

SUSTAINED ELEVATED INTRAOCULAR PRESSURES AFTER INTRAVITREAL INJECTION OF BEVACIZUMAB, RANIBIZUMAB, AND PEGAPTANIB

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Purpose: To investigate elevated intraocular pressures (IOP) (defined by a measurement >25 mmHg at a follow-up visit) after an intravitreal injection of anti-vascular endothelial growth factor agents for age-related macular degeneration.

Methods: Retrospective review of medical records.

Results: A total of 127 patients (155 eyes) received an intravitreal injection of anti-vascular endothelial growth factor agents (bevacizumab, ranibizumab, or pegaptanib) ranging from 1 to 39 injections for more than a period of 30 to 1759 days. Among this population, 12 patients (14 eyes; 9.4%) developed elevated IOP >25 mmHg. Of these, 7 patients (5.5%) developed sustained elevated IOP (IOP >25 mmHg on 2 separate visits requiring glaucoma medication or surgery), of which 8 eyes required topical medications and 1 eye underwent glaucoma surgery. Mean IOP of injected eyes receiving intravitreal injection was 15.2 ± 2.4 mmHg, and the mean IOP was 14.9 ± 2.6 mmHg for noninjected eyes. Among eyes that had elevated IOPs, there was no association with injection frequency, number of injections, or anti-vascular endothelial growth factor agent used.

Conclusion: Elevated IOP, sustained or unsustained, after intravitreal injection is not uncommon. No association with patient demographics or injection history was identified in the authors' study population.

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The exudative form of age-related macular degeneration, characterized by choroidal neovascularization, is considered a significant leading cause of severe visual loss in the elderly population in the developed world.^{1,2} Vascular endothelial growth factor (VEGF) has been implicated in the development of choroidal neovascularization membranes, and recently, there has been an increased use of intravitreal injections (IVIs) of anti-VEGF agents (i.e., bevacizumab and ranibizumab) to treat this condition.^{3–5} Pegaptanib

sodium (Macugen; Eyetech Pharmaceuticals/Pfizer, Inc, New York, NY) is a Food and Drug Administration–approved aptamer capable of binding isoforms of VEGF that are ≥ 165 amino acids in length and was the first widely used intraocular anti-VEGF agent.³ Ranibizumab (Lucentis; Genentech, South San Francisco, CA) is a 48-kDa, VEGF-A recombinant, humanized monoclonal antibody, designed specifically for intraocular use.⁴ Bevacizumab (Avastin; Genentech) is a larger molecule (150 kDa) with 2 antigen-binding sites that was originally designed for antiangiogenic therapy in malignancies but is increasingly being used off-label in the treatment of exudative age-related macular degeneration, as recent studies^{6,7} have shown its efficacy similar to that of ranibizumab.

Studies investigating transient increases in intraocular pressure (IOP) measurements after IVI of anti-VEGF agents have consistently shown that despite the rapid increase in IOP measurements at the time of injection, in most cases, normalization of IOP

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measurements takes place within the first 30 minutes to 60 minutes.^{8–10} The MARINA and ANCHOR trials revealed no sustained increases in IOP measurements with ranibizumab treatment. The VISION and PACORES trials also failed to show any increases in IOP measurements with pegaptanib and bevacizumab treatments, respectively.^{4,11–13} However, recently, there have been several case reports^{14–18} (28 patients) of sustained elevated IOP measurements in eyes receiving either ranibizumab (9 cases) or bevacizumab (19 cases).

This retrospective review of medical records intended to evaluate the prevalence of sustained elevated IOP measurements in a large series of patients with age-related macular degeneration who received multiple IVIs of the three currently available anti-VEGF agents (bevacizumab, ranibizumab, and/or pegaptanib).

Methods

This retrospective review of medical records evaluated patients treated with IVIs of anti-VEGF agents for age-related macular degeneration at the Jules Stein Eye Institute at the University of California, Los Angeles (UCLA). The study was approved by the UCLA Institutional Review Board. Medical records were identified from patients examined by 5 retina specialists (C.A.M., D.S., J-P.H., T.A.M., and M.B.G.) during the period of 2005 to 2010. Inclusion criterion for the study required patients to have been treated with IVIs of ranibizumab, bevacizumab, and/or pegaptanib for age-related macular degeneration. Exclusion criteria included the absence of preinjection and postinjection IOP measurements, previous diagnosis of glaucoma, previous use of glaucoma medications, diagnosis of diabetes, or alternative diagnosis of other retinal disorders. Standard demographic information, IOP measurements (preinjections and postinjections), pin-hole visual acuity, injection number, injection dates, injection drug, injecting physician, intraocular lens status, presence or absence of choroidal neovascularization, and IOP-lowering medications were all recorded from each chart review.

