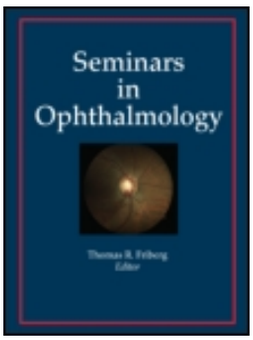

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Incidence and Management of Elevated Intraocular Pressure with Antivascular Endothelial Growth Factor Agents

Gelareh Abedi[1], Ron A. Adelman[2], and Sarwat Salim[3]

[1]*University of Texas Health Science Center San Antonio, San Antonio, Texas, USA,* [2]*Yale Eye Center, New Haven, Connecticut, USA, and* [3]*University of Tennessee Health Science Center, Memphis, Tennessee, USA*

ABSTRACT

Purpose: To review recent literature regarding ocular hypertension following intravitreal antivascular endothelial growth factors (anti-VEGF). *Method*: An electronic literature search was performed using MEDLINE, OVID, and PubMed. Key search terms were elevated IOP, anti-VEGF, sustained IOP elevation in anti-VEGF, chronic intraocular pressure elevation in anti-VEGF, high IOP with anti-VEGF, acute elevation in intraocular pressure with anti-VEGF, glaucoma and anti-VEGF. *Result*: Transient elevation of intraocular pressure after intravitreal anti-VEGF injection is due to temporary increase in volume, and the acute spike generally does not affect a healthy eye. Caution should be taken in a glaucomatous eye, and pretreatment with an IOP-lowering medication is recommended. Persistent elevation of intraocular pressure is more common than previously thought and may be correlated to several factors including increased number of intravitreal injections. *Conclusion*: Persistent ocular hypertension may be associated with intravitreal anti-VEGF injections. Physicians should be aware of this condition and monitor their patients for persistent ocular hypertension, especially in eyes with preexisting glaucoma. Prompt diagnosis and treatment can prevent potential loss of vision.

Keywords: Anti-vascular endothelial growth factor, bevacizumab (Avastin), glaucoma, intraocular pressure, intravitreal ranibizumab (Lucentis)

INTRODUCTION

Vascular endothelial factor (VEGF) is an important component of ocular homeostais and is produced by several cell types, including retinal pigment epithelium, pericytes, Müller cells, and astrocytes. Several forms of VEGF, including VEGF-A through VEGF-E, have been identified. The VEGF-A family is responsible for vascular proliferation. Chronic VEGF-A inhibition may lead to ischemic retina as shown in several animal models and clinical studies.[1–3] On the other hand, an increased level of VEGF can lead to a variety of ocular pathologies. To combat this, intravitreal antivascular endothelial growth factors (anti-VEGF), such as pegaptanib sodium (Macugen; Eyetech Pharmaceuticals/Pfizer, Inc., New York, NY), bevacizumab (Avastin, Genentech, South San Francisco, CA), and ranibizumab (Lucentis, Genentech, South San Francisco, CA) have been widely used in a variety of ocular disorders, including choroidal neovascularization and retinal vascular diseases. Human VEGF-A is composed of eight exons with six main isoforms of 121, 145, 165, 183, 189, and 206 amino acids. Pegaptanib sodium was the first form of anti-VEGF approved by Food and Drug Administration in 2004 for intravitreal injections in age-related macular degeneration (ARMD). Pegaptanib is capable of binding all VEGF isoforms greater than 165 amino acids in length. In 2005, bevacizumab became available for an off-label use in treating ARMD. Bevacizumab, originally used to treat colon carcinoma, is a 150-kDa molecule with two antigen-binding sites. The advantage of bevacizumab is its ability to block all six VEGF isoforms and

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Correspondence: Sarwat Salim, MD, Associate Professor; Director, Glaucoma Service, University of Tennessee Health Science Center, 930 Madison Avenue, Suite 470, Memphis, TN 38163, USA. E-mail: ssalim@uthsc.edu

therefore control disease more effectively. The Food and Drug Administration approved ranibizumab in 2006 for treating ARMD. Ranibizumab is a smaller molecule (approximately 48-kDa) and is a fragment of VEGF-A recombinant, humanized monoclonal antibody. In addition, ranibizumab has a higher affinity for VEGF, resulting in a 5- to 20-fold greater potency on a molar basis.[4] Although these injections are relatively safe, one complication is elevated intraocular pressure (IOP) with acute, transient, delayed, persistent, or chronic presentation. This paper reviews and summarizes the recent literature on intraocular pressure elevation resulting from intravitreal anti-VEGF injection.

