Intraocular Pressure Elevation Following Intravitreal Injection with Antivascular Endothelial Growth Factor

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Abstract
As the prevalence of both glaucoma and AMD increase with age, there is a considerable chance of having glaucoma in patients who develop CNV in eyes with age-related macular degeneration. This review discusses in great detail the impact of VEGF agents on IOP in terms of both, short-term elevation and long-term effects.

INTRODUCTION
In the last five years intravitreal injections of antivascular endothelial growth factor (VEGF) agents for treatment of choroidal neovascularization (CNV) in eyes with age-related macular degeneration have become the preferred practice pattern. Currently three different agents are used for intravitreal injections: bevacizumab (avastin) – a humanized 148 kDa monoclonal antibody, ranibizumab (lucentis) – a 48 kDa antibody fragment, and pegaptanib (macugen) – a 50 kDa oligonucleic acid aptamer.

Injection of solutions intravitreally may result in elevation of intraocular pressure (IOP). It has been related to the acute volume change that occurs after any substance injection. The characteristics of major studies on intravitreal injection of anti-VEGF agents are elaborated in Table 1.

When referring to IOP elevation following intravitreal injection one must differentiate between short-term and long-term changes. The majority of studies regarding anti-VEGF agents reveal short-term IOP rise but recently there have been a few reports on long-term IOP elevation in selected patients.

SHORT-TERM IOP ELEVATION
There is no agreement among investigators as to the actual occurrence of IOP pressure rise after intravitreal injection of anti-VEGF. Following their studies of intravitreal injections with pegaptanib and bevacizumab, Gragoudas et al and Spaide et al stated that “there was no evidence of a sustained elevation in IOP” and that “no IOP rise occurred”. Yet no data regarding the time and method of IOP measurement and IOP values were provided.

Other investigators report a substantial number of cases with postinjection IOP elevation, with an immediate elevation of IOP that may reach very high values, up to 87 mm Hg. In addition, the fact that paracentesis was required for lowering of IOP following 4.1% of intravitreal injections in the VISION study, points to a substantial number of patients developing significantly increased IOP. Kim et al reported an immediate postinjection IOP ≥ 50 mm Hg in 3% of cases. In the MARINA study IOP of 40 mm Hg and 50 mm Hg occurred in 2.3% and 0.6% of patients, respectively. IOP ≥ 30 mm Hg within the first hour was documented in 13% of patients injected with 0.3 mg ranicizumab and 17.6% of those injected with 0.5 mg. Falkenstein et al reported IOP ≥ 30 mm Hg in 14% at 10 minutes postinjection. Although those eyes experienced significant drop in IOP from 10 to 15 minutes after injection the mean IOP was still significantly higher than the baseline values. The authors state that there was a trend to drop to baseline with the next few hours but the actual data was not provided.

Another area of study diversity is the preference of the method of IOP measurement. Some investigators preferred the Goldmann applanation tonometry while others used the Tonopen. A combination of the two methods has also been described, when preinjection IOP was measured by the Goldmann tonometer while the Tonopen was used postinjection. One should bear in mind that the Tonopen agrees well with Goldmann tonometer measurements for pressures < 20 mm Hg, but for pressures >20 mm Hg it tends to underestimate the Goldmann tonometer measurements by an average of 4.2 mm Hg.

The hazard of short-term IOP elevation following intravitreal injection is the risk of short-term occlusion of the retinal artery. It has been customarily evaluated by indirect viewing of the retinal artery for pulsation, and by confirming vision of hand motion and finger count following the procedure.

The level of the IOP spike is probably related to various factors. One of the factors is the volume of the injected agent. Another factor is the needle size: higher IOP spikes were observed with a smaller needle bore size (30 or 32 gauge) compared to larger needle size (27 gauge needle). Scleral rigidity and size of the globe are other possible factors.
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Currently, there is no consensus regarding the optimal time for initial IOP examination, the time intervals, and the duration of follow-up for postinjection monitoring. This diversity is depicted in the design of the studies.4,6-10

LONG-TERM IOP ELEVATION

Studies reporting on intermediate and long-term effects of anti-VEGF intravitreal injections on IOP are scarce. In the MARINA and ANCHOR trials2,7 ranibizumab had no long-term effect on mean IOP as assessed by monthly preinjection measurements during the 2-year follow-up. IOP was increased on average 1 hour after ranibizumab injections at protocol-mandated IOP assessments. However, the absence of corresponding changes in preinjection measurements suggested that the postinjection increases were transient.