Intravitreal injections of ranibizumab (0.5 mg/100 μ L), bevacizumab 1.25 mg/100 μ L), and pegaptanib (1.6 mg/90 μ L) were administered via standard techniques for IVI. For anesthesia, 2 techniques were used, either subconjunctival lidocaine injection or the application of a sterile cotton-tipped applicator soaked with a topical 0.5% tetracaine over the intended injection site for 3 minutes. Screening IOP measurements were measured primarily by Reichert Tono-Pen XL (Reichert Inc., Depew, NY) applanation tonometry.

For IOP measurements >25 mmHg, confirmatory Goldmann applanation tonometry (Haag Streit USA and Reliance Medical Products, Mason, OH) measurements were used in lieu of the initial Tono-Pen values. Preinjection IOP measurements were recorded immediately before injection on the day of initiation of therapy. The IOP measurements after each injection were measured at the next office visit (1 month later) before any additional injections. Distance corrected and uncorrected visual acuities were measured by Snellen visual charts.

We used an a priori definition of elevated IOP measurements as any measurement >25 mmHg, and we defined sustained elevated IOP measurements as pressures >25 mmHg on at least 2 separate visits or any IOP measurement >25 mmHg that required glaucoma medication or glaucoma surgery. Additional medical and ocular history was collected in seven patients who presented with sustained elevated IOP measurements. These patients with sustained elevated IOP measurements were placed in one of four subgroups: 1) patients with bilaterally injected eyes with bilateral elevations in IOP measurements, 2) patients with bilaterally injected eyes with an unilateral elevation in IOP measurements, 3) patients with unilaterally injected eyes with an unilateral elevation in IOP measurements, 4) patients with unilaterally injected eyes with a bilateral elevation in IOP measurements. Because the majority of IOP measurements were made with the Tono-Pen, which is known to have greater variability and less accuracy than applanation tonometry, we attempted, whenever possible, to determine if there was confirmation of the increased IOP measurements by applanation methods. Because the Tono-Pen is frequently used as a screening tool in vitreoretinal practices, we also evaluated the variability of repeated Tono-Pen measurements for each eye and across the entire cohort of cases to determine if our original threshold for elevated IOP measurements was clearly outside of the normal range of IOP measurements.

To avoid misinterpretation of a limited number of IOP measurements, we evaluated each patient's entire set of IOP measurements over the study period to determine not just the average IOP measurements but whether their measurements indicated a trend toward increasing, decreasing, or stable IOP measurements during the course of their treatment. We looked at the collective set of patient IOP measurement data over a set period (300 days from the time of the first IVI) to determine whether there was any pattern of increasing, decreasing, or stable IOP measurements among individuals as the number of injections they have received during this 300-day interval increased. A

slope of ± 0.01 is equivalent to a change of 3 mmHg over the 300-day period.

Results

A total of 127 charts of patients who had received IVI of anti-VEGF agents by 5 retinal specialists (C.A.M., T.A.M., J-P.H., D.S. and M.B.G.) were reviewed (Figure 1). The mean age of the cohort was 81 ± 10 years and included 47 men and 80 women with 99 patients receiving unilateral treatment and 28 receiving treatments for both eyes during the follow-up period.

Of the entire cohort of 254 eyes, 155 eyes were injected. Of the 155 eyes, 67 eyes were phakic and 88 were pseudophakic. A more detailed summary of the key demographics is available in Table 1. The average preinjection and final posttreatment IOP measurements, as measured by Tono-Pen, were 14.5 ± 3.4 mmHg and 15.1 ± 3.7 mmHg, respectively. The average pretreatment and final posttreatment pinhole visual acuities for injected eyes were 20/100 and 20/80, respectively. The average pinhole visual acuity for the noninjected eyes that were monitored during the same period as the injected eyes was 20/50. The median follow-up period of the entire cohort was 417 ± 388 days, and the median follow-up period of

the patients with sustained elevated IOP measurements was 928 ± 489 days. Of our cohort, a total of 50 eyes received ranibizumab, 61 received bevacizumab, and 6 received pegaptanib as monotherapies. A total of 28 eyes received ranibizumab and bevacizumab, and 1 eye received ranibizumab and pegaptanib, and 2 eyes received bevacizumab with pegaptanib. Finally, a total of seven eyes received all three anti-VEGF agents of ranibizumab, bevacizumab, and pegaptanib. Every combination of single and multiagent treatment regimens were found in our cohort and a detailed report is shown in Table 1.

