The acute and chronic effects of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure: A Review

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Key Words: Intraocular Pressure; Intravitreal Injection; Anti-vascular endothelial growth factor; Glaucoma; Macular degeneration

Abstract

The acute and chronic effects of repeated intravitreal anti-vascular endothelial growth factor (VEGF) injections on intraocular pressure (IOP) have not been fully characterized and the development of sustained ocular hypertension could adversely affect patients who are at risk of glaucomatous optic neuropathy. As expected, volume-driven, acute ocular hypertension immediately follows intravitreal injection, but this pressure elevation is generally transient and well-tolerated. Several medications have been investigated to limit acute ocular hypertension following anti-VEGF therapy, but the benefits of pretreatment are not conclusive. Chronic, sustained ocular hypertension, distinct from the short-term acute ocular hypertension following each injection, has also been associated with repeated intravitreal anti-VEGF injections. Risk factors for chronic ocular hypertension include the total number of injections, a greater frequency of injection, and pre-existing glaucoma. Proposed mechanisms for chronic ocular hypertension include microparticle obstruction, toxic or inflammatory effects on trabecular meshwork, as well as alterations in outflow facility by anti-VEGF agents. Although limiting anti-VEGF therapy could minimize the risk of both acute and chronic ocular hypertension, foregoing anti-VEGF therapy risks progression of various macular diseases with resulting permanent central vision loss. While definitive evidence of damage to the retinal nerve fiber layer is lacking, patients receiving repeated injections should be monitored for ocular hypertension and those who subsequently develop sustained ocular hypertension should be periodically monitored for glaucomatous changes with an optic nerve optical coherence tomography (OCT) and static visual fields.

I. Introduction

Anti-vascular endothelial growth factor (anti-VEGF) therapy has proliferated over the past decade. In 2004, intravitreal pegaptanib (Macugen®) was the first anti-VEGF agent approved for any ophthalmic indication after administration every 6 weeks was shown to decrease vision loss by half compared to sham in the treatment of neovascular AMD (nAMD).[41] Subsequently, in Genentech's MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of nAMD) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration Study) trials investigating monthly intravitreal ranibizumab (Lucentis®) in nAMD, subjects experienced a mean improvement in visual acuity of 7.2 and 11.3 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters, respectively, at 1 year, compared to a mean loss of 10.4 and 9.5 ETDRS letters in the sham and verteporfin control groups, respectively.[16, 96] Ranibizumab 0.5 mg was approved for the treatment of nAMD in 2006, a major milestone because, for the first time, a treatment improved vision in nAMD, as opposed to simply ameliorating decline. Several years later, Regeneron's VIEW (Vascular Endothelial Growth Factor VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration) randomized control trials (RCTs) of intravitreal aflibercept (Eylea®) demonstrated monthly and bimonthly regimens of aflibercept were non-inferior to monthly ranibizumab over a 1-year time period,[44] and led to the approval of aflibercept 2 mg for the treatment of nAMD in 2011. Simultaneously, off-label intravitreal bevacizumab 1.25 mg (Avastin®) was found to be noninferior to ranibizumab in the Comparison of AMD Treatments Trials (CATT), a National Institutes of Health sponsored RCT.[77]

Anti-VEGF therapy for the treatment of diabetic macular edema (DME) and macular edema due to retinal vein occlusions was subsequently adopted, after several studies demonstrated a significant benefit for these indications.[15, 18, 27] Because of the remarkable benefit of anti-VEGF therapies in these disorders, their use has exploded from essentially 0 in 2004 to over 16 million intravitreal anti-VEGF injections performed in 2016, comprising a global market of over $8 billion annually (www.market-scope.com). Coinciding with this burst in anti-VEGF therapy, reports of associated sustained ocular hypertension surfaced. Confounding this issue, however, is an aging population at risk of both developing glaucoma and acquiring pathologies necessitating anti-VEGF therapy. In addition, both vein occlusion and diabetes are known risk factors for glaucoma. Consequently, the acute and chronic ocular hypertensive effects of repeated anti-VEGF therapy has not been effectively characterized.[55, 56, 63] We review the short- and long-term effects of intravitreal anti-VEGF injections on IOP and the optic nerve, as well as the prophylactic measures that have been investigated to reduce immediate post-injection IOP spikes. In addition, this review presents the theoretical mechanisms for anti-VEGF-related chronic ocular hypertension.

II. Short-term ocular hypertensive effects of intravitreal anti-VEGF injections

Anti-VEGF regimens typically involve long-term monthly or periodic intravitreal injections (IVI) of 50 µl of therapy via a small gauge needle, most often without paracentesis. As expected, ocular hypertension immediately follows from a volume effect, but this is generally transient and well-tolerated in the vast majority of patients.

A. Intraocular pressure trend following anti-VEGF injection

A significant, transient rise in IOP occurs following anti-VEGF injection of 50 µl into an average vitreous volume of 4.5 -5.0 ml. Figure 1 demonstrates the IOP trend immediately

following injection and it is a weighted average of 14 studies that are summarized in Supplemental Material Table 1.[25, 30, 31, 33, 38, 51, 62, 66, 71, 73, 82, 85, 101, 113] IOP rises to an average of 46 mmHg and then quickly decreases to pre-injection measurements within 1 hour in eyes without significant abnormalities in trabecular meshwork outflow facility.

B. **Risk factors for acute ocular hypertension following injection**

Numerous risk factors for the severity of acute ocular hypertension following IVI have been investigated, including the absence of post-injection subconjunctival reflux, smaller needles, tunneled injection techniques, and a prior diagnosis of glaucoma.

