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Ophthalmic Technology Assessment

The Effect of Anti-Vascular Endothelial Growth Factor Agents on Intraocular Pressure and Glaucoma

A Report by the American Academy of Ophthalmology

Ambika Hoguet, MD,[1] Philip P. Chen, MD,[2] Anna K. Junk, MD,[3,4] Prithvi Mruthyunjaya, MD, MHS,[5] Kouros Nouri-Mahdavi, MD, MS,[6] Sunita Radhakrishnan, MD,[7] Hana L. Takusagawa, MD,[8] Teresa C. Chen, MD[9]

Purpose: To assess the effect of intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents on immediate and long-term intraocular pressure (IOP) elevation and glaucoma.

Methods: Literature searches of the PubMed and Cochrane databases, last conducted in April 2018, yielded 253 unique citations. Of these, 41 met the inclusion criteria and were rated according to the strength of evidence. Two articles were rated level I, 17 were rated level II, and 15 were rated level III; an additional 7 were excluded because of poor study design and lack of relevance to the topic under evaluation.

Results: The studies that reported on short-term IOP elevation (i.e., between 0 and 60 minutes) showed that an immediate increase in IOP is seen in all patients when measured between 0 and 30 minutes of intravitreal injection and that the IOP elevation decreases over time. The data on long-term IOP elevation were mixed; 7 studies reported that between 4% and 15% of patients developed sustained elevation of IOP at 9 to 24 months after injection, whereas 6 studies found no long-term change in IOP from 1 to 36 months after injection. Pretreatment with glaucoma medications, anterior chamber tap, vitreous reflux, longer intervals between injections, and longer axial lengths were associated with lower IOP elevations after injection. Data were mixed on the relationship between IOP increase and the type of intravitreal injection, number of intravitreal injections, preexisting glaucoma, and globe decompression before injection. There were no data on the onset or progression of glaucoma in the studies reviewed in this assessment.

Conclusions: Intravitreal injection of anti-VEGF agents results in an immediate and transient increase in IOP. A long-term increase in IOP also may be seen, and further studies are needed to determine at-risk populations. Although there is some suggestion in the literature, there is currently insufficient data to determine the impact of intravitreal anti-VEGF injections on glaucoma progression. Although pretreatment with glaucoma medications, performing anterior chamber paracentesis, or increasing the interval between injections may reduce the impact of transient IOP elevation, the clinical significance and associated risks of these interventions are unknown. *Ophthalmology 2019;126:611-622 © 2018 by the American Academy of Ophthalmology*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Glaucoma Panel was to assess the effect of intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents on intraocular pressure (IOP) and glaucoma.

Background

The intravitreal injection of anti-VEGF has revolutionized the management of several diseases of the posterior segment that are characterized by neovascularization or macular

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edema. The anti-VEGF agents include ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA), bevacizumab (Avastin; Genentech, Inc), pegaptanib (Macugen; Bausch & Lomb Inc., Rochester, NY), and aflibercept (Eylea; Regeneron, Tarrytown, NY). They have provided significant benefit to patients with diseases such as diabetic macular edema, neovascular age-related macular degeneration, myopic choroidal neovascularization, and other pathologies characterized by retinal or choroidal neovascularization, and they have a favorable safety profile.[1] Their relationship to IOP elevation and resulting glaucoma therefore remains an important clinical question.

Several theoretical mechanisms have been proposed to describe the relationship between these agents and a resulting elevation of IOP. These include an inflammatory response,[2] a direct toxic effect of anti-VEGF agents to the trabecular meshwork (TM),[3] injury to the TM from injection of a high volume of fluid,[4] or a mechanical blockade of the TM by protein aggregates or contaminant particles.[5,6]

Because of the increasing use of anti-VEGF agents, it is important to understand the relationship among anti-VEGF treatments, IOP, and the onset or progression of glaucoma. A timely recognition of IOP elevation related to anti-VEGF injection may postpone the onset or progression of glaucoma and mitigate resulting visual loss.

Questions for Assessment

The focus of this assessment is to address the following questions: (1) What is the effect of intravitreal anti-VEGF injections on short- and long-term IOP and does it predispose patients to glaucoma? (2) What are the factors that modulate changes in IOP after intravitreal injection of anti-VEGF agents?

Description of Evidence

Literature searches conducted on April 18, 2018, in the PubMed and the Cochrane Library databases resulted in 253 articles. Articles that did not evaluate patients receiving intravitreal injections were excluded, resulting in 82 articles. The following search terms were used: *Intraocular pressure* OR *glaucoma* OR *ocular hypertension* OR *iop*; (*Pegaptanib* OR *bevacizumab* OR *ranibizumab* OR *aflibercept* OR *macugen* OR *avastin* OR *Antivascular endothelial growth factor* OR *anti-vascular endothelial growth factor* OR *anti-vegf* OR *"Vascular Endothelial Growth Factor A/antagonists and inhibitors"* [Mesh] OR *"Angiogenesis Inhibitors"* [Mesh] OR *"Receptors, Vascular Endothelial Growth Factor"* [Mesh]) AND *(Intravitreal OR intravitreal injection*)*. Search (*randomized* OR *nonrandomized* OR *RCT* OR *"cohort studies"* OR *"cohort study"* OR *"outcomes re"* OR *"case control"* OR *"case series"* OR *randomized controlled trial* OR *comparative trial* OR *review*). Filters used were *Humans*, *English*.