Average injection number was 7 ± 7 with a range of 1 injection to 39 injections, although 50% of the 127 eyes received <5 injections (see **Figure 1, Supplemental Digital Content 1**, <http://links.lww.com/IAE/A44>, which demonstrates the distribution of injection number for the entire cohort). The average injection frequency of our cohort was 7.1 ± 2.6 injections per year (see **Figure 2, Supplemental Digital Content 2**, <http://links.lww.com/IAE/A45>, which demonstrates the distribution of injection frequencies among cohort with 2 or more injections). In eyes that had received >5 injections, the range of injection frequencies was evenly distributed around the mean (see **Figure 3, Supplemental Digital Content 3**, <http://links.lww.com/IAE/A46>,

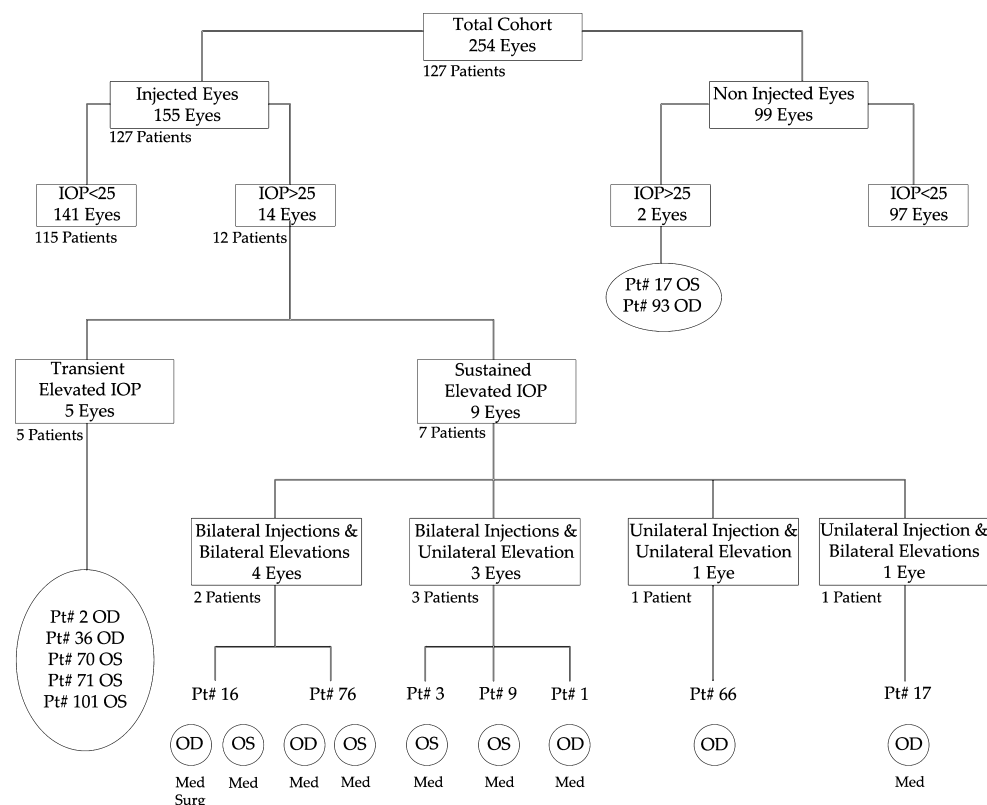


Fig. 1. Flow chart of entire cohort.

Table 1. Key Demographics of the Entire Cohort, Noninjected Eyes, and Injected Eyes