The greatest risk factor for acute ocular hypertension is the absence of subconjunctival reflux. Table 1 presents four studies that investigated the effect of subconjunctival reflux on immediate post-injection IOP and reveals that the IOP immediately following IVI averages 20 mmHg lower in patients with reflux.[69, 72, 88, 101] The occurrence of reflux is often overlooked by busy clinicians and is difficult to quantitate, but represents a potentially important risk factor for ocular hypertension following IVI. Reflux depends on the injection technique and size of the needle. Larger bore needles create a wider needle track through the sclera, resulting in a greater chance of reflux. Several studies have demonstrated that smaller bore needles have less post-injection reflux and a higher IOP.[50, 69, 87, 88] Similarly, tunneled injection techniques allow the needle track to be pinched off by the edge of the sclera, reducing the amount of reflux and increasing post-injection IOP.[69, 87]

A second important risk factor for severe, acute ocular hypertension and delayed recovery is a prior history of glaucoma.[10, 66] Bakri et al. found that 10 minutes after IVI of bevacizumab, triamcinolone, or pegaptanib, only 75% of glaucomatous patients recovered to an IOP of less than 35 mmHg in contrast with 95.5% of patients without glaucoma.[10] This observation supports the notion that glaucomatous eyes suffer from pathologically compromised aqueous humor outflow; however, studies demonstrating a correlation between the diagnosis of glaucoma and the severity of ocular hypertension following IVI are primarily limited by small sample sizes. Further investigations are necessary to confirm and quantify this observation.

Another suspected risk factor for acute ocular hypertension is a smaller vitreous volume manifested by a short axial length. The literature supporting this hypothesis is mixed.[17, 38, 39, 47, 71, 87] Surprisingly, the volume of injected drug has not been confirmed to be a risk factor. Bakri et al. assessed three different volumes (triamcinolone 0.1 mL, pegaptanib 0.09 mL and bevacizumab 0.05 mL) and found no difference in the post-injection IOP change;[10] however, this observation is likely confounded by the variety of needle gauges used for the different medications. Triamcinolone is generally injected with a 27-gauge needle, resulting in a greater incidence of reflux and counteracting the hypertensive effects of the greater volume injected. It seems intuitive that larger volumes would likely result in greater IOP change when controlling for confounding variables.

C. **Studies supporting medical prophylaxis for acute ocular hypertension following IVI**

Several medications have been investigated to limit acute ocular hypertension following anti-VEGF therapy, and five studies, discussed in detail below, have found topical agents to be mildly effective at prophylactically decreasing IOP (Figure 3).[26, 65, 86, 91, 107] A major limitation of

these studies is the lack of recording and control for subconjunctival reflux. Additionally, each study uses different IOP cutoffs and observation times following injection, making comparison between studies difficult. Finally, the clinical benefit of a mild decrease in a short-duration IOP spike remains unclear.

1. Apraclonidine

Apraclonidine decreases aqueous production and increases both trabecular and uveoscleral outflow.[108] These pressure-dependent and pressure-independent mechanisms are effective at reducing the IOP spike following anterior segment laser procedures, cataract surgery and vitrectomy, making apraclonodine a promising investigational agent to limit acute ocular hypertension following IVI.[95] El Chehab et al. prospectively assessed the effect of 1 drop of 1% apraclonidine administered prophylactically 2 hours prior to injection. The study included 250 patients who were randomized to five study arms, receiving either prophylactic apraclonidine, oral acetazolamide, brimonidine-timolol, dorzolamide-timolol, or no prophylaxis (control). Immediately following injection, the average IOP measured 37.3 mmHg in the apraclonidine group in comparison to 46.4 mmHg in the control group. The proportion of patients with an IOP of >45 mmHg was 65.5% in the control group and 7.7% in the apraclonidine group. At 15 minutes, the proportion of patients with an IOP of >25 mmHg was 0.0% in the apraclonidine group and 36.6% in the control group.[26] Consequently, apraclonidine appeared more effective than oral acetazolamide at decreasing acute ocular hypertension following IVI, and appeared similarly effective to the brimonidine-timolol and dorzolamide-timolol topical formulations.

2. Timolol

Timolol decreases aqueous production and is well tolerated by patients.[14] Pece et al. prospectively randomized 150 patients to receive either no prophylactic medication, timolol 0.1% gel the evening before injection, or timolol 0.1% gel 2 hours prior to injection. Five minutes following injection, the use of timolol gel 2 hours prior to injection resulted in an average pressure of 25.5 mmHg in comparison to 29.3 mmHg in the control group. The proportion of patients with an IOP spike of > 40 mmHg was reduced from 18% to 2% with the use of timolol 2 hours prior to injection. The use of timolol 0.1% gel the evening before injection had no effect on IOP control.[91] While direct comparison with other protocols is challenging, these results are suggestive that timolol gel is slightly less effective than the apraclonidine, dorzolamide-timolol and brimonidine-timolol formulations evaluated by Chehab et al.[26]

3. Dorzolamide-Timolol

Timolol decreases aqueous production through sympathetic blockade of the nerve endings in the ciliary epithelium [14] and dorzolamide reduces aqueous production by blocking carbonic anhydrase.[75] Three studies have assessed the prophylactic effect of the dorzolamide-timolol combination prior to IVI. A summary of the studies and their IOP-lowering effects are displayed in table 2.[26, 65, 86] All three studies demonstrated a mild decline in IOP immediately following injection. Kim et al. observed that the

dorzolamide-timolol group had a modest decrease in IOP in comparison to the control group at 5 minutes (14.1 mmHg versus 28.2 mmHg) and at 1 hour (10.7 mmHg versus 18.7 mmHg), but dorzolamide-timolol was not more effective than the brinzolamide-timolol combination.[65] These studies suggest that dorzolamide-timolol has similar efficacy to apraclonidine and brimonidine-timolol at mildly lowering the severity of post-injection acute ocular hypertension.

4. Brimonidine-timolol

Brimonidine suppresses aqueous production, increases uveoscleral outflow and has possible neuroprotective properties.[42, 97] Two studies have investigated the prophylactic effect of brimonidine-timolol drops.