Recently, eleven cases11-13 with sustained postinjection IOP increase were reported. Kahook et al11 described six cases with sustained elevation of IOP following intravitreal injection of bevacizumab. Their mean age was 78, and five of them were women. Only one patient had glaucoma and two others had suspected glaucoma. Mean follow-up from first injection was 10.2 months (range 1.5 - 24). The mean number of total intravitreal injections was 5.7 (range 1-10). No data was provided regarding visual fields or gonioscopy at the preinjection state. Pressure rise following injections ranged from 27 mm Hg to 42 mm Hg.

Bakri et al12 described four cases of persistent ocular hypertension following intravitreal ranibizumab. Their mean age was 76, and three of them were women. None had a previous history of glaucoma or ocular hypertension. IOP following the intravitreal injection ranged from 30 to 50 mm Hg.

Jalil et al13 described a 75-year-old man with sustained IOP elevation, rising up to 56 mm Hg, following the fourth injection of bevacizumab.

The mechanism of this long-term, sustained pressure rise following intravitreal injection of anti-VEGF agents is unclear. Likewise, risk factors for such persistent IOP elevation are unknown. It has been hypothesized12 that those large molecules may accumulate in the trabecular meshwork, thereby blocking aqueous outflow and leading to increased IOP. The half-life of bevacizumab in the vitreous is 5.6 days,15 but clearance from the trabecular meshwork may be longer, resulting in persistent effect in that tissue. Thus elevated IOP postinjection is more likely to occur with bevacizumab, being a 148 kDa full-length antibody11,13. In comparison, ranibizumab is an antibody fragment which has a molecular weight of 48 kDa.5 One may presume that passage through the trabecular meshwork would be faster for this antibody fragment, leading to less occurrence of pressure elevation. However, cases with postinjection increase in IOP have been described with ranibizumab as well.12

We suggest another possible mechanism for pressure increase following injection of anti-VEGF agents, based on their affinity to endothelial growth factors. Interference with activity of endothelial growth factors may adversely affect the endothelial cells lining of the trabecular meshwork, resulting in damage to these cells, disruption of their function and decreased outflow. In the VISION study postinjection IOP >35 mm Hg occurred in 44 (15%) of the patients receiving 3 mg pegaptanib sodium, but only in 27 (9%) of the patients in the group receiving 0.3 mg pegaptanib sodium.3 The volume of the injected agent was the same in both groups. This may support the hypothetical role of anti-VEGF activity in damaging the trabecular meshwork endothelium. Glaucoma patients and the elderly may be more prone to this presumed “toxic” effect, of anti VEGF antibodies due to their existing compromised facility of aqueous outflow.

GLAUCOMA PATIENTS

Most studies on intravitreal injection of anti-VEGF agents do not include patients with glaucoma or ocular hypertension.9 Some reports1,5,7 did not elaborate on the status of glaucoma or ocular hypertension in the patients included in the studies. A few studies included patients with ocular hypertension and unknown.

Table 1: Major studies on treatment of neovascular age-related macular degeneration with intravitreal injections of anti-VEGF agents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Design</th>
<th>Anti-VEGF</th>
<th>Patients (n)</th>
<th>Patients (n) with glaucoma/OHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gragoudas</td>
<td>2004</td>
<td>Prospective</td>
<td>Pegaptanib</td>
<td>1186</td>
<td>NR</td>
</tr>
<tr>
<td>Brown</td>
<td>2006</td>
<td>Prospective</td>
<td>Ranibizumab</td>
<td>423</td>
<td>NR</td>
</tr>
<tr>
<td>D’Amico</td>
<td>2006</td>
<td>Prospective</td>
<td>Pegaptanib</td>
<td>1190</td>
<td>68</td>
</tr>
<tr>
<td>Rich</td>
<td>2006</td>
<td>Retrospective</td>
<td>Bevacizumab</td>
<td>50</td>
<td>NR</td>
</tr>
<tr>
<td>Spaide</td>
<td>2006</td>
<td>Retrospective</td>
<td>Bevacizumab</td>
<td>266</td>
<td>NR</td>
</tr>
<tr>
<td>Hariprasad</td>
<td>2006</td>
<td>Retrospective</td>
<td>Pegaptanib</td>
<td>79</td>
<td>ND</td>
</tr>
<tr>
<td>Rosenfeld</td>
<td>2006</td>
<td>Prospective</td>
<td>Bevacizumab</td>
<td>716</td>
<td>NR</td>
</tr>
<tr>
<td>Hollands</td>
<td>2007</td>
<td>Prospective</td>
<td>Bevacizumab</td>
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<td>16</td>
</tr>
<tr>
<td>Falkenstein</td>
<td>2007</td>
<td>Prospective</td>
<td>Bevacizumab</td>
<td>70</td>
<td>none</td>
</tr>
<tr>
<td>Kim</td>
<td>2008</td>
<td>Retrospective</td>
<td>All three</td>
<td>112</td>
<td>20</td>
</tr>
</tbody>
</table>