Entire cohort	
Total patients in study	127
Men	47
Women	80
Average age, years	81 ± 10
Number of eyes with pseudophakia	137
Number of eyes with phakia	116
Number of eyes with aphakia	1
Median follow-up of entire cohort, days	417 ± 388
Average IOP base, mmHg	14.4 ± 3.4
Average IOP end, mmHg	15.3 ± 3.7
Average visual acuity base	20/80
Average visual acuity end	20/60
Number of eyes with IOP >25 mmHg	16
Number of eyes with sustained IOP >25 mmHg	10
Noninjected eyes	
Average IOP base, mmHg	14.2 ± 3.4
Average IOP end, mmHg	15.6 ± 3.6
Average visual acuity base	20/50
Average visual acuity end	20/50
Number of eyes with IOP >25 mmHg (of noninjected eyes)	2
Number of eyes with sustained IOP >25 mmHg (of noninjected eyes)	1
Injected eyes	
Total number of eyes injected	155
Number of eyes with pseudophakia	88
Number of eyes with phakia	67
Number of eyes with aphakia	0
Number of unilaterally treated eyes	99
Number of bilaterally treated eyes	28
Average injection number	7 ± 7
Average number of injections in a year	7.1 ± 2.6
Median follow-up of injected eyes, days	402 ± 397
Number of eyes with ranibizumab	50
Number of eyes with bevacizumab	61
Number of eyes with pegaptanib	6
Number of eyes with ranibizumab + bevacizumab	28
Number of eyes with ranibizumab + pegaptanib	1
Number of eyes with bevacizumab + pegaptanib	2
Number of eyes with ranibizumab + bevacizumab + pegaptanib	7
Average IOP base, mmHg	14.5 ± 3.4
Average IOP end, mmHg	15.1 ± 3.7
Average visual acuity base	20/100
Average visual acuity end	20/80
Number of eyes with IOP >25 mmHg (of injected eyes)	14
Number of eyes with sustained IOP >25 mmHg (of injected eyes)	9

which compares the injection frequency of each eye relative to the number of injections it received). To assess the possibility that increased frequency of injections might contribute to changes in IOP measurements over time, each eye was categorized into the number of injections they had received over a 300-day period and plotted against the slopes calculated from the linear regression of all the individual's IOP measurements during that time interval. No relationship was found between the frequency of injections that an eye received and any progressive increase or decrease in their IOP measurements during the 300-day interval (Figure 2). No relationship was found between the total injection

number per individual and any gradual elevation in IOP measurements as shown in Figure 3, which presents the collective IOP measurements after each injection number (the IOP measurement recorded at the next office visit immediately after the injection).

Throughout this study, all IOP measurements were initially screened with a Reichert Tono-Pen XL applanation tonometer. The average IOP measurements of injected eyes that did not show any values >25 mmHg was 15.2 ± 2.4 mmHg, and the average IOP measurements of noninjected eyes was 14.9 ± 2.6 mmHg.

Based on the mean and standard deviations calculated for the Tono-Pen IOP measurements (see