Theoulakis et al. prospectively investigated the prophylactic effect of 1 drop of brimonidine-timolol given twice a day, the day prior to and the day of injection. Eighty-eight patients were randomized to equally sized groups, one receiving brimonidine-timolol and the other receiving no drops. At 5 minutes the treated group had an average IOP of 28.4 mmHg compared to an average pressure of 34.1 mmHg in the control group. At 15 minutes, none of the patients in the treatment group had a pressure of >20 mmHg, as compared to 34% in the control group.[107]

El Chehab et al., as previously discussed, assessed the effect of 1 drop of brimonidine-timolol given 2 hours prior to injection. Fifty patients were randomized to receive either brimonidine-timolol or four other investigational arms (control, apraclonidine, oral acetazolamide, dorzolamide-timolol). Immediately following injection, the IOP was 38 mmHg in the brimonidine-timolol group and 46.4 mmHg in the control group. At 15 minutes, the percentage of patients with an IOP of >25mmHg was 0% in the brimonidine-timolol group and 36.6% in the control group.[26] Brimonidine-timolol showed a greater prophylactic effect than control, and was similarly effective to apraclonidine and dorzolamide-timolol topical formulations.

5. Brinzolamide-timolol

Brinzolamide-timolol combines the aqueous suppression from carbonic anhydrase inhibition with the aqueous suppression from ciliary epithelial sympathetic pathway blockage.[14, 46] Kim et al. prospectively investigated the effects of 1 drop of brinzolamide-timolol given 1 hour prior to injection. Patients were divided into three groups: 84 in the brinzolamide-timolol arm, 53 in the dorzolamide-timolol arm and 29 in the control arm. After 5 minutes, the IOP in the brinzolamide-timolol group averaged 14.87 mmHg as compared to 28.21 mmHg in the control arm. After 1 hour, the average IOP in the brinzolamide-timolol group was 13.61 mmHg, in comparison to 18.72 mmHg in the control arm. Topical brinzolamide-timolol showed similar effectiveness to dorzolamide-timolol.

D. **Studies not supporting medical prophylaxis for acute ocular hypertension following IVI**

Oral acetazolamide is a potent carbonic anhydrase inhibitor [98], and its effectiveness in angle-closure glaucoma makes it a promising agent in the prophylaxis against acute ocular hypertension following IVI. Surprisingly, two studies have assessed

oral acetazolamide prior to injection and noted no IOP lowering effect, although it is possible that the dosing and timing were not optimized for this indication.

Murray et al. compared 12 patients receiving 500 mg PO acetazolamide 60-90 minutes prior to injection with 12 control patients. There was no statistically significant difference in pressures immediately after, 5 minutes after or 10 minutes after the injection. At 30 minutes, the average IOP in the treatment arm was 15.7 mmHg and in the control arm was 20.6 mmHg, which was statistically significant.[83]

El Chehab et al. compared 50 patients receiving 250 mg of oral acetazolamide given 2 hours prior to injections with three other treatment arms (apraclonidine, dorzolamide-timolol, brominidine-timolol) and 50 patients in a control arm. No difference in IOP was found between the control arm and the oral acetazolamide arm.[26]

E. **Other prophylactic measures for acute ocular hypertension following IVI**

1. Anterior chamber paracentesis

More effective than topical and oral treatments, anterior chamber (AC) paracentesis effectively prevents a post-injection IOP spike, but introduces additional risks of infection and iatrogenic injury. Knip et al. demonstrated the effectiveness of an AC paracentesis, showing that the average immediate post-injection IOP was 15.3 mmHg in the paracentesis group as compared to 47.1 mmHg in the control group. At 2 minutes and at 30 minutes there was no statistically significant difference between groups.[70]

Despite the effectiveness, there are risks of performing an AC paracentesis. A study assessing 560 paracenteses showed 4 complications (0.7%).[109] Two patients experienced inadvertent injection of sterile air into the anterior chamber which spontaneously resolved without adverse consequences. One patient experienced a small anterior lens capsule laceration that was self-sealing, but left a localized opacity and another patient experienced an allergic reaction to povidone iodine.[109] Other case studies have demonstrated complications such as endophthalmitis and infectious keratitis.[5, 45, 57]

Although AC paracentesis involves some minimal risk, in patients at risk of glaucomatous progression who are known to experience transient vision loss related to severe acute ocular hypertension following IVI, an anterior chamber paracentesis could be appropriate. In these patients, the transient vision loss is likely from severely elevated pressures that result in hypoperfusion to the retina.

2. Ocular decompression

One study assessed the effect of ocular decompression by cotton swabs on post-injection acute ocular hypertension. Forty-eight patients were divided into two groups. One group was anesthetized with a cotton swab soaked in 4% lidocaine and received ocular decompression, and a control group received 3.5% lidocaine gel anesthetic without ocular decompression. The immediate post-injection IOP was 25.7 mmHg in the decompression group and 30.9 mmHg in the control group. The proportion of patients with IOP of >50 mmHg was 10% in the decompression group and 35% in the control group.[43] These findings support the beneficial effect of moderate

ocular pressure prior to injection. A similar principle has been applied using the Honan Intraocular Pressure Reducer, which applies gentle pressure to an eye before a procedure. One study supported the prophylactic anti-hypertensive effect of this device, while another study showed no benefit.[52, 67]

F. **Summary of studies investigating prophylaxis against acute ocular hypertension following intravitreal injection**

Numerous medications have been investigated to prophylactically reduce acute ocular hypertension following anti-VEGF IVIs, and most topical drops have a similar mild effectiveness at decreasing IOP. Surprisingly, oral acetazolamide has little effect at lowering IOP based on material currently published. Overall, the benefits of pretreatment with ocular anti-hypertensive agents prior to IVI is not conclusive, mainly because of the questionable clinical benefit in slightly decreasing IOP over the short duration before IOP normalizes. However, it can be argued that patients with advanced glaucomatous optic neuropathy may benefit from a slight reduction in pressure and prophylactic treatment can be considered, particularly because these patients are more susceptible to further damage from increased pressures and may be at increased risk of higher IOP spikes over a greater duration of time due to underlying outflow pathology. An AC paracentesis is a more effective, albeit riskier, method at preventing acute ocular hypertension in at-risk patients.