The titles and abstracts of these articles were reviewed by the panel, and 58 were selected for full-text review. Of these, 41 met the following inclusion criteria: (1) the study reported on original research, (2) the population consisted of at least 20 adults (aged ≥18 years) treated with anti-VEGF intravitreal injections, and (3) changes in IOP were reported before and after injection. Studies of patients who underwent intravitreal injections for neovascular glaucoma or those who also received intravitreal steroid injections were excluded from this review.

The panel methodologist (K.N.-M.) assigned a level of evidence to the articles that met the inclusion criteria based on the standardized grading system adopted by the American Academy of Ophthalmology. A level I rating was assigned to well-designed, well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort series and lower-quality randomized studies; and a level III rating was assigned to case series, case reports, and lower-quality cohort and case-control studies. Two studies were rated level I, 17 were rated level II, and 15 were rated level III. Seven of the 41 studies were excluded (4 for poor study design and 3 for lack of relevance to the topic under evaluation).

Published Results

The mean age of patients in the studies ranged from 61 to 85 years. The indication for intravitreal injection of anti-VEGF agents included neovascular age-related macular degeneration, diabetic macular edema, branch retinal vein occlusion, central retinal vein occlusion, and degenerative myopia. All references to medications are for glaucoma medications. Unless otherwise noted, standard techniques were used for intravitreal injections; 0.05 ml volume of the intravitreal agent of choice was injected via a 27-, 30-, or 32-gauge needle using a sterile technique.

Short-term Increases in Intraocular Pressure

Summary. Fourteen studies reported on the short-term pressure effects of anti-VEGF injections (Table 1). Of these, 13 were prospective and 1 was retrospective. Some studies compared intravitreal injections using standard techniques with a particular modification (e.g., Honan balloon or medications before surgery); the results of the standard techniques are summarized in this section. The median number of patients enrolled in these studies was 56 (range, 12−853), with a median of 60 injected eyes (range, 12−853). The intravitreal injections administered included bevacizumab, ranibizumab, aflibercept, and pegaptanib. In almost all cases, the mean preinjection IOP was 18 or lower; only 1 study included a small subset of patients (1.7%) who had a pretreatment IOP over 30.[7] Among the studies that reported the IOP immediately or at 1 minute after injection, 100% of patients had an increase in IOP, with reported mean postinjection IOPs ranging from 28.3 to 55.2 mmHg.[8-15] At 10 to 15 minutes after injection, the mean IOP had decreased to a range from 22.8 to 25.8 mmHg[8,13] and at 30 minutes to a mean range from 17.6 to 24.5 mmHg.[9,14,15] In those studies that measured IOP at several time intervals up to 1 hour after injection, the IOP continued to decrease over time, suggesting that the spikes in IOP after injection were transient.

Table 1. Short-term Intraocular Pressure Changes after Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents

Author, Year	Level of Evidence	N Eyes	Study Design	Method of Applanation	Mean IOP before Injection (mmHg)	Time of Initial IOP Check (Minutes after Injection)	Postinjection IOP (Mean)	Comments
Carnota-Mendez et al,[18] 2014	II	77	RCT	Perkins tonometer (Haag-Streit, Essex, UK)	14.5	1	NR	54.6% (77/141 injections) showed IOP >30 mmHg
Hong and Jee,[8] 2012	II	30	Prospective RCT	GAT (Haag-Streit)	15.93	0	42.74	
Gregori et al,[12] 2014	II	48	RCT	Tonopen (Reichert, Depew, NY)	15.9	0	41.2	
Katayama et al,[17] 2014	II	14	RCT	GAT	16.1	3	20.9	
Kim et al,[10] 2011	II	60	Prospective, nonrandomized	GAT	16.93	0	55.22	
Knip and Välimäki,[15] 2012	II	21	RCT	iCare (Raleigh, NC)	14.6	2	47.1	
Martinez-de-la-Casa et al,[20] 2012	II	49	Prospective cohort	NR	NR	NR	NR	0.4% with IOP elevation >5 mmHg
Murray et al,[9] 2014	II	12	RCT	Tonopen	15.1	0	44.5	
Pang et al,[11] 2015	II	34	Prospective, nonrandomized	GAT	14.9	0	30.8	
Singer et al,[7] 2012	II	790	Prospective cohort	NR	NR	60	NR	6.6% and 9.2% of injected patients (0% untreated) with IOP >30 mmHg
Theoulakis et al,[16] 2010	II	44	RCT	GAT	17.7	5	34.1	
Cacciamani et al,[13] 2013	III	25	Prospective case series	Tonopen	16.52	1	38.44	
Hariprasad et al,[14] 2006	III	79	Retrospective case series	NR	15.73	30	24.47	
Heier et al,[19] 2006	III	62	Case series	NR	NR	NR	NR	22.6% with transient IOP increase >10 mmHg from baseline

GAT = Goldmann Applanation Tonometry; IOP = intraocular pressure; NR = not reported; RCT = randomized controlled trial.

None of the studies included information on whether additional glaucoma medications were required.

