Management of Immediate and Sustained Intraocular Pressure Rise Associated with Intravitreal Anti-VEGF Injection Therapy

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ABSTRACT

Purpose of review: To summarize the findings of recent reports of short-term and sustained intraocular pressure (IOP) rise associated with intravitreal anti-vascular endothelial growth factor (VEGF) injections and to guide the management of this infrequent complication.

Recent findings: Short-term increases in IOP are common immediately after intravitreal anti-VEGF injection. IOP takes longer to reach a safe level in patients with a history of glaucoma or ocular hypertension. Pre-injection medicinal therapy and ocular decompression therapy may blunt this short-term IOP rise. Sustained increases in IOP are relatively infrequent, but are likely to necessitate intervention for IOP-lowering. A "pro re nata" (PRN) injection protocol may obviate the need for intervention. The pathophysiology of sustained IOP rise is poorly understood, but may relate to repackaging processes undertaken by the pharmacies that compound these agents.

Summary: Treating physicians should be aware of the potential for short-term and sustained IOP rise associated with intravitreal anti-VEGF injection therapy. Considerations for management include prophylactic IOP-lowering with medicinal therapy and/or pre-injection ocular decompression for patients with a history of glaucoma or ocular hypertension and switching to a "PRN" injection protocol in patients suffering a sustained rise in IOP.

Key Words: glaucoma, macular degeneration, vascular endothelial growth factor

INTRODUCTION

The introduction of intravitreal anti-vascular endothelial growth factor (VEGF) injections as primary therapy for exudative age-related macular degeneration (ARMD) represents a monumental achievement in the field of clinical ophthalmology. As shown in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration (ANCHOR) phase III clinical trials, monthly intravitreal injections prevent the loss of visual acuity in approximately 95% and may actually improve visual acuity in up to 40% of treated patients with ARMD [1, 2]. Recently, the randomized Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) demonstrated that treatment with intravitreal bevacizumab injections results in similar efficacy when compared to ranibizumab [3*].

Although the MARINA, ANCHOR, and CATT studies all demonstrated a relatively low rate of ocular and systemic adverse events, recent reports suggest that intraocular pressure (IOP) rise associated with anti-VEGF injection therapy may have negative clinical consequences both in the immediate and long-term post-injection period. This review aims to summarize these recent findings, as reported in the literature, and also to guide the management of this infrequent complication.

SHORT-TERM INTRAOCULAR PRESSURE RISE

The MARINA and ANCHOR trials both found transient increases in IOP after injection in the respective treatment groups, but with very few patients experiencing a rise to 40 mm Hg or more.

However, the injection protocol did not mandate IOP measurement within 1 hour of injection and so IOP rise during this time frame was not reported [1, 2].

In order to investigate the immediate short-term effects of anti-VEGF injection on IOP, Gismondi and colleagues performed a prospective study of 54 eyes of 54 patients treated with intravitreal ranibizumab [4]. In this study, the investigators measured IOP immediately before, 5 seconds, 5, 10, 15, 30, 60 minutes, and 1 day after injection. Indeed, the group found that a considerable increase in IOP occurs within 30 minutes of intravitreal injection. The differences between pre- and post-injection IOP were significant after 5 seconds, 5, 10, 15, and 30 minutes ($P=0.0001$), but not at 1 hour ($P=0.064$) and 1 day ($P=0.449$). An important finding in this study was that 88.9% of study subjects experienced an IOP rise > 30 mm Hg at 5 seconds post-injection.

A retrospective series performed by Kim and colleagues revealed similar findings in 120 eyes of 112 patients receiving intravitreal injections of ranibizumab, bevacizumab, pegaptanib, and triamcinolone acetonide [5]. Among all patients, mean IOP immediately after injection was 44 mm Hg (range, 4 – 87 mm Hg) with 36% of eyes experiencing a rise to 50 mm Hg or greater. Although IOP was reduced to less than 30 mm Hg in 96% of eyes by 15 minutes, eyes with a history of glaucoma took significantly longer to reach this level ($P=0.002$). Other series investigating short-term IOP changes also found that IOP tended to return to a safe level in the majority of patients by 10 – 30 minutes post-injection, but did not investigate immediate post-injection IOPs [6-8].