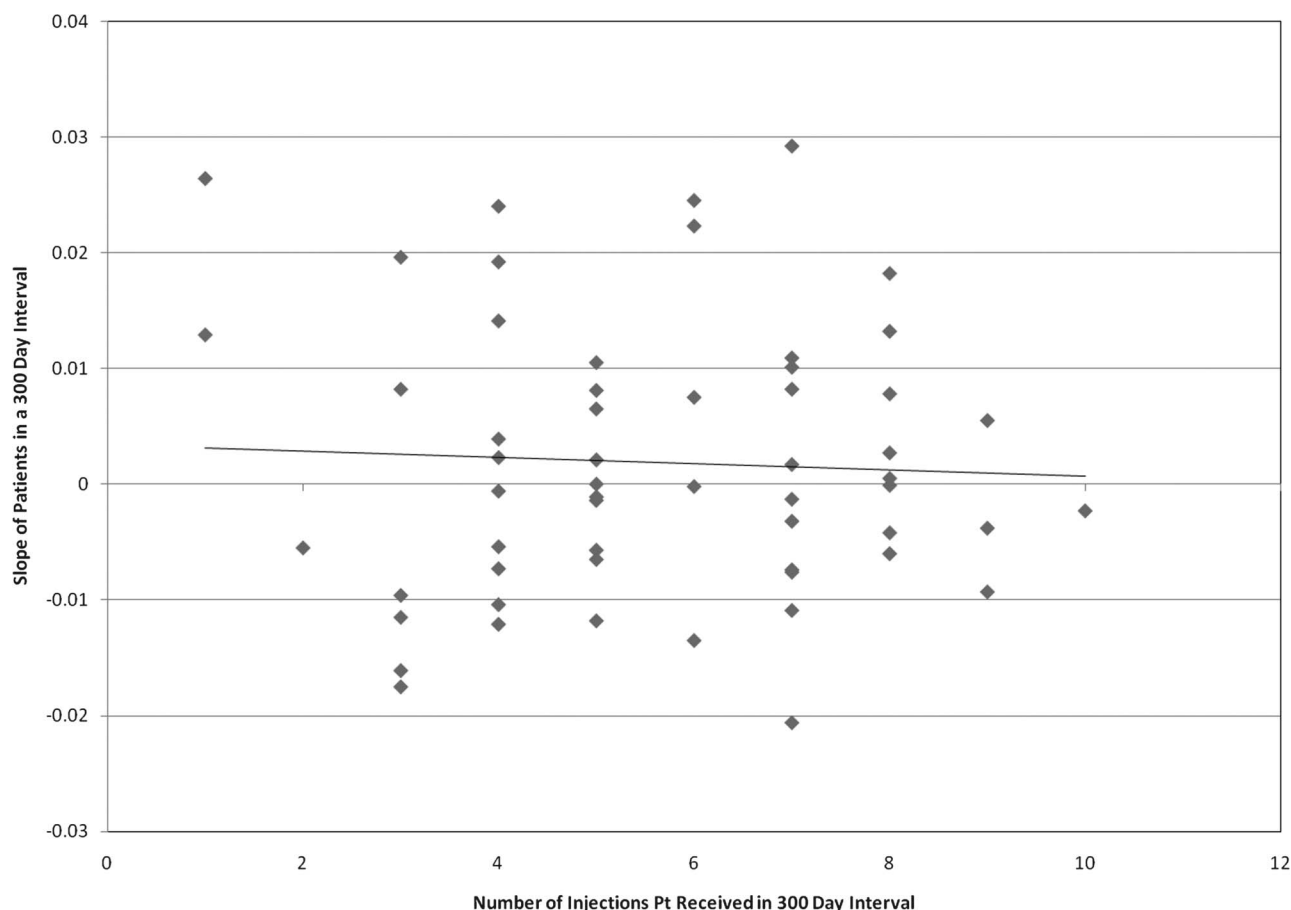


Fig. 2. Changing trends of IOP measurements as a function of injection frequency. The entire set of IOP measurements for each eye (for which there were multiple IOP measurements over a minimum of 300 days) was fitted to a linear regression (graphs not shown). A slope of ± 0.01 is equivalent to a 3 mmHg change over the 300-day period. The slopes of these linear regressions were then plotted in the scatter plot, with respect to the number of injections that each eye received over a 300-day period (the injection frequency). The line is the linear regression of all the data points representing the cumulative impact of a changing frequency of injections with respect to an upward or downward drift of IOP measurements during the study period. A total of 57 patients were compared in this analysis, those who had injection intervals <300 were excluded along with patients with both sustained and unsustained elevated IOP measurements.

Figure 4, Supplemental Digital Content 4, <http://links.lww.com/IAE/A47>, which shows standard deviations of all the measured IOPs of an eye vs. mean IOP measurements for that eye), we would predict that no more than 2 eyes might be expected to experience an IOP measurement of 25 or higher that would solely be because of the variability in their Tono-Pen measurements. Based on this finding, it is appropriate to consider a Tono-Pen measurement of >25 mmHg to be likely pathologic. In all cases, applanation tonometry confirmed these elevated IOP measurements and provided additional justification for clinical attention.

A total of 14 eyes (9.6%) were found to have IOP measurements >25 mmHg. Of these, 9 eyes (5.7% of all injected eyes) were found to have sustained elevated IOP measurements, as defined in this study. Of these, eight eyes were eventually placed on IOP-lowering medications, and one eye required glaucoma surgery. The 7 patients who had sustained elevated pressures were

subcategorized into the 4 groups: 1) bilateral injections and bilateral sustained elevations in IOP measurements: 2 patients, 2) bilateral injections and unilateral sustained elevations in IOP measurements: 3 patients, 3) unilateral injection and unilateral sustained elevation in IOP measurements: 1 patient, and 4) unilateral injection and bilateral sustained elevations in IOP measurements: 1 patient (see Table 1, **Supplemental Digital Content 5,** <http://links.lww.com/IAE/A48>, which shows a tabular representation of the patients based on categories of unilateral and/or bilateral IVIs and/or elevated IOP measurements).

Summary of Cases With Sustained Elevated Intraocular Pressure Measurements

Of the nine eyes with elevated IOP measurements, eight eyes required pressure-lowering medications and one required surgical intervention. Six eyes had cataract, two eyes were pseudophakic, and one eye had a normal