Studies That Measured Initial Intraocular Pressure at 0 to 30 Minutes after Intravitreal Injections

Among studies that reported on short-term IOP spikes after intravitreal injections, 5 (level II evidence) prospectively evaluated IOP immediately after injection and at several time intervals after treatment.[8-12] Five additional studies, although not reporting on immediate postinjection IOP, prospectively evaluated the initial IOP in patients within 5 minutes of intravitreal injection.[13,15-17] Four of these studies were level II evidence,[15-18] and 1 study was level III.[13] The number of eyes ranged from 12 to 77 in the control arm of these studies (i.e., intravitreal injection only, without additional intervention before or after). One study used a 27-gauge needle for injections as opposed to the standard 30-gauge needle.[15]

Measurements of the mean IOP (± standard deviation) taken immediately or within 2 minutes after injection ranged from 31.1±15.2 to 55.2±14.7 mmHg.[8-13,15] In all studies, the IOP decreased when measured at subsequent time intervals: At 3 minutes, the mean IOP ranged from 20.9±2.1 to 40.4±8.2 mmHg;[8,10,17] at 5 minutes, the mean IOP ranged from 31.4±14.4 to 34.1±2.7 mmHg;[9,16] at 10 minutes, the mean IOP ranged from 24.5±11.7 to 28.3±4.2 mmHg;[8-10,16] and at 30 minutes, the mean IOP decreased to a range of 17.6±5.0 to 20.6±9.5 mmHg.[9,15,16] Further decline of IOP was measured in only 2 studies; it was reported to be 18.1±1.5 mmHg[16] at 60 minutes and 12.3±2.5 mmHg at 1 week after injection.[15] Presented as percentages, 9% to 45% of eyes had an IOP of 50 mmHg or higher immediately or within 2 minutes of injection,[11,12,15,18] 32% of eyes had an IOP of 40 mmHg[11] or higher, and 55% to 98% of eyes had an IOP of 30 mmHg or higher immediately after injection.[11,12] At 15 minutes after injection, 3% to 8% of patients had an IOP of 30 mmHg or higher.[12,15] Katayama et al[17] (level II) reported that 86% (12/14) of eyes sustained an elevated IOP above baseline and over 21 mmHg at 30 minutes (mean 4.0±4.3 mmHg above pretreatment IOP). In the studies that measured IOP at longer time points, IOP normalized in all patients between 30 minutes[18] and 1 week.[15]

Studies That Measured Initial Intraocular Pressure at 30 Minutes or Later after Intravitreal Injections

Four studies reported on IOP changes that were measured only at or after 30 minutes after intravitreal injection of an anti-VEGF agent.[7,14,19,20] Two were level II evidence,[7,20] and 2 were level III evidence.[14,19] The number of eyes enrolled in the studies ranged from 49 to 790. Most of the IOP changes were reported as percentages; only 1 study reported a mean (± standard deviation) of 24.5±2.7 mmHg IOP at 30 minutes, which represented a mean increase of 8.8±7.2 mmHg from baseline.[14]

In the remaining studies, between 8.5% and 22.5% of patients showed IOP elevations (>30 mmHg or an increase of 10 mmHg from baseline) at 30 to 60 minutes after injection.[7,14,19] Martinez-de-la-Casa et al[20] (level II) reported that 0.4% of patients had an IOP spike over 5 mmHg from baseline at 1 hour after injection; none had an IOP spike over 10 mmHg. Intraocular pressure normalized by the next measurement at 60 minutes or 1 to 7 days later.[14,19]

In summary, intravitreal injection of anti-VEGF agents generally resulted in immediate postinjection elevations of IOP that, in the majority of patients, returned to normal within a short period of time, typically within 1 hour. The long-term effects of these IOP elevations are unknown.

Long-term Elevations of Intraocular Pressure

Summary. Fourteen studies reported on long-term IOP elevation in patients who received anti-VEGF injections (Table 2). Of these, 5 were prospective and 9 were retrospective. The median number of patients enrolled in these studies was 127 (range, 30−23 776), with a median of 210 eyes (range, 30−23 776). The intravitreal injections administered included bevacizumab, ranibizumab, aflibercept, and pegaptanib. The median number of injections was 7, with a mean of 8.1. The median follow-up period was 79.8 weeks. When reported, the mean IOP before injection was 18 mmHg or lower. Eight studies reported that between 2.6% and 14.8% of patients had postinjection IOP elevations at 9 to 24 months of follow-up, according to predetermined criteria defined by the individual studies.[21-28] Six studies reported no change in IOP on follow-up that ranged from 1 to 36 months or when compared with a control group that did not receive intravitreal injections. In the studies that reported an elevation of IOP, the median and average number of patients were higher (median, 467; mean, 3756) compared with the average number of patients in studies that reported no elevation of IOP (median, 51.5; mean, 98.7). The mean and median follow-up periods were longer in the studies reporting an elevation in IOP (median, 84 weeks vs. 34 weeks; mean, 84.2 weeks vs. 54.9 weeks).[22,29-34]