III. Long-term effects of intravitreal anti-VEGF injections

A. Studies associating sustained ocular hypertension with chronic anti-VEGF injections

Repeated intravitreal anti-VEGF injections have been associated with chronic ocular hypertension, distinct from the short-term acute ocular hypertension following each injection, in a subset of patients. Numerous case reports and case series have suggested this phenomenon and those with incidence rates are summarized in Table 3.[2-4, 6, 19, 34, 59, 76, 79, 80, 93, 99, 110] In some cases, the ocular hypertension was severe enough to warrant surgical filtration.[23, 104]

Post hoc analyses of major anti-VEGF trials have provided the best evidence in support of this phenomenon. While numerous retrospective case series have similarly supported this finding, as demonstrated in Table 3, their nonrandomized nature and typically smaller cohort provide inferior quality of evidence. On analysis of the MARINA and ANCHOR studies, Bakri et al. noted the proportion of patients who had at least one visit with an increase in pre-injection IOP of 6 mmHg or more from baseline with a concurrent IOP ≥21 mmHg was 26.1% in the 0.5 mg ranibizumab group, 23.6% in the 0.3 mg Ranibizumab group and 13.6% in the sham/PDT groups.[9] The proportion of patients with at least one IOP measurement of 21 mmHg or more was 39.9% in the 0.5 mg ranibizumab group, 37.0% in the 0.3 mg ranibizumab group and 29.1% in the sham/PDT groups.[9] These findings are suggestive that a subgroup of patients develop sustained ocular hypertension due to chronic anti-VEGF therapy and are also suggestive of a possible dose-related response. A post-hoc analysis of DRCR data found that 9.5% of patients in the ranibizumab plus prompt or deferred focal/grid laser group experienced sustained IOP elevation versus 3.5% of patients in the sham injection plus focal/grid laser treatment group.[13] The difference in the percentage of affected patients between the DRCR and MARINA/ANCHOR trials is due to different definitions of sustained ocular hypertension. Similar findings were presented in a post-hoc analysis of the IVAN study.[32] Additionally, a recent population-based,

nested, case-control study in Canada found that patients receiving 7 or more annual injections had a greater odds ratio of undergoing glaucoma drainage surgery than controls.[23] The major limitations of these and other studies listed in Table 3 are their retrospective nature and their uncontrolled methods of IOP measurement, as IOPs were variably measured with the use of a tonopen or Goldmann applanation tonometer. Glaucoma trials typically utilize standardized protocol-driven IOP measuring regimens, such as requiring two masked individuals to measure IOP with only Goldmann applanation tonometry, to minimize the risk of bias or error.

Risk factors for chronic ocular hypertension in these studies are intuitive. The total number of injections was demonstrated to be a risk factor,[11, 40, 48, 49, 93, 99] as was a greater frequency of injections[79] and a pre-existing diagnosis of glaucoma prior to initiation of IVIs.[22, 40] Fruend et al. observed that ranibizumab, as compared to aflibercept, had higher rates of ocular hypertension, with 8.4% of patients on monthly ranibizumab having an IOP of greater than 21mmHg on two consecutive visits compared to 3.2% and 2.7% of patients who received 2 mg and 0.5 mg of aflibercept every month, respectively.[34] While the Freund et al. analysis has been the only study to directly compare aflibercept with ranibizumab, ranibizumab was not associated with greater rates of sustained OHTN in comparison to bevacizumab in other studies.[2, 3, 40, 48, 68] In fact, Good et al. observed that patients receiving ranibizumab had lower rates of sustained OHTN compared to bevacizumab (3.1% versus 9.9%).[40] It remains to be seen if one medication is consistently associated with higher rates of sustained OHTN. A history of cataract extraction or a posterior capsulotomy, with a theoretical increased rate of diffusion of medication to the anterior chamber, were not observed to be risk factors.

Recently, Wen et al. investigated the conventional outflow facility of patients receiving chronic anti-VEGF therapy, utilizing electronic Schiøtz tonography. They found a small but statistically significant decrease in outflow facility in patients with a greater number of IVIs (≥20). Additionally, they found eyes with contralateral ocular hypertension had a two-fold reduction in outflow facility following anti-VEGF therapy as compared to the contralateral eye.[112] This functional study supports the observation that the total number of injections is a risk factor for sustained ocular hypertension. It also supports the notion that chronic anti-VEGF therapy can reduce outflow capacity. Finally, it is suggestive of a two-hit hypothesis, where patients with underlying ocular hypertension and pathological outflow capacity, are at increased risk of further outflow reduction due to chronic anti-VEGF therapy. A two-hit hypothesis may also explain why only a fraction of patients developed sustained ocular hypertension.

A multitude of theoretical mechanisms have been described in an effort to explain the reduced outflow capacity and the sustained rise in IOP observed in a subset of patients receiving recurrent intravitreal anti-VEGF injections. One of the proposed mechanisms involves microparticle obstruction of the trabecular meshwork.[20] Some studies have demonstrated that silicone microdroplets from syringes and protein aggregates from medication packaging or delivery equipment can obstruct aqueous outflow.[7, 60, 74] This is of particular relevance with the advent of prefilled ranibizumab syringes, and patients receiving this therapy should be observed for the development of sustained ocular hypertension due to possible microparticle obstruction from materials that become dissolved in the anti-VEGF solution. Kahook et al. reported variations in the concentration of high-molecular-weight protein aggregates in different samples of compounded and repackaged bevacizumab.[60] In addition, Good et al. reported a sustained IOP elevation in 9.9% of patients receiving bevacizumab compared with 3.1% in patients

receiving ranibizumab. Given that bevacizumab (149 kDa) is approximately 3 times larger than ranibizumab (48 kDa), it is thought that the high-molecular-weight proteins may accumulate in the trabecular meshwork and obstruct aqueous outflow.[2, 8, 40]

Another proposed mechanism involves the direct effects on trabecular meshwork cells by intravitreal anti-VEGF agents. In vitro studies by Kahook et al. demonstrated that 4 mg/mL of bevacizumab slows the metabolism and replication of trabecular meshwork cells.[58] This was not demonstrated with lower concentrations of bevacizumab (2 mg/mL) or with ranibizumab;[58] However, Kernt et al. reported no toxic effects to the trabecular meshwork with bevacizumab at the 1.25 mg/0.05 mL concentration used in intravitreal injections.[61] Others have proposed that monomer antibodies, aggregated proteins, or other high molecular weight molecules may incite an underlying inflammatory reaction leading to trabeculitis with impaired aqueous humor outflow.[37, 81, 105]