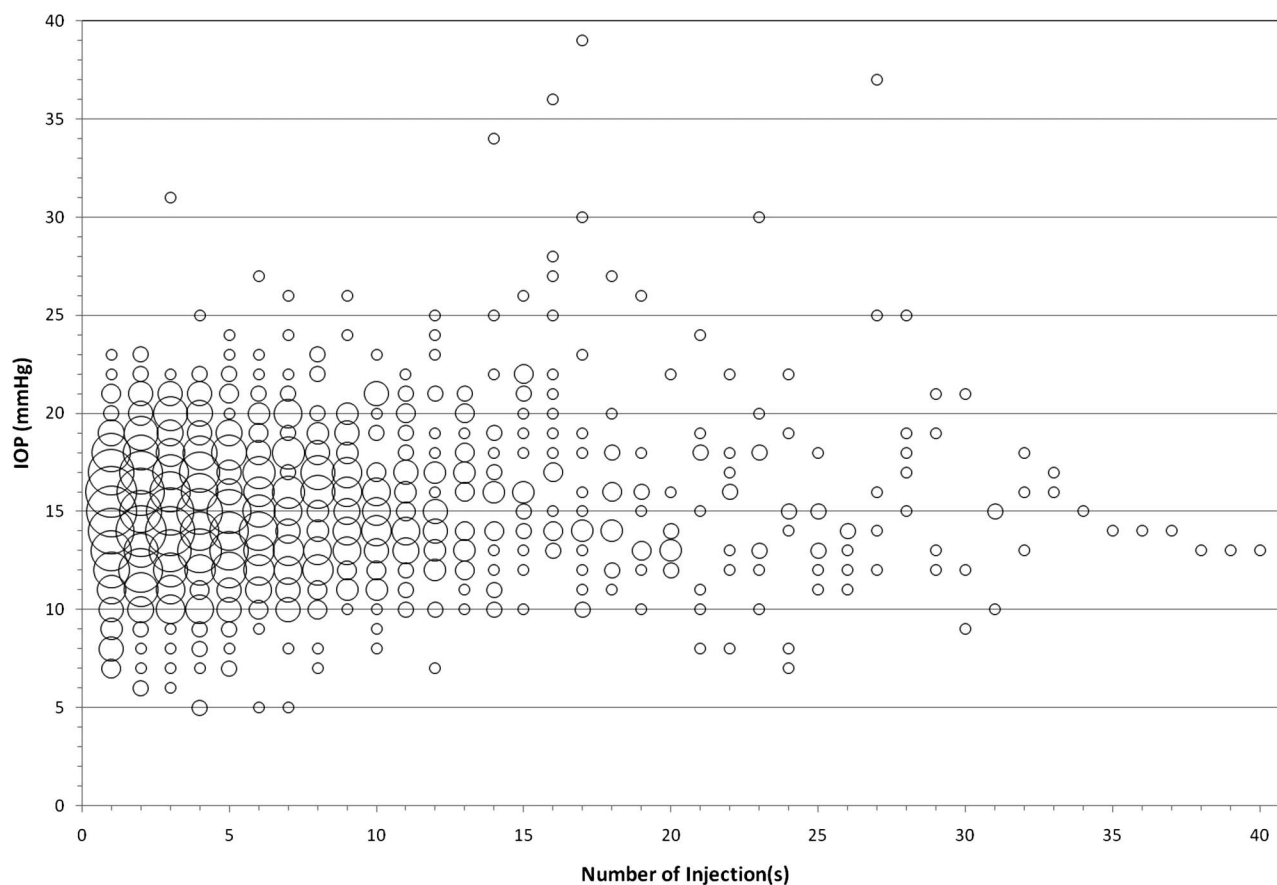


Fig. 3. Bubble scatter plot of all the measured IOP measurements of all 155 injected eyes versus the injection number (total injection number = 1146). Size of bubble relates to the number of patients who had that specific IOP measurement at that specific injection number.

lens without any sclerotic changes. All eyes had confirmed age-related macular degeneration with choroidal neovascularization. The average preinjection and postinjection IOP measurements were 15.2 ± 3.8 mmHg (range, 10–22 mmHg) and 20 ± 9.1 mmHg (range, 11–39 mmHg), respectively. The average IOP measurement of the contralateral noninjected eyes was 18.5 mmHg ± 4.3 (range, 9–24 mmHg) and did not exhibit any upward trend during the injection cycle of the contralateral injected eye. The average interval of time in which injections occurred was 928 ± 489 days (range, 210–1564 days). The average number of injections to elevated pressures was 9.6 ± 7.7 (range, 1–24). The average injection frequency was 6.9 ± 2.1 injections per year (range, 3.4–9.7 injections per year). Of the nine eyes, four eyes started to have elevated pressures immediately after ranibizumab, three after bevacizumab, and two after pegaptanib. Of the nine eyes, eight required pressure-lowering medications, and one of the eight eyes required a trabeculectomy after which the eye was taken off pressure-lowering medications. One eye of the nine did not receive any pressure-lowering medications. No eyes were required to be taken off the injection regimen

because of elevated pressures. Two eyes continued to have elevated IOP measurements >25 mmHg: because of medical noncompliance in one eye and the other eye was from the patient with the unilateral injection and bilateral elevations. (See **Figure 5, Supplemental Digital Content 6**, <http://links.lww.com/IAE/A49>, which demonstrates a more detailed report of the small group of patients who had sustained elevated IOP measurements.)