Studies That Reported on Intraocular Pressure Elevation with Long-term Follow-up

Of the 8 studies that reported on IOP elevations with long-term follow-up after anti-VEGF injection, 5 were level III evidence,[21,23,25-27] 2 were level II,[22,28] and 1 was level I.[24] The number of eyes included in these studies ranged from 155 to 23 776. The definition of what qualified as an elevated IOP varied. Silva et al[28] did not provide a definition for IOP elevation; Al-Abdullah et al[21] defined IOP elevation as an increase of 6 mmHg or higher, more than 20% above baseline, or an IOP above 24 mmHg on 2 or more consecutive measurements. Likewise, Mathalone et al[27] defined IOP elevations as 22 mmHg or higher and a change from baseline of more than 6 mmHg on at least 2 consecutive visits that took place 30 or more days apart. Two additional studies reported the percentage of patients who presented with an IOP more than 5 mmHg above baseline on 2 or more consecutive visits.[24,25] Freund et al[24] reported on IOP elevation over 10 mmHg from baseline as well as on patients with an IOP above 21 mmHg. Choi

Table 2. Changes in Intraocular Pressure and Medications after Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents

Author, Year	Level of Evidence	N Eyes	Study Design	N Injections (Mean)	Method of IOP Measurement	Preinjection IOP (Mean)	Time of Postinjection IOP Check	IOP after Surgery (Mean)	Change in Medications
Freund et al,[24] 2015	I	2457	RCT	Q4 wks after 2 initial monthly injections	GAT or Tonopen, consistent for each patient	14.95	96 wks	2.2% with IOP increase >10 mmHg	6.8% started IOP-related medications
Atchison et al,[22] 2018	II	23 776	Retrospective	7.9	NR	15.3	96.8 wks	2.6% with IOP increase ≥6 mmHg and >21 mmHg	0.6% of treated eyes (vs. 0.4% of control) required laser trabeculoplasty; 0.4% (vs. <0.1% of controls) needed surgery
Boyer et al,[29] 2014	II	114	Prospective cohort	17	GAT (majority)	NR	38.5 wks	NR; IOP increases not significant compared with sham group	0.9% needed additional medications
Gado and Macky,[30] 2014	II	30	RCT	4.3	GAT	17	6 mos	16	No changes
Silva et al,[28] 2013	II	210	Prospective cohort	6.1	NR	NR	24 mos	NR; IOP increased between 1.2 and 2.5 mmHg from baseline	NR
Al-Abdullah et al,[21] 2015	III	760	Retrospective case series	5.32	GAT	17.2	8.93 mos	17.47	0.6% needed more glaucoma medications; increased total injections associated with elevated IOP
Choi et al,[23] 2011	III	155	Retrospective case series	7	Tonopen; high IOP verified with GAT	14.5	NR	15.1	5.5% required medications/surgery
Güler et al,[31] 2014	III	43	Prospective case series	1	GAT	14.32±4.25	1 mo	13.23	NR
Hoang et al,[25] 2012	III	207	Retrospective case series	20.8	GAT	NR	NR	NR; 11.6% with IOP elevation	NR
Kim et al,[26] 2014	III	724	Retrospective case series	9.5	GAT	14.1	12 mos	14.2	3 (all with glaucoma) required additional or new medications
Mathalone et al,[27] 2012	III	201	Retrospective case series	4 (median)	GAT	14.8	NR	15.5	10.4% required initiation of IOP-lowering medications, 0.5% of patients with preexisting glaucoma needed additional topical medication
Rusu et al,[32] 2014	III	53	Retrospective case series	6.6	GAT	14	173.9 wks	13.79	NR
Wehrli et al,[33] 2012	III	302	Retrospective case series	8.3	NR	NR	NR	NR; 0.017% with delayed ocular hypertension	NR
Yoganathan et al,[34] 2006	III	50	Retrospective case series	NR	NR	NR	34 wks	14.2	NR

GAT = Goldmann applanation tonometry; IOP = intraocular pressure; NR = not reported; RCT = randomized controlled trial.

et al[23] provided the percentage of patients who had an IOP above 25 mmHg.

The incidence of IOP elevation ranged from 2.6% to 14.8% depending on the study and the follow-up time period.[21-28] In a post hoc analysis of data from 2 randomized, controlled, phase II trials, Freund et al[24] (level I) reported that 10% of patients had IOP above 21 mmHg at 52 weeks after entry into the trial; this increased to 15% of patients at 96 weeks. Of these patients with elevations in IOP (who had no diagnosis of glaucoma), 4% had an IOP elevation more than 10 mmHg from baseline at 96 weeks. Atchison et al[22] (level II), in a post hoc analysis of patients using the Intelligent Research in Sight (IRIS) registry, found that 2.6% of patients who received intravitreal injections had an IOP increase of 6 mmHg or higher (to achieve a new IOP above 21 mmHg); this was compared with an IOP rise in 1.5% of untreated fellow eyes. Elevations of IOP in this study were compared with baseline IOP data (before beginning intravitreal injections) at least 1 year before the most recent injection.[22] These data suggest that, with prolonged treatments, IOP elevations may become more frequent.