PREVALENCE OF ELEVATED INTRAOCULAR PRESSURE

Prevalence of elevated IOP with the use of anti-VEGF agents is quite variable in the literature. Wehrli et al., in a retrospective chart review of 302 eyes treated with intravitreal anti-VEGF and 224 control eyes without baseline ocular hypertension, did not find any difference between the two groups in the incidence of ocular hypertension. Their definition of ocular hypertension not only included patients with IOP $\geq$ 22 mm Hg on two consecutive visits but also those with IOP spike of $\geq$26 mm Hg on a single visit with concomitant initiation or augmentation of glaucoma therapy.[5] On the other hand, Good et al. found a significant rise in IOP. They studied 215 eyes of ARMD patients who received intravitreal anti-VEGF. They separately analyzed patients with preexisting glaucoma and patients without a history of glaucoma and found that patients with preexisting glaucoma had a 33% chance of sustained elevated IOP vs. 3.1% of patients without prediagnosed glaucoma.[6]

PATHOGENESIS OF ELEVATED INTRAOCULAR PRESSURE

Many factors contribute to elevated IOP after injecting anti-VEGF. These factors could be innate to a particular anti-VEGF such as issues surrounding repackaging of bevacizumab or external such as patient characteristics. These factors are discussed in detail below.

Intrinsic Anti-VEGF Factors

Several papers have suggested that silicone oil microdroplets and high-molecular-weight aggregates in the anti-VEGF can lead to obstruction of aqueous humor flow and subsequent elevated IOP.[7–8] Bevacizumab comes in a single-use, preservative-free vial of 100 mg/4 ml, and the compounding pharmacy divides that into 1.25 mg/0.05 cc in plastic syringes.[7] Li et al.[8] obtained repackaged bevacizumab from four external compounding pharmacies and looked at several factors, such as incubation at different temperatures and mechanical shock. They found that repackaged bevacizumab had a wide range of particle counts; silicone oil was responsible for most of these particles. They concluded that repackaged bevacizumab in plastic syringes is contaminated with silicone oil microdroplets and protein aggregates and freezing-thawing can further increase the level of particle contaminants.

Extrinsic Factors

Patient presentation and the clinical indication(s) for receiving anti-VEGF are quite important. Prior to injecting anti-VEGF, several key factors such as the presence of glaucoma and its management along with the underlying pathology requiring injection of anti-VEGF should be considered. Intravitreal anti-VEGF injections can be divided into two broad categories: those given for choroidal neovascularization, and those given for retinal vascular diseases and the secondary complications of retinal vascular disease such as neovascular glaucoma. Though patients suffering from ARMD and the variety of diseases causing choroidal neovascularization such as toxoplasmosis, Best's disease, pathologic myopia, Vogt-Koyanagi-Harada, angioid streaks, and traumatic choroidal rupture may have primary open angle glaucoma as a separate disease, generally they do not have secondary glaucoma due to neovascularization of the angle. Nevertheless, it is crucial to consider each patient's glaucoma as a comorbidity that could cause significant and irreversible damage in patients receiving intravitreal anti-VEGF injection. Patients with a significantly cupped optic nerve may not be able to tolerate the slight fluctuation in IOP, and also it may take a longer time for their IOP to return to baseline.[9] On the other hand, patients suffering from retinal vascular disease are at a greater risk of developing neovascular glaucoma. Higashide et al. retrospectively reviewed 84 eyes of 70 patients with neovascular glaucoma who received an intravitreal injection of bevacizumab for treating anterior chamber neovascularization. The frequency of injections ranged from one to five injections, and 99% of the injections were intravitreal. They noted central retinal artery occlusion as a common complication in this group of patients.[10]

Another factor to be considered is the angle anatomy in patients with neovascularization. It must be noted that, once the angle is completely covered by neovascularization with contraction of the fibrovascular membrane and secondary angle closure, intravitreal injection of anti-VEGF will not lead to

opening of the angle. Such patients proceed to requiring glaucoma surgeries such as glaucoma drainage devices. Administering an anti-VEGF is still a reasonable option in such cases to control intraoperative hemorrhage.