In addition to the mechanical obstruction and the potential toxic and inflammatory effects on the trabecular meshwork, some have proposed alterations in outflow facility by anti-VEGF agents. VEGF receptors have been found to be expressed on the trabecular meshwork and Schlemm's canal endothelial cells. Schlemm's canal cells express vascular endothelial (VE) cadherin, an endothelial cell adhesion molecule.[92] VEGF stimulation promotes the endocytosis of VE cadherin, and VEGF blockade can disrupt this barrier function and reduce endothelial cell permeability.[36] Other in vitro models have similarly demonstrated that VEGF induces endothelial fenestrations.[29] In addition, nitric oxide has been shown to increase anterior chamber aqueous outflow through a reduction in trabeculocyte size and smooth muscle contractility with Schlemm's canal vasodilation. Anti-VEGF therapy disrupts the normal nitric oxide signaling pathway by inhibition of nitric oxide synthase.[94] Animal studies have demonstrated that VEGF increases aqueous humor outflow facility and that blockage of VEGF receptors leads to ocular hypertension.[35] Anti-VEGF inhibition of the disassembly of the endothelial intercellular junctions, decrease in the endothelial fenestrations, and inhibition of nitric oxide production are a few of the biochemical mechanisms that may explain the impaired outflow and sustained rise in IOP.

Although there is no clear consensus on which of these proposed mechanisms contributes most to the rise in IOP, various studies support that anti-VEGF injections may have an effect on the trabecular meshwork pressure-dependent outflow system.

B. Studies not associating sustained ocular hypertension with chronic anti-VEGF injections

The main limitation of post-hoc analyses supporting the ocular hypertensive effects of anti-VEGF IVIs is that IOP was not the primary outcome measured. Consequently, IOP measurement was not standardized and both applanation and tonopen methods were used to varying degrees.[54] Publication bias may also limit the submission and acceptance of studies observing no increase in rates of sustained ocular hypertension. Another source of bias is the inclusion of the cases that initiated a study, which may artificially elevate observed incidence rates of ocular hypertension. Finally, other studies have demonstrated conflicting results. Wehrli et al. did not observe an increased risk of sustained ocular hypertension in patients receiving frequent intraocular injections as compared to fellow untreated eyes, and similar results were demonstrated in other studies summarized in Table 4.[12, 64, 68, 84, 111, 114] The strengths of the

Wehrli et al. and Kim et al. studies are their fellow-eye control and large patient number.[68, 111] Interestingly, Kim et al. found higher rates of sustained ocular hypertension in patients with underlying glaucoma and a history of retinal vein occlusion.[68] Even though not correspondingly observed by Wehrli et al., these findings may support the notion that patients with underlying outflow pathology are susceptible to the effects of repeated anti-VEGF therapy. While the studies by Kim et al. and Wehrli et al. are well-constructed retrospective analyses, the evidence provided by the retrospective analysis of the MARINA, ANCHOR and DRCR studies, all of which support the hypothesis of a subset of patients developing sustained OHTN, provide better quality evidence due to their larger size and lower likelihood for selection bias.

C. Effect of repeated injections on the retinal nerve fiber layer

Average retinal nerve fiber layer (aRNFL) thinning on optic nerve OCT is expected if anti-VEGF agents and associated ocular hypertension are harmful to ganglion cells and their axons. Most studies have found no correlation between repeated injections and aRNFL thickness.[21, 24, 28, 53, 100, 102, 106] One study, in contrast, found an aRNFL thinning of -5.5 µm following a mean of 4.8 injections.[78] Two studies found an aRNFL thinning in injected eyes but found a similar thinning in the control eyes.[90, 103] Overall, these studies suggest a minimal average effect of repeated anti-VEGF injections on aRNFL thickness in patients receiving multiple injections. However, there are major limitations in the interpretation of these results. All of the studies mentioned above excluded patients with a history of glaucoma and therefore cannot allow for any conclusions about repeat injections on aRNFL thickness in patients with glaucoma – though the disease process itself would be expected to show progressive aRNFL thinning. In addition, 6 of 8 studies that investigated the effect of injection frequency had fewer than 7 mean injections, and 5 of 8 studies that investigated duration of follow-up observed patients for less than 15 months. These studies may be missing patients who develop aRNFL thinning after a greater number of injections given over a longer period of time. Additionally, as observed by the post hoc analysis of the MARINA, ANCHOR and DRCR studies, only a subset of patients develop sustained ocular hypertension, and analysis of patients as a whole who receive anti-VEGF IVIs may miss the proportion of affected patients.

One study has evaluated the effect of an underlying diagnosis of glaucoma on the aRNFL thinning. Park et al. found that a greater number of injections was associated with aRNFL thinning in glaucomatous patients compared to those without glaucoma.[89] These results are consistent with studies finding a greater IOP rise in patients with an underlying diagnosis of glaucoma and repeated injections;[22, 40] however, an obvious limitation of the Park study is the lack of control for natural glaucoma progression, as these patients may have had RNFL thinning regardless of IVI. Overall, glaucomatous patients may be more susceptible to RNFL thinning with repeated anti-VEGF injections given the underlying damage to the ganglion cells, their axons, the trabecular meshwork and downstream outflow pathways; however, available evidence does not definitively support this hypothesis.