Four of the studies reported on patients requiring additional glaucoma treatment because of IOP elevation; none of these included a control group of glaucoma patients who did not receive intravitreal injections. Choi et al[23] found that 5.3% (8/155) of the eyes enrolled in their study, none of whom had a previous diagnosis of glaucoma, needed additional intervention to lower IOP; 8 were placed on IOP-lowering medications, and 1 needed glaucoma surgery. Freund et al[24] found that between 6% and 8% of patients were treated with IOP-lowering medications (depending on dosage and frequency of anti-VEGF injections; overall rate 6.8%). Kim et al[26] reported that 1.1% (8/724) of patients had glaucoma at baseline. Of these, 25% (2/8) required additional medications, and 12.5% (1/8) were not treated at the time of inclusion in the study and required initiation of glaucoma therapy.[26] Hoang et al[25] reported that no medication changes were required despite reporting an IOP elevation in 11.6% (24/207) of treated patients. Although this study included 13.5% (28/207) of patients with glaucoma, the authors did not specify how many IOP elevations occurred within this subset of enrolled patients. The other studies did not report on whether additional interventions were required.

Studies That Reported No Intraocular Pressure Change on Long-term Follow-up

Although the previous studies reported on the existence of sustained IOP elevation, 6 additional studies found that there was no evidence of IOP elevation on long-term follow-up.[29-34] Of these, 2 were level II evidence[29,30] and 4 were level III.[32-34] The number of eyes included ranged from 40 to 302. Wehrli et al[33] defined an IOP elevation as an IOP of 22 mmHg or above at 2 consecutive visits, with an increase from baseline of more than 6 mmHg or an IOP elevation of more than 26 mmHg at 1 visit. The remaining studies did not provide a definition of elevated IOP.

In a post hoc analysis on all IOP measurements from the first 2 years of the Vascular Endothelial Growth Factor Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N) study, Boyer et al[29] reported that 24.5% of treated patients (vs. 21.5% of untreated patients) had at least 1 measurement of IOP above 22 mmHg over a mean follow-up period of 38.5 weeks; these changes in IOP were not statistically significant when compared with the sham group ($P = 0.63$). Among those subjects with sustained high IOP, 10.7% had a history of glaucoma.[29] In a retrospective review, Wehrli et al[33] similarly reported IOP elevations, yet these were not statistically significant compared with a control group (incidence of elevated IOP was seen in 0.51% in injected vs. 1% noninjected patients per eye year).

Four other authors reported no change in IOP on follow-up in their study population. Of these, 2 had a relatively short follow-up period: Gado and Macky[30] reported a maximum IOP of 21 mmHg in treated patients over a 3- to 6-month follow-up;[30] Güler et al[31] reported a mean IOP of 13.2±4.4 mmHg at 1-month follow-up. Two additional studies did not find IOP elevations over a longer follow-up period: Yoganathan et al[34] reported that no cases of elevated IOP were noticed in their patient sample after a median of 34 weeks, and Rusu et al[32] reported no change in mean IOP over an average follow-up period of 173.9 weeks.

In summary, the results show that although data on the possibility for intravitreal injections to cause long-term IOP elevation are mixed, the studies remain limited by variability in study design and definitions of IOP elevation. Although the follow-up period varied, the mean and median number of patients enrolled in studies that reported an IOP elevation were higher compared with the studies that reported no elevation of IOP.

Modulating Factors

Summary. Pretreatment with brimonidine, brimonidine/timolol, or acetazolamide was shown to help lower IOP, as was an anterior chamber tap after an intravitreal injection.[9,15-18,35] In addition, the presence of vitreous reflux, when observed, contributed to a lower IOP after injection.[11,18,36] A shorter interval between injections may be related to IOP increase.[27]

Data on the relationship between IOP and the type of intravitreal injection,[21,22,32,33] the number of intravitreal injections,[15,22,23,25,37,38] preexisting glaucoma,[12,22,26,29,33] axial length,[13,36] and globe decompression before injection[8,10,12] are mixed. Table 3 list the factors that affect IOP after intravitreal injection.

Prophylactic Medications or Anterior Chamber Tap

To determine whether treatment to lower IOP administered before injecting an anti-VEGF agent helps to lower post-injection IOP elevations, 5 studies randomized patients to receive brimonidine/timolol,[16-18] oral acetazolamide,[5,9,18] or anterior chamber tap before surgery.[15,18] Although these pretreatments helped reduce IOP spikes that were otherwise seen after an intravitreal injection, the clinical impact of

Table 3. Summary of Factors That Effect Intraocular Pressure after Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents

Modifying Factors	Level of Evidence	Notes
Factors that reduce IOP elevation after injection:		
Pretreatment with medications:[9,15-18] Brimonidine/timolol Brimonidine Acetazolamide	II: 3 studies	Postinjection IOP was reduced compared with patients who were not pretreated with medications, but pretreatment did not prevent the occurrence of an IOP spike.
Anterior chamber tap[15,17,35]	I: 1 study II: 2 studies	Reduction in IOP spikes was seen in patients who received a paracentesis compared with patients who did not. A greater decrease of RNFL thickness was seen in control patients versus those who received an anterior chamber tap after injection.[35]
Vitreous reflux[11,18,36]	II: 3 studies	Larger-bore needle (30 vs. 32 gauge) and straight scleral injection of the anti-VEGF agent (vs. tunneled in sclera before injection) reduced immediate postinjection IOP.
Factors that increase IOP elevation postinjection:		
Shorter interval between injections[27]	III: 1 study	A greater IOP elevation was seen when the interval between injections was <8 wks.
Factors with mixed evidence relating to IOP postinjection:		
Shorter axial length/smaller anterior chamber depth[13,39]	II:1 study III: 1 study	Shorter axial length was associated with higher IOP in 1 study.[13] One study showed no relationship with axial length but showed that a smaller anterior chamber depth was related to a higher IOP after injection.[39]
Type of intravitreal injection[21,22,32,33]	II: 1 study III: 3 studies	There was a significant IOP increase compared with control with bevacizumab and ranibizumab, not with aflibercept. There was no difference between ranibizumab and bevacizumab. Patients previously treated with ranibizumab or bevacizumab had lower IOP on switching to aflibercept.
Number of intravitreal injections[12,23,25]	III: 4 studies II: 2 studies	Mean number of injections was higher in patients with IOP elevation in 4 studies;[22,25,35,38] 2 studies saw no association.[15,23]
Preexisting glaucoma[12,22,26,29,33]	II: 3 studies III: 2 studies	Three studies showed a relationship with a history of glaucoma and IOP elevations after injection;[22,26,29] 2 studies showed no relationship.[12,33]
Globe decompression before injection[8,13,15]	II	Cotton swab for anesthesia (compared with viscous lidocaine gel) reduced postinjection IOP spike;[12] use of Honan balloon before injection showed a reduced IOP spike in 1 study[10] but not in another.[8]

IOP = intraocular pressure; RNFL = retinal nerve fiber layer; VEGF = vascular endothelial growth factor.

these interventions (e.g., the effect on long-term IOP and prevention of glaucoma progression) were not studied.

Carnota-Méndez et al[18] (level II) randomized patients to receive brimonidine/timolol versus no treatment 5 minutes before injection and found that the use of brimonidine/timolol reduced IOP by approximately 3 mmHg but did not prevent an IOP spike. Likewise, Theoulakis et al[16] (level II) randomized 88 normotensive patients to receive brimonidine/timolol (on the day before injection at 8 AM, 8 PM, and immediately after injection) versus no treatment. They found that IOP was significantly lower in the treated group compared with the control group at 5, 10, 15, 30, and 60 minutes after injection. Ninety-one percent of control patients (40/44) had an IOP above 30 mmHg at 5 minutes compared with 18% (8/44) in the treatment group. At 10 minutes, 6.8% (3/44) of patients in the control group and no patients in the treatment group had an IOP above 30 mmHg.

Murray et al[9] (level II) prospectively randomized 24 patients to receive prophylactic oral acetazolamide given 60 to 90 minutes before injection or no treatment; they found no difference between the 2 groups in the reduction of IOP after injection. (The IOP was checked at an unknown time point within 30 minutes of injection.) Although the immediate (<30 minutes) postinjection IOP was not affected, IOP was lower in the treated group at 30 minutes (20.6 vs. 15.8 mmHg, $P = 0.013$).[9]

Katayama et al[17] (level II) randomized 56 patients receiving intravitreal bevacizumab to be given brimonidine drops (90 minutes before injection), oral acetazolamide (250 mg 90 minutes before injection), anterior chamber paracentesis, or no treatment immediately after injection. They reported no difference in IOP elevation between controls and those who received brimonidine; however, the IOP increase was less with acetazolamide and anterior chamber paracentesis groups at 3 and 10 minutes. Pretreatment with any of these measures helped reduce or minimize IOP spikes at 30 minutes compared with the control group ($P < 0.05$ for comparison of all 3 treatment groups with the control group), and no adverse events were noted.[17] Knip and Välimäki[15] (level II) reported the results of another randomized prospective study that measured IOP after anterior chamber paracentesis. The authors found that an IOP spike of 50 mmHg or above at 2 minutes after pegaptanib injection occurred in none of the eyes that received an anterior chamber paracentesis compared with

45% of eyes that did not. No cases of endophthalmitis were reported in the 41 patients treated over a 10-month period.[15]

Soheilian et al[35] (level I) prospectively compared 90 eyes with or without anterior chamber paracentesis and measured IOP as well as changes on OCT retinal nerve fiber layer (RNFL) at several time points between 2 minutes and 30 minutes after injective. They found that the mean increase in IOP at 2 minutes after injection was 26.4±5.7 mmHg in the control group compared with a decrease in IOP of 1.3±2.4 mmHg in the group that received an anterior chamber paracentesis. This was the only study that examined the effect of this intervention on the optic nerve: at 3 months, an average RNFL thickness change of −2±2 μm from baseline was seen in the control group compared with 0±2 μm in group that received a paracentesis, indicating that RNFL thickness decreased more in the untreated group ($P < 0.001$). No cases of hypotony, inflammation, or endophthalmitis were reported.[35]

Vitreous Reflux

Three authors reported that the presence of vitreous reflux was associated with lower postinjection IOP. Carnota-Méndez et al[18] (level II) reported that the observation of unintentional vitreous reflux, seen in 22.7% of injections (32/141), significantly reduced the incidence of a postinjection IOP spike at 1 minute ($P < 0.001$). Pang et al[11] (level II) found that postinjection IOP was higher in the group injected with a 32-gauge needle compared with a 30-gauge needle (41.4 vs. 30.8 mmHg, $P = 0.003$). Less vitreous reflux was observed with the 32-gauge compared with the 30-gauge needle after injection (18 eyes with reflux in the 30-gauge group vs. 4 eyes with reflux in the 32-gauge group).