Pathophysiology

The pathogenesis of short-term IOP elevation after anti-VEGF injection most directly relates to an increase in intraocular fluid volume. Other potential variables influencing intraocular pressure rise include axial length, scleral thickness, scleral rigidity, and ocular outflow facility [9]. In a biomechanical model, Kotliar, et al studied the effect of intravitreal injection of 0.1 mL 0.9% NaCl solution in hyperopic, emmetropic, and myopic eyes. Eyes with shorter axial length had higher IOP immediately after injection ($P<0.05$) [10]. In their prospective clinical study, Gismondi and colleagues [4] also found a relationship between shorter axial length and IOP increase 5 seconds post-injection (linear regression analysis; $R^2=0.28$, $P=0.007$).

Management

Short-term IOP increases of the magnitude described by Gismondi and colleagues [4] may have minimal clinical impact on the majority of patients undergoing anti-VEGF injection therapy. Current evidence suggests that otherwise healthy eyes can tolerate a short-term IOP rise with no permanent effects on visual function [11]. However, the effects of these spikes in IOP pose a real threat to the health of the optic nerve in individuals with advanced glaucomatous optic neuropathy. Prior studies have demonstrated clear visual field progression [12] and even loss of fixation [13] associated with short-term IOP spikes following cataract surgery. Considering that affliction with both exudative ARMD and glaucoma is not uncommon, awareness and proper management of this issue by the treating physician is critical.

To this end, the treating physician should perform careful slit-lamp biomicroscopy in all patients undergoing injection therapy prior to administering an intravitreal injection and note the appearance of the optic nerve. Signs of glaucomatous optic neuropathy including generalized

cupping, focal rim thinning, or disc hemorrhage should serve as warning signs of potential optic nerve compromise and higher risk for visual dysfunction post-injection. Refractive error should also be noted as eyes with shorter axial length (with resultant hyperopic error) are at higher risk for post-injection IOP rise [4, 10]. Assuming that anti-VEGF injection therapy is absolutely indicated, the treating physician should strongly consider measures to prophylactically blunt an immediate IOP spike post-injection in these patients.

Theoulakis and colleagues performed a prospective, masked, randomized controlled study investigating the use of prophylactic fixed combination brimonidine 0.2% and timolol 0.5% (Combigan^{TM}, Allergan, Inc.; Irvine, CA) to blunt IOP spikes after intravitreal injection of ranibizumab [14**]. In this study, one eye of 88 consecutive patients with ARMD was randomized to placebo (artificial tears) or to Combigan eye drops given twice a day the day before and the day of injection. Results demonstrated lower mean post-injection IOP (28.4$\pm$1.1 mm Hg; range, 25 – 33 mm Hg) in the treatment group compared to the placebo group (34.1$\pm$2.7 mm Hg; range, 28 – 40 mm Hg) at 5 minutes post-injection ($P<0.001$). Morlet and Young found that pre-injection ocular decompression with a mercury bag reduced post-injection IOP from a mean of 44.5 mm Hg to 20.6 mm Hg ($P<0.001$) in patients receiving intravitreal ganciclovir injections for CMV retinitis [15]. Results of these two studies provide evidence that pre-injection medicinal therapy or ocular decompression may blunt a post-injection spike in glaucomatous eyes undergoing anti-VEGF therapy. Should IOP rise in spite of these efforts, and there is deemed to be an irreversible threat to vision, anterior chamber paracentesis should be performed [16].