IV. Macular disease and the risks of forgoing anti-VEGF therapy

Foregoing anti-VEGF therapy risks progression of various macular diseases. The MARINA study demonstrated a dramatic improvement in mean visual acuity of 7.2 ETDRS letters after one year of ranibizumab therapy compared to a loss of 10.4 ETDRS letters without treatment (for a net 17.6 ETDRS letter benefit); at one year, monthly treatment decreased the risk of losing 15 ETDRS letters from 37.8% to 5.5%.[96] Unfortunately, a decreased intensity of anti-VEGF treatment in an as-needed regimen may

yield an inferior result, as the CATT study demonstrated a mean difference of 2.4 ETDRS letters in favor of the monthly versus the as-needed regimen after two years.[77]

The benefit of anti-VEGF therapy has been similarly demonstrated in macular edema in diabetic retinopathy and retinal vein occlusions.[15, 18, 27] For example, in the DRCR protocol I study of diabetic macular edema (DME), subjects in the ranibizumab/deferred laser group experienced a mean gain of 9 ETDRS letters after 2 years, in contrast to those in the prompt laser group who experience a mean improvement of only 3 ETDRS letters.[27]

In the BRAVO study of macular edema due to branch retinal vein occlusion, subjects in the ranibizumab group experienced a mean gain of 18.3 ETDRS letters at 6 months in contrast to those in the sham group who experienced a mean improvement of only 7.3 ETDRS letters at 6 months.[18] In the CRUISE study of macular edema associated with central retinal venous occlusions, subjects in the ranibizumab group experienced a mean gain of 14.9 ETDRS letters at 6 months in contrast to those in the sham group who experienced a mean improvement of only 0.8 ETDRS letters.[15]

For macular edema with diabetic retinopathy or branch vein occlusion, an alternative to anti-VEGF medications could be macular laser photocoagulation, which generally reduces vision loss by 50%.[1] Unfortunately, for exudative AMD, no effective alternative therapy exists and forgoing anti-VEGF therapy places patients at a significantly increased risk of vision loss.

V. Conclusion

Although anti-VEGF therapy is well tolerated in the vast majority of patients, acute and chronic ocular hypertension following treatment merits consideration. We have discussed the degree and timing of ocular hypertension immediately following anti-VEGF IVIs. IOP typically rises acutely following IVI with normalization within 30-60 minutes. In glaucomatous patients, this ocular hypertension is more dramatic and of longer duration. Numerous medications have been investigated to reduce prophylactically acute ocular hypertension, and all topical drops have a similar mild effect in decreasing IOP following IVI. Surprisingly, oral acetazolamide has little effect on lowering IOP following IVI based on material currently published. Overall, the benefits of pretreatment with ocular anti-hypertensive agents prior to IVI is not conclusive, mainly because of the questionable clinical benefit in slightly decreasing IOP over the short duration before IOP normalizes; however, it can be argued that patients with advanced glaucomatous optic neuropathy may benefit from a slight reduction in pressure, and prophylactic treatment can be considered because these patients are more susceptible to further damage from increased pressures and may be at increased risk of higher IOP spikes over a greater duration of time. An AC paracentesis is a more effective, albeit riskier, intervention to prevent acute ocular hypertension in at-risk patients.

Chronically, a subset of patients likely develop persistent ocular hypertension. Several studies did not find a correlation between chronic anti-VEGF therapy and sustained OHTN. However, post hoc analyses of the MARINA, ANCHOR and DRCR studies provides the best quality evidence that a subset of patients develop a clinically significant elevation in intraocular pressure following chronic anti-VEGF intravitreal therapy. Evaluation of these studies are suggestive that patients who have underlying outflow pathology, as manifested by an underlying diagnosis of glaucoma, ocular hypertension or a history of retinal vein occlusion, are at particular risk of developing sustained ocular hypertension and these patients should be closely monitored for the development of sustained pressure elevation. A history of cataract extraction or posterior capsulotomy were not consistently identified as risk factors,

and the particular anti-VEGF utilized was not conclusively observed as a risk factor. Further studies are necessary to clarify which particular anti-VEGF therapy, if any, has increased rates of sustained ocular hypertension. Although definitive evidence of damage to the retinal nerve fiber layer is lacking, patients receiving repeated injections should be monitored for the development of ocular hypertension and those who develop sustained ocular hypertension should be periodically monitored for glaucomatous changes with an optic nerve OCT and static visual field. Referrals to a glaucoma specialist should be considered in patients with concerning features.

This review allows for a better risk-benefit analysis for clinicians providing frequent intravitreal anti-VEGF injections. Future studies, potentially assessing subconjunctival reflux, are needed to further clarify the role of prophylactic medications prior to IVI for acute ocular hypertension. In addition, longer-duration prospective studies or larger, population-based retrospective studies focusing on progression of glaucomatous optic neuropathy following IVI could help clarify the long-term risk of anti-VEGF therapy and aid in identifying which subset of patients are at risk of developing sustained ocular hypertension.

Literature Search

Prospective randomized trials, prospective cohort studies, and retrospective studies that reported on IOP following intravitreal injections of anti-VEGF agents were searched using Medline through November, 2017. Key words included in the search included intraocular pressure, IOP, optical coherence tomography, OCT, intravitreal, intraocular, anti-VEGF, VEGF, vascular endothelial growth factor, Lucentis, ranibizumab, Avastin, bevacizumab, Eylea, aflibercept, Macugen, pegaptanib, injection, and injections. Inclusion criteria included prospective randomized trials, retrospective case series, retrospective case reports and injection of anti-VEGF medications. Exclusion criteria included literature reviews, summaries, editorials, letters, and steroid injections. Those publications deemed eligible following review of the abstract were obtained in full. In addition, references were reviewed for possible publications missed by the initial review.

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Supplemental Material

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Table 1.

Effect of subconjunctival reflux on ocular hypertension immediately following intravitreal anti-VEGF injections. This table demonstrates the effect of subconjunctival reflux on ocular hypertension immediately following IVI. A 19.9 mmHg difference exists between eyes that experience reflux with those that do not.

Study	Medications and Volume	Needle gauge	Number of patients		IOP increase from baseline immediately following IVI (mmHg)	
			With reflux	Without reflux	With reflux	Without reflux
Sharei 2010	Ranibizumab 0.05 mL	30	20	23	17.4	33
Pang 2015	Ranibizumab 0.05 mL, aflibercept 0.05 mL	30 and 32	22	43	8.3	29.6
Lemos 2014	Bevacizumab 0.05 mL	30	62	229	7.7	28.6
Knecht 2009	Ranibizumab 0.05 mL, bevacizumab 0.05 mL	30	20	10	5.2	22.5
Weighted Average IOP (mmHg)					**9.0**	**28.9**

Table 2. **The effect of dorzolamide-timolol at reducing acute post-IVI ocular hypertension.**