Knecht et al[36] (level II) prospectively randomized 60 patients receiving intravitreal ranibizumab or intravitreal bevacizumab injections to receive a tunneled versus straight scleral intravitreal injection. They found that with a tunneled injection, 82% had an immediate IOP elevation above 30 mmHg (mean IOP, 36.0±8.1 mmHg) compared with 59% with a straight injection (mean IOP, 30.2±12.1 mmHg), but there was no difference at 5 minutes after injection. More vitreous reflux was noted in the straight group (66.7%) compared with the tunneled group (26.7%), and IOP change was less in patients with reflux than those without reflux ($P < 0.0001$).[36]

Type of Intravitreal Anti-Vascular Endothelial Growth Factor Agent Used

Four studies analyzed the effect of the type of intravitreal agent used on IOP. In a post hoc analysis of data from the IRIS registry, Atchison et al[22] (level II) found that a clinically significant increase in IOP (described as an IOP elevation above 6 mmHg for an overall IOP above 21 mmHg) at a mean follow-up of 678 days was seen in 1.9%, 2.8%, and 2.8% of patients treated with aflibercept, ranibizumab, and bevacizumab, respectively. This increase in IOP was higher than in untreated fellow eyes in the bevacizumab and ranibizumab group but not the aflibercept group.[22] Al-Abdullah et al[21] (level III) measured postinjection IOP elevation in patients receiving ranibizumab, bevacizumab, or ranibizumab plus bevacizumab. They found that none of the eyes (0/4) in the ranibizumab group had persistent IOP elevation, whereas the rate of persistent IOP elevation in the bevacizumab only group was 4.8% (32/672 eyes) and that of the ranibizumab plus bevacizumab group was 14.3% (12/84 eyes). However, the number of eyes that received only ranibizumab was too small to draw meaningful conclusions about IOP elevation and the type of anti-VEGF agent.[21] In a retrospective chart review, Rusu et al[32] (level III) found that the IOP was lower in patients switched to aflibercept after previous treatments with ranibizumab or bevacizumab ($P = 0.049$). They compared the first, last, and mean IOP for the period of treatment with aflibercept and found that the IOP was lower in patients switched to aflibercept after previous treatments with ranibizumab or bevacizumab. However, each eye served as its own control, which confounds the results of the study, because these patients had received an intravitreal injection with a different agent in the past.[32] Wehrli et al[33] (level III) showed that the rate of delayed ocular hypertension did not differ in eyes injected with bevacizumab only or ranibizumab only.

Number of Anti-Vascular Endothelial Growth Factor Injections

The data on whether the number of injections given is correlated with IOP are mixed. Atchison et al[22] (level II) found that of the 413 patients who received at least 25 injections over a period of 1 or more years, an increased range in pressure rise (from 0% to 3.2%) was seen compared with fellow untreated eyes. Hoang et al[25] (level III) found that the mean number of injections was higher in those with IOP elevation greater than 5 mmHg compared with those who had an IOP elevation less than 5 mmHg (i.e., 24.4 injections; range, 9−39 vs. 20.4 injections; range, 3−48). They reported increased odds of elevated IOPs among patients receiving 29 or more injections compared with 12 or fewer injections over an average follow-up of 148.6 weeks.[25] Likewise, Moraru et al[37] (level III) retrospectively evaluated 58 eyes that received intravitreal injections; they reported a 2.1-mmHg higher IOP in patients who received more than 6 injections at the 1-year follow-up compared with an IOP elevation of 0.9 mmHg in patients who received fewer than 6 injections. In another retrospective study, Vo Kim et al[38] (level III) reported that in eyes with an IOP elevation of 6 mmHg or above at a mean follow-up of 13.8 months, the number of injections was higher (10.2 injections in eyes with an IOP change of ≥6 mmHg vs. 6 injections in eyes with an IOP change of <6 mmHg; $P = 0.0004$).

However, Knip and Välimäki[15] (level II) did not find any association between the number of injections and IOP in 24 patients who underwent multiple injections (2−3 over 10 months). In addition, Choi et al[23] (level III) found no relationship between frequency of injections and progressive change in IOP over a 300-day interval, nor

was there a relationship between the total injection number and any gradual IOP elevation.

Shorter Interval between Injections

Mathalone et al[27] (level III) reported that the interval between injections in eyes with a sustained IOP elevation was shorter than in eyes without a sustained IOP elevation ($P = 0.01$); in addition, the prevalence of IOP elevation was higher when the interval between injections was less than 8 weeks compared with over 8 or more weeks ($P = 0.009$).[27]

Axial Length/Chamber Depth

Cacciamani et al[13] (level III) found a strong inverse correlation between axial length and IOP rise at 1 minute ($R^2 = 0.752$; $P < 0.001$) and 15 minutes ($R^2 = 0.559$; $P < 0.001$) in 25 patients who received intravitreal injections. Patients with shorter axial lengths appeared to have a higher postinjection IOP rise. All eyes were phakic, and anterior chamber depth or central corneal thickness measurements were not provided in this study.[13]