TRANSIENT ELEVATED INTRAOCULAR PRESSURE

It is a well-known fact that a transient elevation in IOP occurs with intravitreal injection. The most commonly injected volume of anti-VEGF into the vitreous cavity is 0.05 cc; this volume can elevate IOP by approximately 10 to 20 mm Hg from the patient's baseline and can last 30–60 min. However, normalization is rapid.[11–13] Falkenstein et al. reviewed 122 injections of intravitreal Avastin for ARMD with the majority of eyes (59%) having a single injection. IOP measured at 3, 10, and 15 min showed an increase with a mean IOP of 36 mm Hg at 3 min with a spontaneous fall to a mean of 24 mm Hg at 10 min. All eyes had an IOP below 30 mm Hg at 15 min.[14] Acute angle-closure glaucoma immediately following intravitreal injection of bevacizumab has also been reported.[15]

LABILE INTRAOCULAR PRESSURE

Although this phenomenon is rare, severe fluctuations in IOP are possible. Martel et al. reported a case involving a patient with unilateral ARMD who received intravitreal ranibizumab. The patient initially presented with hypotony and shallow choroidal detachment five days after the intravitreal injection followed by an acute increase in IOP resulting from focal atrophic area in the ciliary body from 7 to 9 O'clock (corresponding to the site of intravitreal injection). The authors noted that injury to the angle structure, although rare, is a serious complication and recommended ultrasound biomicroscopy to elucidate angle changes in the instance of labile IOP.[16]

PERSISTENTLY ELEVATED INTRAOCULAR PRESSURE

In contrast to transiently elevated IOP, more controversy surrounds persistently elevated IOP. The two major prospective multicenter clinical trials, MARINA and ANCHOR, evaluating anti-VEGF for treating ARMD did not show any sustained IOP with ranibizumab use.[17–18] The VISION and PACORES trials also failed to show any elevated IOP with pegaptanib and bevacizumab treatments, respectively.[19–20] Wehrlie reported that in ARMD patients without glaucoma the incidence of developing delayed ocular hypertension was 0.51% per eye-year vs. 1% per eye-year for the control group. In eyes with ARMD and glaucoma, the incidence of delayed ocular hypertension was 3.1% per eye-year vs. 5.7% incidence per eye-year for control eyes. Neither of these differences was significant, and the authors reported a lack of significant difference between elevated IOP in control vs. eyes receiving anti-VEGF.[5] On the other hand, several case reports and retrospective chart reviews have reported sustained elevation of IOP after intravitreal injections.[6,12,21–25] A subgroup analysis by Bakri et al. showed that 2.1% of eyes in the MARINA and 3.6% of the eyes in the ANCHOR trials had at least a 6 mm Hg increase in IOP from baseline.[26] In a retrospective review by Tseng et al., 25 eyes of 23 patients with ARMD who had increased IOP while on intravitreal ranibizumab and/or bevacizumab were studied. They reported a mean IOP of 29.8 mm Hg after a mean of 20 intravitreal anti-VEGF injections. The authors hypothesized that serial anti-VEGF injections could lead to sustained IOP elevation.[27] A similar paper by Hoang et al. reviewed 207 charts with a six-month follow-up period. They reported that on two or more consecutive visits, 11.6% of treated vs. 5.3% of control eyes experienced IOP elevation of greater than 5 mm Hg. Patients with higher IOP had a greater number of intravitreal injections. Therefore, the authors concluded that a greater number of intravitreal injections are associated with IOP elevation of greater than 5 mm Hg.[28]