Study	IVI drug and volumes	Dorzolamide-timolol regimen	Number of patients	Key findings
El Chehab 2013	Ranibizumab 0.05 mL	1 drop of dorzolamide-timolol given 2 hours before injection	- 50 patients in dorzolamide-timolol arm, - 50 patients in each of 4 other arms: - Control - Apraclonidine - Oral acetazolamide - Brimonidine-timolol	Immediately following injection, the IOP was 36.9 mmHg in the dorzolamide-timolol arm and 46.4 mmHg in the control arm; an IOP spike of >45 mmHg occurred in 20.0% of the dorzolamide-timolol arm and 65.5% in control arm. Dorzolamide-timolol was not more effective than apraclonidine or brimonidine-timolol.
Kim 2013	Ranibizumab 0.05 mL or Bevacizumab 0.05 mL	1 drop of dorzolamide-timolol given 1 hour before injection	- 53 patients in the dorzolamide-timolol arm - 84 in the brinzolamide-timolol arm - 29 in the control arm	At 5 minutes, the dorzolamide-timolol group had an IOP of 14.1 mmHg compared to control group of 28.2 mmHg. At 1 hour, the average IOP was 10.7 mmHg in the dorzolamide-timolol group and 18.7 mmHg in the control group. Dorzolamide-timolol was not more effective than brinzolamide-timolol.
Ozcaliskin 2015	Bevacizumab 0.05 mL	1 drop of dorzolamide-timolol given 2 hours before injection	- 75 patients in treatment arm - 76 patients in control arm	At 1 minute, average IOP of was 29.8 mmHg in the treated arm and 34.4 mmHg in the control arm. At 30 minutes, the average pressure equalized.

Table 3. Studies findings a subgroup of patients experiencing sustained ocular hypertension following repeated intravitreal injections.

Study	Cohort	Med	# of IVI before OHTN	Follow-up	Key IOP inclusion criteria	Key findings
Adelman 2010	116 patients with AMD	B, R	13.3	--	IOP >21 mmHg on 2 separate measurements	- 3.4 % of patients developed OHTN - Average IOP prior to injections: 13 mm Hg - Average IOP when OHTN developed: 31.75 mmHg - YAG capsulotomy a possible risk factor
Baek 2010	152 patients with AMD and DME	B	--	18.7 months	IOP increase of 5mmHg above baseline IOP on 2 consecutive visits	- 5.9% of patients developed sustained OHTN - Number of injections was a risk factor
Choi 2011	155 eyes with AMD	R, B, P	9.6	13.9 months	IOP >25 mmHg on at least two separate visit	- 5.5% of eyes developed sustained OHTN - Number of injections, medication used and injection frequency were not risk factors - One eye required trabeculectomy - Anti-VEGF agent used was not a risk factor
Good 2011	215 eyes with AMD	B, R	5	--	IOP ≥ 22 mmHg lasting ≥ 30 days on at least two separate visits and a change from baseline of >6 mmHg	- 6% of patients developed sustained OHTN - 33% of patients with pre-existing glaucoma developed sustained OHTN - 9.9% of patients receiving bevacizumab developed sustained OHTN, in comparison to 3.1% of patients receiving ranibizumab
Hoang 2012	207 consecutive patients with AMD	B, R	24.4	37.2 months	Multiple	Percentage of patients with >5mmHg increase on ≥2 consecutive visits - Treated: 11.6% - Control: 5.3% Percentage of patients with >10 mmHg increase on ≥2 consecutive visits - Treated: 4.8% - Control: 0.5% The total number of injections was a risk factor for IOP elevation
Mathalone 2012	201 eyes with AMD	B	5	15.7 months	IOP ≥22 mmHg and a change from baseline of ≥6 mmHg at two consecutive visits at least >30 days apart	- Sustained IOP was found in 11% of patients - Risk factors included male gender and interval between injections of less than 8 weeks - Pre-existing glaucoma and YAG capsulotomy were not risk factors
Menke 2013	320 eyes with AMD	R	13.0	22.7 months	--	- Mean increase in IOP was 0.8 mmHg - Seven eyes showed a final IOP between 22 and 25 mmHg - Duration of treatment was associated with greater increase in pressure
Agard 2014	217 eyes with AMD	B, R	6.1	--	IOP >25 mmHg on 2 consecutive visits	- 4.6 % of patients developed sustained OHTN - 1.4% of patients had sustained IOP > 30 mmHg - Average IOP for sustained OHTN group: 29 mmHg - OAG at presentation was associated with an increased risk of sustained IOP > 25 mmHg (12.9% versus 3.2%, $p < 0.001$) - YAG capsulotomy was not a risk factor
Bakri 2014	1125 patients with AMD, from MARINA and	R	--	24 months	Multiple cutoff criteria	IOP of 21 mmHg or more with a concurrent IOP increase of 6 mmHg or more from baseline ($p <0.0001$ for all comparisons):

	ANCHOR studies, excluding patients that were crossed over to the treatment arm					- Ranibizumab 0.5 mg: 26.1 % - Ranibizumab 0.3 mg: 23.6 % - Sham: 13.6 % IOP of 25 mmHg or more with a concurrent IOP increase of 6 mmHg or more from baseline (p <0.003 for all comparisons): - Ranibizumab 0.5 mg: 9.6% - Ranibizumab 0.3 mg: 9.4% - Sham: 3.7% Control in this study was the fellow eye, which did not show a similar pattern of sustained OHTN
Al-Abdullah 2015	760 eyes with diabetic macular edema	B, R	5.45	17.9 months	IOP increase of >6mmHg from baseline OR IOP of >24 on 2 or more consecutive visits	- 1.7 % of patients developed sustained OHTN - Total number of injections was a risk factor for sustained OHTN - YAG capsulotomy or pseudophakia was not a risk factor
Bressler 2015	582 eyes, 322 of which received ranibizumab plus prompt or deferred laser. Retrospective analysis of DRCR study	R	--	36 months	IOP of 22 mmHg or more with a concomitant increase in IOP of 6 mmHg or more from baseline at 2 consecutive visits	Percentage of patients with sustained OHTN at 1 year - Ranibizumab: 5.7% - Sham 2.0% Percentage of patients with sustained OHTN at 3 years - Ranibizumab: 9.5% - Sham: 3.4%
Freund 2015	2419 patients with AMD	A, A0.5 , R	--	96 weeks	Various criteria	- IOP >21 mmHg at 2 consecutive visits: Rq4: 8.4%, A2q4: 3.2%, A2q8: 4.2%, A0.5q4: 2.7% - IOP >5 mmHg from baseline at 2 consecutive visits: Rq4: 19.7%, A2q4: 14.1%, A2q8: 12.6%, A0.5q4: 11.1% - Ranibizumab was associated with greater OHTN rates.
Foss 2016	AMD patients in IVAN trial, 610 patients	R, B	--	23.6 months	Various criteria	- For every month, there was a statistically significant increase in preinjection IOP of 0.02mmHg/month - Anti-VEGF agent used and pre-existing glaucoma diagnosis was not a risk factor for OHTN throughout the study - Pseudophakia was associated with a lower IOP