Discussion

Transient increases in IOP measurements after the injection of anti-VEGF agents have been well described. However, recent studies have shown that pressure elevations can occur over a prolonged period. Interestingly, this phenomenon was not described in the initial large-scale studies of each individual anti-VEGF agent and although mechanisms such as low-grade inflammatory reactions, direct damage to outflow tracks, outflow track occlusion, and other mechanisms have been proposed, the exact cause of the sustained elevated IOP measurements continues to

be poorly understood.^{4,11–19} This study aimed to validate this observation, determine any associated risk factors for the development of this complication, and develop a definition of what can be classified as sustained elevated IOP, while providing specific criterion for clinicians to look for in their patients. Because of this, despite the Tono-Pen's greater variability, we elected to screen with this method as Tono-Pen measurements are reflective of the means by which many clinicians screen and monitor IOP in the retina of patients who are returning for frequent IVIs and retinal assessments. We assessed the variability of these measurements and attempted to identify threshold changes of IOP measurements that may serve as a warning sign for clinicians to suspect the development of sustained elevated IOP. We chose an a priori IOP measurement of >25 mmHg on 2 separate occasions to define sustained elevated IOP out of consideration of the variability of Tono-Pen measurements, and this is supported by the data that we have obtained. Despite the variability of the Tono-Pen-based IOP measurements, we can see that the IOP standard deviations are generally within an acceptable range and that an IOP measurement of 25 mmHg or greater is likely to represent a true deviation from the normal level.

To prevent misinterpretation of a small number of IOP measurements, we looked not only at the average IOP measurements but also at the collective set of IOP measurements over a set period of 300 days to determine whether there was any pattern of change in IOP measurements correlating with the number of injections received during this time. A slope of ± 0.01 is equivalent to a change of 3 mmHg over the 300-day period. We hypothesized that the increase in pressure should correlate with the number of injections. We purposely chose to analyze those eyes that did not have evidence of sustained IOP because those cases of elevated IOP measurements might represent special or idiosyncratic causes and might confound a more subtle general effect of intraocular injections. Based on the relatively flat slope in Figure 2, we did not observe any association between the frequency of injections an eye received and a change in IOP measurements. Additionally, as in Figure 3, we did not observe any association between the number of injections and increase in IOP measurements among those who did not show a sustained elevation in IOP measurements. We found no evidence that one can predict a tendency toward increasing measured IOP as one continues to administer IVIs. Thus, our observed cases suggest that sustained elevated IOP measurements are independent of the frequency of injections and can occur after a single IVI and after as many as 39 injections. These

findings argue against the recent theory that sustained elevated IOP measurements are being caused by outflow track obstruction by high-molecular-weight protein aggregates found in injection packing.¹⁹ Our data do not conclusively rule out this possibility but do highlight the need to investigate other causal factors that are independent of injection frequency or number.^{14,16,17,19}

Some previous case reports^{15,16,18} have speculated that an increase in IOP may be more specific to either ranibizumab or bevacizumab, while other studies^{14,17} have suggested that this can occur with either drug. Our study supports this latter assertion but also brings to attention that sustained elevated IOP measurements can occur after intravitreal pegaptanib injection. To our knowledge, there has been no previously reported cases of sustained increased IOP measurements immediately after pegaptanib injections, although there have been a total of two reported cases of sustained pressure elevations in patients who initially had pegaptanib injections before switching to intravitreal bevacizumab and/or ranibizumab injections. At this point, we have insufficient data to determine if the risk is different between these three anti-VEGF agents. Injection technique and potential syringe contaminants have been implicated, but we would have predicted that such causes would be reflected by the number of injections. However, this was not observed in our data.

Comparison between two eyes of the same individuals takes advantage of the normally observed high cross correlation of findings between the two eyes of the same individual and lessen the effects of technique and other factors on IOP measurements. In the subset of patients without elevated IOP measurements, a total of 6 patients (6.3%), among 95, were found to have a difference in the average IOP measurements of ≥ 4 mmHg between the treated and untreated eye. However, this subset of individuals greatly experiences low sampling size of IOP measurements. We found no evidence that this small number of individuals would be at a greater risk of developing sustained elevated IOP because we did not observe a similar trend for disparate IOP measurements among our case group before the time at which they developed sustained increased IOP measurements.

