOP as the anti-VEGF effect wears off. In contrast, with the monthly dosing regimen used in the phase 3 ANCHOR and MARINA ranibizumab trials,²⁵ VEGF inhibition might be more uniformly maintained, reducing the potential for this hypothesized rebound phenomenon. We should note that, despite the initial analyses of the ANCHOR²⁶ and MARINA²⁷ trials that showed no evidence for ranibizumab causing IOP elevations, a more recent analysis by Bakri et al found a statistically significant increase in the number of treated eyes having IOPs above 21 mm Hg versus eyes receiving sham injections over the 24-month follow-up period of these studies (Bakri SJ. IOP in Eyes Treated With Monthly Ranibizumab: A Post Hoc Analysis of Data From the MARINA and ANCHOR Trials. AAO Annual Meeting, October 15, 2010; Chicago, IL).

In summary, a favorable risk-to-benefit profile for intravitreal anti-VEGF therapy with ranibizumab and/or bevacizumab compared with alternative treatments has led to these treatments becoming the standard of care for treating neovascular AMD. However, our series as well as other recent reports seem to suggest that sustained ocular hypertension may occur with repeated injections of these agents. Although these cases seem to represent fewer than 5% to 10% of all eyes receiving treatment, continued injections may cause further increases in IOP, which may in turn

necessitate multiple topical antiglaucoma agents and, in some eyes, laser trabeculoplasty and/or glaucoma filtration surgery. Where appropriate, a change to an OCT-guided as-needed dosing regimen may help reduce the risk for further elevation in IOP by decreasing the frequency of intravitreal anti-VEGF treatment. Further research to establish the relationship between anti-VEGF therapy and sustained ocular hypertension is warranted, and the clinician should be cognizant of this uncommon but important phenomenon.

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