MANAGEMENT

Following intravitreal injection of anti-VEGF, a transient increase in IOP occurs. In a normal, nonglaucomatous eye with healthy optic nerve, this transient IOP fluctuation is unlikely to cause permanent damage.[29] Such spikes in a patient with significant underlying glaucoma, however, can have detrimental effects. According to Aref, given that glaucoma is a common comorbidity in patients who are being treated with anti-VEGF for a variety of retina diseases, it is critical that the treating physician pays particular attention to the optic nerve by doing a careful slit-lamp biomicroscopy examination of the optic nerve head. Any generalized cupping, focal rim thinning, or presence of disc hemorrhages should raise concern. A patient's refractive error should also be noted since patients with shorter axial length are at greater risk of IOP elevation.[30] In a study by Kotlier et al., short-term volume changes in myopic, hyperopic, and emmetropic eyes were calculated. In this study, though, the authors looked at 0.1-cc injection of intravitreal triamcinolone. They concluded that hyperopic eyes were more prone to higher IOP fluctuation.[31] It should be noted that the majority of intravitreal anti-VEFG injections are half the volume of intravitreal

triamcinolone injections. Finally, phakic vs. aphakic or pseudophakic status of the patient may make a difference in pressure fluctuation. Hollands et al. conducted a prospective study looking at changes in short-term IOP in patients receiving bevacizumab. Regression analysis of their data showed a trend toward phakic patients having a higher intraocular pressure after 30 min of anti-VEGF injection.[32]

Theoretically, a pseudophakic or aphakic eye has more space for distribution of medication, and the eye has a greater chance of coping with the immediate fluctuation of intraocular pressure. Also, there is a higher percentage of liquefied vitreous and a more direct route from the vitreous cavity to the anterior chamber.

If a patient is suffering from moderate to severe glaucoma, it is advisable to pretreat the patient with IOP-lowering medications 30 to 60 min prior to injecting an anti-VEGF. Checking visual acuity immediately after the injection or checking the IOP following the injection would also help to determine a patient's status. If the pre-injection IOP is high, one can consider an anterior chamber tap before injecting an intravitreal anti-VEGF. After the anterior chamber tap, placing the intravitreal injection should be done with care since the eye may be slightly soft.

Many studies have reported that delayed, sustained IOP elevation in patients receiving anti-VEGF is not uncommon. Furthermore, an increasing body of evidence correlates the delayed and sustained IOP to the frequency of injections. Several steps can be taken to decrease the risk of this complication. First, a thorough glaucoma work-up and examination are recommended in patients with ocular hypertension. Also, physicians can consider switching the patients from fixed-interval treatment to as-needed regimen. Some patients' IOP may be stabilized by the change in frequency of intravitreal anti-VEGF. If the patient continues to have elevated IOP, medical/surgical management is usually necessary.

CONCLUSION

An overwhelming body of evidence points to both short-term and long-term elevation in IOP following injection of intravitreal anti-VEGF. Patients with shorter axial length, previous diagnosis of glaucoma, and repeated anti-VEGF injections seem to be at a higher risk for developing persistent, elevated IOP. In such cases, prophylactic use of IOP-lowering medications and administering anti-VEGF injections on an ''as needed'' basis may be beneficial. Prompt recognition and treatment of patients can prevent permanent visual loss. The Food and Drug Administration recently approved aflibercept (Eylea, VEGF-Trap Eye, Regeneron, Inc., Tarrytown, NY) for treating ARMD. One advantage of aflibercept, a fusion protein, is that it requires less frequent injections. Because several studies have shown a positive correlation between the number of intravitreal injections and IOP elevation, the advent of aflibercept is of great interest and further studies are needed to elucidate its influence on IOP behavior.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