Our cases of sustained elevated IOP measurements certainly confirm the reports of others that sustained elevated IOP measurements can occur after IVIs. However, our observations and analyses do not support but cannot rule out any of the currently proposed explanations, which include low-grade inflammatory reactions not detectable by standard slit-lamp examination, direct drug toxicity to the physiologic functioning of the trabecular meshwork,

and mechanical obstruction by injected materials in the trabecular meshwork. The etiology of this problem remains unknown, and we have to consider more idiosyncratic factors for its pathogenesis, including the unique genetic makeup of each individual patient. Some cases may well be the result of an ascertainment bias because of the frequent screening of IOP measurements in an elderly population. The observation of one patient with an elevated IOP measurement in his untreated eye would support this assertion.

Limitations of this retrospective study include missing data and variability concerning treatment practices. Additionally, there are issues with variability with pressure measurements from the Tono-Pen. Our data does support our contention that the Tono-Pen is a reasonable screening tool, but confirmation of elevated IOP measurements with applanation tonometry is still important. Clinicians should generally use at least two occasions of elevated IOP measurements before concluding that the pressure elevation is sustained and warrants ongoing therapy. Certainly one should strongly consider lowering an elevated IOP measurement before administration of an IVI, but sustained treatment may not be necessary after a sporadic occurrence. We have an insufficient number of cases of bilateral injections to predict the extent to which the occurrence of elevated IOP measurements in one treated eye will influence the probability of a similar complication in the other eye of the same individual. Larger and prospective studies should be better able to define the presence and extent of such a relationship between the two eyes of a treated individual, and this would be invaluable for determining the degree to which there is an intrinsic (genetic, pigment dispersion syndrome, etc) basis for this complication.

Key words: intravitreal injections, elevated intraocular pressure, sustained elevated intraocular pressure.

References

1. Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. *Am J Ophthalmol* 2004;137:486–495.
2. Ferris FL III, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984;102:1640–1642.
3. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;351:2805–2816.
4. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–1431.
5. Spaide RF, Laud K, Fine HF, et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006;26:383–390.
6. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006;113:363–372.e5.
7. Subramanian ML, Ness S, Abedi G, et al. Bevacizumab vs ranibizumab for age-related macular degeneration: early results of a prospective double-masked, randomized clinical trial. *Am J Ophthalmol* 2009;148:875–882.e1.
8. Bakri SJ, Pulido JS, McCannel CA, et al. Immediate intraocular pressure changes following intravitreal injections of triamcinolone, pegaptanib, and bevacizumab. *Eye* 2009;23:181–185.
9. Gismondi M, Salati C, Salvat ML, et al. Short-term effect of intravitreal injection of ranibizumab (Lucentis) on intraocular pressure. *J Glaucoma* 2009;18:658–661.
10. Hariprasad SM, Shah GK, Blinder KJ. Short-term intraocular pressure trends following intravitreal pegaptanib (Macugen) injection. *Am J Ophthalmol* 2006;141:200–201.
11. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432–1444.
12. VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group, D'Amico DJ, Masonson HN, et al. Pegaptanib sodium for neovascular age-related macular degeneration: two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology* 2006;113:992–1001.e6.
13. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, et al. Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). *Graefes Arch Clin Exp Ophthalmol* 2008;246:81–87.
14. Bakri SJ, McCannel CA, Edwards AO, Moshfeghi DM. Persistent ocular hypertension following intravitreal ranibizumab. *Graefes Arch Clin Exp Ophthalmol* 2008;246:955–958.
15. Jalil A, Fenerty C, Charles S. Intravitreal bevacizumab (Avastin) causing acute glaucoma: an unreported complication. *Eye* 2007;21:1541.
16. Kahook MY, Kimura AE, Wong LJ, et al. Sustained elevation in intraocular pressure associated with intravitreal bevacizumab injections. *Ophthalmic Surg Lasers Imaging* 2009;40:293–295.
17. Adelman RA, Zheng Q, Mayer HR. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. *J Ocul Pharmacol Ther* 2010;26:105–110.
18. Good TJ, Kimura AE, Mandava N, Kahook MY. Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. *Br J Ophthalmol* 2010. Epub ahead of print.
19. Kahook MY, Liu L, Ruzycski P, et al. High-molecular-weight aggregates in repackaged bevacizumab. *Retina* 2010;30:887–892.