SUSTAINED INTRAOCULAR PRESSURE RISE

Both the MARINA and ANCHOR trials found that, on average, monthly Ranibizumab injection therapy had no long-term effect on intraocular pressure during a 2-year period of follow-up [1, 2]. However, a recent post-hoc analysis of the data from these clinical trials revealed that 2.1% of eyes in the MARINA and 3.6% of eyes in the ANCHOR trials experienced an increase in IOP $\geq$ 6 mm Hg from baseline, reaching a value $\geq$ 25 mm Hg on $\geq$ 2 consecutive visits during the 2 year follow-up period (compared to 0.4% and 0% in the control groups, respectively) [17]. Adelman reported similar findings in 4 out 116 patients (3.45%) without a prior history of ocular hypertension or glaucoma who experienced a sustained rise in IOP after multiple intravitreal injections of bevacizumab and/or ranibizumab [18*]. Among these four eyes, pre-injection IOP rose from a mean of 13 mm Hg (range, 8-15 mm Hg) to 31.75 mm Hg (range, 28-36 mm Hg). Bakri et al also described four eyes that experienced an IOP rise from a pre-injection mean of 17.5 mm Hg (range, 15-22 mm Hg) to a post-injection mean of 40.0 mm Hg (30-50 mm Hg) [19].

In a recent retrospective case series, Tseng and colleagues describe 25 eyes of 23 patients who developed a sustained increase in IOP after undergoing a mean of 20.0 (range, 8-40) intravitreal injections of bevacizumab and/or ranibizumab for exudative ARMD [20**]. All eyes in this series were previously ocular normotensive and IOP increased from a mean baseline level of 16.9 mm Hg (range, 14-21 mm Hg) to a mean peak level of 35.8 mm Hg (range, 23-58 mm Hg). The major strength of this retrospective series was a relatively long follow-up period (mean 47.9 weeks) after the detection of elevated IOP, revealing that all eyes that were continued on anti-

VEGF therapy required anti-glaucoma intervention. Of the entire series, 23 eyes required an intervention, including 3 eyes that ultimately required filtration surgery.

Good et al reviewed the charts of 215 eyes receiving one or more bevacizumab and/or ranibizumab injections for exudative ARMD [21**]. Overall, 6% of eyes experienced sustained IOP elevation and required medical or surgical therapy. This rate was significantly higher in patients with a history of pre-existing glaucoma compared to those with no history of glaucoma (33% vs. 3.1% respectively; $p<0.001$). When comparing the frequency of injections and total number of injections received between the group experiencing sustained IOP rise and those that remained ocular normotensive, no difference was found. However, a higher rate of sustained IOP rise was found among eyes receiving only bevacizumab compared to eyes receiving only ranibizumab (9.9% vs. 3.1% respectively; $p=0.049$). A summary of the studies reporting on sustained IOP rise after multiple intravitreal anti-VEGF injections is displayed in the **Table**.

Pathophysiology

The pathophysiology of sustained IOP rise associated with anti-VEGF therapy is more difficult to ascertain than the pathophysiology of short-term IOP spikes. Several theories have been proposed, including a permanent decrease in outflow facility due to repeated IOP spikes with each injection and subsequent damage to the trabecular meshwork, direct pharmacological toxicity, and chronic trabeculitis. Although a single case report by Sniegowski and colleagues [22] reports evidence of trabecular inflammation associated with the injections, an anterior chamber reaction, peripheral anterior synechiae, and/or direct evidence of trabeculitis were not observed in any of the cases included in larger series [20, 21**]. Studies investigating potential pharmacological toxicity reveal conflicting results [23, 24].

Although the CATT revealed similar efficacy for both bevacizumab and ranibizumab, treatment with the former is currently an “off-label” practice that often requires repackaging of the medicine by a compounding pharmacy. Kahook and colleagues investigated the hypothesis that the repackaging of bevacizumab causes a formation of protein aggregates that may then mechanically obstruct trabecular outflow [25**]. When compared to samples obtained from the original bevacizumab vial, syringes obtained from compounding pharmacies were found to contain 10 times the number of large (>1 um) protein particles. In a separate study [26*], the investigators found that repeated freeze-thawing and mechanical shock (simulating the repackaging and shipping process) of samples obtained from compounding pharmacies caused leaching of silicone oil microdroplets from the syringes and subsequent protein aggregation. Indirect evidence for a clinical consequence of these findings comes from the retrospective series performed by Good et al [21**] that revealed a higher rate of sustained IOP elevation in ranibizumab-treated eyes treated at 1 of the 2 treatment centers (15.3% vs. 2.4% respectively; p=0.03) which repackaged the bevacizumab from an outside compounding pharmacy rather than repackaging the medication on site prior to injection. However, other factors are likely to be involved as the series by Tseng et al [20**] revealed that 11 of the 25 cases of sustained IOP rise were in eyes that had only received ranibizumab, which was not subjected to the repackaging process.