1. Marneros AG, Fan J, Yokoyama Y, et al. Vascular endothelial growth factor expression in the retinal pigment epithelium is essential for choriocapillaris development and visual function. *Am J Pathol* 2005;167:1451–1459.
2. Peters S, Heiduschka P, Julien S, et al. Ultrastructrual findings in the primate eye after intravitreal injection of bevacizumab. *Am J Ophthalmol* 2007;143:995–1002.
3. Manousaridis K, Talks J. Macular ischemia: A contraindication for anti-VEGF treatment in retinal vascular disease. *Br J Ophthalmol* 2012;96:179–184.
4. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina* 2006;25(8):859–870.
5. Wehrli SJ, Tawse K, Levin MH. A lack of delayed intraocular pressure elevation in patients treated with intravitreal injection of bevacizumab and ranibizumab. *Retina* 2012;32(7):1295–301.
6. Good TJ, Kimura AE, Mandava N, et al. Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. *Br J Ophthalmol* 2011;95: 1111–1114.
7. Kahook MY, Liu L, Ruzycki P, et al. High-molecular-weight aggregates in repackaged bevacizumab. *Retina* 2010;30: 887–892.
8. Liu L, Ammar DA, Ross LA, et al. Silicone oil microdroplets and protein aggregates in repackaged bevacizumab and ranibizumab: Effects of long-term storage and product mishandling. *Invest Ophthalmol Vis Sci* 2011;52: 1023–1034.
9. Kim JE, Mantravad AV, Hur EY, et al. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. *Am J Ophthalmol* 2008;146:930–934.
10. Higashide T, Murotani E, Saito Y, et al. Adverse events associated with intravitreal injection of bevacizumab in eyes with neovascular glaucoma. *Graefes Arch Clin Exp Ophthalmol* 2012;250:603–610.
11. 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.
12. Gismondi M, Salati C, Salvetat ML, et al. Short-term effect of intravitreal injection of ranibizumab (Lucentis) on intraocular pressure. *J Glaucoma* 2009;18:658–661.
13. Hariprasad SM, Shah GK, Blinder KJ. Short-term intraocular pressure trends following intravitreal pegaptanib (Macugen) injection. *Am J Ophthalmol* 2006;141:200–201.

14. Falkenstein IA, Cheng L, Freeman WR. Changes of intraocular pressure after intravitreal injection of bevacizumab (Avastin). *Retina* 2007;27:1044–1047.
15. Semoun O, Blumen Ohana E, de Preobrajensky N, et al. Acute angle-closure complicating an intravitreal injection of bevacizumab. *J Fr Ophthalmol* 2009; 32(1):e1–4.
16. Martel JN, Han Y, Lin SC. Severe intraocular pressure fluctuation after intravitreal anti-vascular endothelial growth factor injection. *Ophthalmic Surg Lasers Imaging* 2011;13:e100–2.
17. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration (MARINA). *N Engl J Med* 2006;355:1419–1431.
18. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration (ANCHOR). *N Engl J Med* 2006;355: 1432–1444.
19. 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.
20. 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.
21. Bakri SJ, McCannel CA, Edwards AO, et al. Persistent ocular hypertension following intravitreal ranibizumab. *Graefes Arch Clin Exp Ophthalmol* 2008;246:955–958.
22. Jalil A, Fenerty C, Charles S. Intravitreal bevacizumab (Avastin) causing acute glaucoma: An unreported complication. *Eye* 2007;21(12):1541.
23. 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.
24. Adelman RA, Zheng Q, Mayer HR. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. *J Ocul Pharmacol Ther* 2010;26: 105–110.
25. Choi, DY, Ortube MC, McCannell CA. Sustained elevated intraocular pressures after intravitreal injections of Bevacizumab, Ranibizumab and Pegaptanib. *Retina* 2011; 31:1028–1035.
26. Bakri SJ, Moshfeghi DM, Rundle A, et al. IOP in eyes treated with monthly ranibizumab: A post hoc analysis of data from the MARINA and ANCHOR trials. Presented as a scientific paper at the AAO Annual Meeting, October 15, 2010, Chicago, IL, USA.
27. Tseng JJ, Vance SK, Della Torre KE, et al. Sustained increased intraocular pressure related to intravitreal anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration. *J Glaucoma* 2012;21: 241–247.
28. Hoang QV, Mendonca LS, Della Torre KE. Effect on intraocular pressure in patients receiving unilateral intravitreal anti-vascular endothelial growth factor injections. *Ophthalmology* 2012;119:321–326.
29. Tranos P, Bhar G, Little B. Postoperative intraocular pressure spikes: The need to treat. *Eye* 2004;18(7):673–679.
30. Aref AA. Management of immediate and sustained intraocular pressure rise associated with intravitreal anti-vascular endothelial growth factor injection therapy. *Curr Opin Ophthalmol* 2012;23:105–110.
31. Kotliar K, Maier M, Bauer S, et al. Effect of intravitreal injections and volume changes on intraocular pressure: Clinical results and biomechanical model. *Acta Ophthalmol Scand* 2007;85:777–781.
32. Hollands H, Wong J, Bruen R, et al. Short-term intraocular pressure changes after intravitreal injection of bevacizumab. *Can J Ophthalmol* 2007;42:807–811.