Table key:
IVI: Intravitreal injection, IOP: Intraocular pressure, AMD: Age-related macular degeneration, R: Ranibizumab, B: Bevacizumab, A: Aflibercept, A0.5: Aflibercept 0.5 mg/0.05 mL, OHTN: Ocular hypertension, DME: Diabetic macular edema, Rq4: Ranibizumab every 4 weeks, A2q4: Aflibercept 2 mg every 4 weeks, A2q8: Aflibercept 2mg every 8 weeks, A0.5q4: Aflibercept 0.5 mg every 4 weeks

Table 4. Studies not finding sustained ocular hypertension following repeated intravitreal injections.

Study	Cohort	Medication	Follow-up	Key IOP inclusion criteria	Key findings
Wehrli 2012	302 eyes with AMD and 226 control fellow eyes	B, R	2 years	IOP ≥22 mmHg on 2 consecutive visits with an increase from baseline of >6 mmHg or IOP > 26 mmHg on a single visit	- 0.5% incidence per eye-year of sustained OHTN in injected eyes compared to 1.0% of control eyes - For patients with glaucoma, 3.1% of patients treated with anti-VEGF developed sustained OHTN, compared to 5.7% of control eyes
Boyer 2014	221 eyes with AMD, 114 treated with P	P	24 months	≥2 measurements of ≥22 mmHg	- 5.3% of patients receiving pegaptanib versus 9.3% in the sham group
Kim 2014 AJO	629 eyes with AMD and 95 eyes with RVO	B, R	35.5 months	IOP increase of >5mmHg over baseline on 2 consecutive visits	- 3.1% of control fellow eyes developed sustained OHTN - 3.0% of patients with AMD developed sustained OHTN - 7.4% of patients with RVO developed sustained OHTN
Kim 2014 J Glauc	83 patients with AMD	B	24 months	Average IOP	- No difference in IOP between groups - No comment on the percentage of patients with an increase in IOP, as only averages were presented - Average of only 3.71 injections

Study key: P: pegaptanib, B: Bevacizumab, R: Ranibizumab, IVI: Intravitreal injection, IOP: Intraocular pressure, mmHg: millimeters of mercury, OHTN: ocular hypertension, AMD: Age-related macular degeneration

Figure 1.

Weighted IOP average following intravitreal injection. This graph presents the acute change in IOP following intravitreal injection. The data for this graph was extracted from material presented in Supplemental Material Table 1. This data was then used to create weighted IOP averages based on the number of patients included in each study for each of the plotted time points. Error bars were created from the weighted standard deviation of the means.

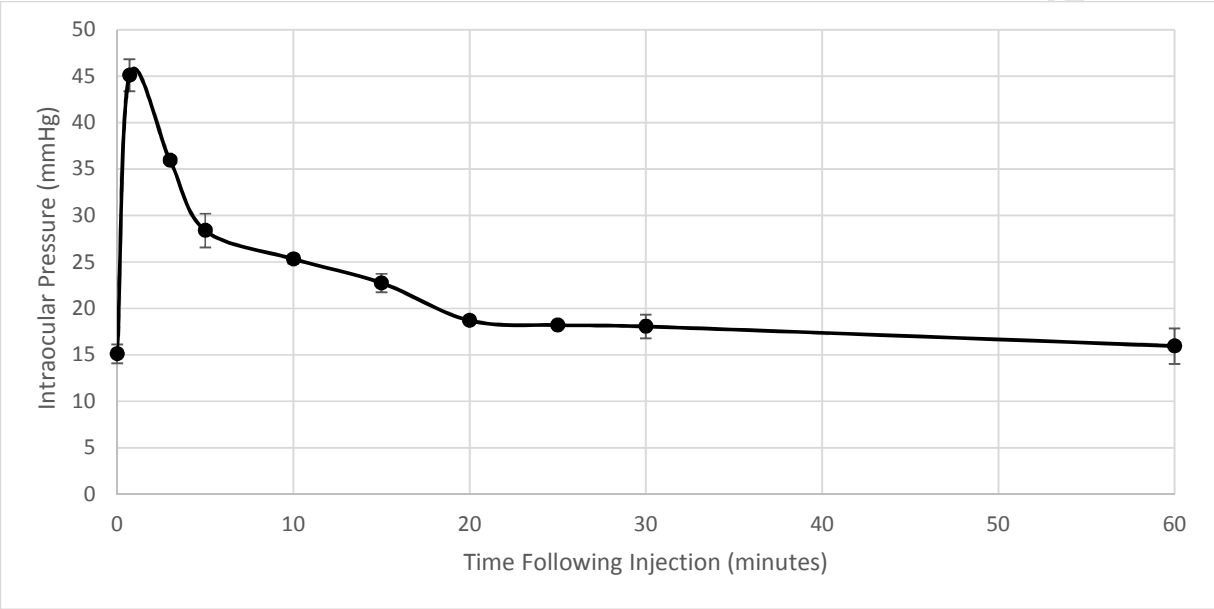

Figure 2.

Prophylactic effect of topical drops given prior to intravitreal injection. The data for this graph was extracted from published material presented in Supplemental Material Table 2. This data was used to create weighted IOP averages based on the number of patients included at each time point. Error bars were not included in this graph due to the paucity of data available and to not give an erroneous impression of statistical significance.