Management

Patients treated in the MARINA and ANCHOR studies received monthly intravitreal injections of ranibizumab or bevacizumab. Once efficacy was demonstrated, this monthly regimen of injection therapy became standard practice for the treatment of exudative ARMD. However, subsequent studies have demonstrated that monthly injections may not be necessary for all

patients. In patients with pre-existing glaucoma and/or sustained IOP increase associated with multiple anti-VEGF injections, a different treatment schedule should be strongly considered.

The prospective optical coherence tomography-guided imaging of patients with neovascular age-related macular degeneration treated with intraocular ranibizumab (PrONTO) study demonstrated that patients treated with a variable-dosing regimen guided by best-corrected Early Treatment Diabetic Retinopathy (EDTRS) visual acuity and optical coherence tomography results could achieve visual results similar to those seen in the MARINA and ANCHOR studies, but with less frequent injections [27, 28]. The safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration (SUSTAIN) study revealed similar results in a phase III, multicenter trial in which patients were re-treated with injection therapy based on prespecified criteria [29**]. This treatment approach has been termed the "as needed" or "pro re nata" (PRN) protocol.

The "treat and extend" protocol involves monthly intravitreal injections until optical coherence tomography reveals resorbed macular fluid [30]. Treatment intervals are then extended until exudation reappears on imaging studies. Gupta and colleagues studied the efficacy of this protocol and described visual outcomes similar to those seen in the MARINA, ANCHOR, and PrONTO studies [30]. Although the "treat and extend" protocol involves fewer injections than the MARINA, ANCHOR, and PrONTO studies, patients undergoing treatment with this strategy typically require more frequent injections than in the "as needed" or "PRN" protocols.

All of the 25 eyes described Tseng et al [20**] experienced a sustained IOP rise while undergoing treatment under the "treat and extend" protocol. Two of the 25 eyes were switched to the "as needed" protocol and IOP subsequently improved without further intervention. This

finding does suggest that decreasing the frequency of injection therapy and following the “as needed” strategy for intravitreal injection therapy may be of benefit to patients experiencing sustained IOP rise and/or those with a history of pre-existing glaucoma.

CONCLUSION

Recent evidence suggests that both short-term and sustained IOP increases associated with anti-VEGF intravitreal injection therapy are of a real clinical concern. Treating physicians should be aware of this infrequent complication and manage these occurrences appropriately. Considerations for management include prophylactic IOP-lowering with medicinal therapy and/or pre-injection ocular decompression for patients with a history of glaucoma or ocular hypertension and switching to an “as needed” injection protocol in patients suffering a sustained IOP rise. Further investigation into the repackaging of bevacizumab by compounding pharmacies is necessary to determine whether specific practices (such as repeated freeze-thawing and mechanical shock) should be regulated in order to decrease the risk of sustained IOP rise associated with multiple injections. Prospective studies to further characterize the incidence and long-term course of sustained IOP rise are also warranted.

KEY POINTS

- Short-term increases in IOP occurring post-intravitreal anti-VEGF injection therapy may take longer to normalize in patients with pre-existing glaucoma or ocular hypertension.
- Pre-injection prophylactic therapy with IOP-lowering medications and/or ocular decompression may blunt a post-operative IOP rise in patients with pre-existing glaucoma or ocular hypertension.
- The etiology of sustained increases in IOP is uncertain, but these events often require IOP-lowering intervention.
- A “PRN” injection protocol may be warranted in patients experiencing a sustained increase in IOP after multiple intravitreal anti-VEGF injections.

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