NR = Not reported.
ND = Study included glaucoma patients but no details disclosed.
patients with glaucoma, but they comprised only a small fraction of the study population. Therefore data in these studies could be applied to normotensive individuals only.

Several investigators monitored the IOP in their patients until it decreased below 30 mm Hg. This approach is probably based on the assumption that once reaching IOP below 30 mm Hg it will continue to decrease with time. Moreover, the common practice by many retina specialists is to check for gross visual acuity following injection to assess optic nerve perfusion but not to check IOP, with the belief that in most eyes IOP decreases below 30 mm Hg within one hour. However, Kim et al have demonstrated that eyes with preexisting glaucoma took significantly longer to achieve an IOP of less than 30 mm Hg compared with eyes without a history of glaucoma, although both groups had a “normalized IOP to less than 30 mm Hg” within 30 minutes.10

In the VISION study 32% of the patients with pre-existing ocular hypertension or glaucoma developed an IOP > 35 mm Hg on at least one injection of pegaptanib.3 While most retina specialists consider IOP below 30 mm Hg as the “safe zone”, this may not be true for patients with glaucoma. Whether IOP decline in glaucoma patients continues at the same rate below 30 mm Hg, remains to be determined. Glaucoma patients may experience a slower return to normal IOP values, due to their already compromised facility of aqueous outflow.

With the increased tendency for repeated monthly injections, patients may experience transient marked elevations of IOP, and the cumulative effect of these repeated insults to the optic nerve head is still unclear. This is especially relevant in patients suffering from glaucoma, where the optic nerve is already damaged to some extent. Furthermore, in cases of normal tension glaucoma or eyes with a significantly compromised optic nerve head, even minor or moderate levels of repeated IOP elevation (30 mm Hg or less) may eventually cause further irreversible optic nerve damage.

TREATMENT

Acute rise of IOP following intravitreal injection of anti-VEGF often responds to topical pressure-reducing agents. Occasionally systemic carbonic anhydrase inhibitors or hyperosmotics may be required. Rarely, pressure cannot be controlled medically and filtering surgery is required. Paracentesis may be advised in selected cases in the acute stage, however it is not without complications. Paracentesis is primarily reserved for cases with extreme IOP elevation, not responding to topical or systemic therapy. In the VISION study, paracentesis was required following 4.1% of intravitreal injections. All of them were performed in one investigation site. This suggests that a substantial number of patients developed significantly increased IOP, despite a minor elevation in the mean IOP of the study population. Reporting of the mean values may lead to underestimation of the extent of severely high IOP postinjection, and to disregarding necessary steps that should be taken to manage it.

Regarding patients with persistent IOP elevation, 10 of the 11 reported cases were controlled with medical therapy, only one required trabeculectomy.11-13

As the prevalence of both glaucoma and AMD increase with age, there is a considerable chance of having glaucoma in patients who develop CNV in eyes with age-related macular degeneration. Better determination of the patients’ glaucoma status prior to injection of anti-VEGF agent is required. The issue of when to discontinue IOP monitoring after intravitreal injection remains undetermined. Several factors such as the agent injected, the patients’ age, presence of glaucoma, number of previous injections and estimation of facility of outflow may all affect this decision. Prospective studies in patients with glaucoma and CNV undergoing intravitreal injections of anti-VEGF agents may help to clear this issue. At present a combined disciplinary approach of both glaucoma and retina specialists is advised for glaucoma patients who require anti-VEGF intravitreal injections.

REFERENCES

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I live in that solitude which is painful in youth, but delicious in the years of maturity.
—Albert Einstein