On the other hand, in a prospective study of 21 patients, Wen et al[39] (level II) did not find a correlation between axial length and postinjection IOP elevation. However, in the subset of patients who were phakic (52%), a smaller anterior chamber depth was associated with a greater elevation of IOP after injection ($R^2 = 0.53$, $P = 0.01$). In addition, narrowing of the temporal anterior chamber angle was apparent after anti-VEGF injection, which may have been associated with clinically significant IOP elevations.[39]

History of Glaucoma

Most of the studies included in this assessment excluded patients with a history of glaucoma or elevated IOP. Of the studies that included these patients in their analysis, the data on whether a history of glaucoma was a significant risk factor for IOP elevation were mixed and limited by sample size and study design. Boyer et al[29] (level II) showed that a history of glaucoma was more common in patients with an IOP above 22 mmHg at 39 weeks compared with those who did not have this history. Likewise, Kim et al[26] (level III) found that a history of glaucoma ($P = 0.001$) and a low baseline IOP ($P = 0.040$) were significant risk factors for IOP elevation after multiple anti-VEGF injections. Atchison et al[22] reported that 3 times more patients who had a significant IOP rise after intravitreal injections had a preexisting diagnosis of glaucoma.

This is in contrast to findings by Gregori et al[12] (level II). They reported on 48 patients receiving an intravitreal injection of ranibizumab; 5 of them had preexisting glaucoma. All eyes with glaucoma were controlled on drops (the number of drops used was not reported), and there was no statistically significant difference in IOP before or immediately after injection in these patients.[12] Wehrli et al[33] (level III) found that in 32 glaucoma patients receiving injections (vs. 270 nonglaucomatous patients), glaucoma eyes did not show a difference in IOP based on the anti-VEGF drug used.

Globe Decompression

Gregori et al[12] (level II) reported on 66 eyes of 48 patients randomized to receive either viscous lidocaine gel or swab soaked in liquid 4% lidocaine placed in the inferotemporal quadrant for anesthesia before intravitreal injection. Immediately after the injection, the swab group had a mean IOP after surgery of 41.2 compared with a mean IOP after surgery of 48.8 mmHg in the gel group ($P = 0.001$). The authors suggested that decompressing the eye with cotton swabs can reduce IOP spikes after the injection.[12]

Kim and Jee[10] (level II), who used a beveled scleral tunnel for injections in 30 eyes, reported on the effect of using a Honan balloon. The mean IOP with the use of a balloon was lower than the IOP without the balloon immediately (43.1±12.3 vs. 55.2±14.7) and 10 minutes after injection (22.8±3.8 vs. 28.3±4.2). However, in a similar study assessing the postinjection IOP of bevacizumab in 60 eyes, Hong and Jee[8] (level II) found no difference in postinjection IOP when a Honan balloon was used for 10 minutes before intravitreal injection.

Long-term Effects of Intravitreal Injections on Glaucoma

The majority of studies listed in this article do not report on the long-term effects of increased IOP on glaucoma. However, there is preliminary evidence that progressive RNFL thinning occurs in eyes treated with intravitreal injections[20] and that a higher number of intravitreal injections is associated with the need for glaucoma surgery.[40]

In a prospective cohort study with a control group, Martinez-de-la-Casa et al[20] (level II) reported on the effects of intravitreal ranibizumab therapy on RNFL thickness in patients with no history of glaucoma or ocular hypertension. Baseline RNFL thickness was 105±12.2 μm in the treatment group compared with 101.8±11.6 μm in the control group. At the end of follow-up (1 year mean, 4.8±1.6 injections per eye), average RNFL thickness in the treatment group was 100.2±11.0 μm; this was a significant change from baseline ($P < 0.0001$). No difference was found in the control group (RNFL thickness of 100.5±10.8 at 1 year, $P = 0.0477$). Thinning of the RNFL was not related to macular thickness.[20]

The aim of this Ophthalmic Technology Assessment is to evaluate the relationship among intravitreal anti-VEGF agents, IOP, and glaucoma in the existing literature. In general, the studies show that short-term elevations in IOP are observed after the injection of an anti-VEGF agent, but the long-term consequences are unknown. Thinning of the RNFL is also observed with injections, but the effect of this on progressive disease and the visual field is unknown. The results presented in this Ophthalmic Technology Assessment are limited by the quality of the studies that have addressed these relationships.

Of the 34 articles analyzed, the majority were level II (50%) and level III (44%) evidence. Most of the studies

included patients without glaucoma, involved a small number of patients, and had limited follow-up. In addition, although in some studies IOP measurements were taken twice, in the majority of studies IOP measurements were taken only once (81.4%), and most but not all measurements were made using Goldmann applanation tonometry (68%). Data from tests that would indicate the onset or progression of glaucoma, including visual fields, RNFL thickness with OCT, or disc photos, were evaluated in only 1 study, which measured RNFL changes after intravitreal injections.[20] Although the studies that reported on short-term (i.e., within 60 minutes) IOP changes after intravitreal injections varied in design, they showed that intravitreal injection of anti-VEGF agents uniformly led to an elevated IOP in the treated eye immediately after injection. Most studies found that the initial IOP elevation diminished if measured 1 hour after injection. The long-term effects of these transient postinjection IOP changes remain unknown, however, because data on the incidence of glaucoma in these patients were not reported.

Some studies found that repeated intravitreal injections were associated with long-term elevations of IOP. Retrospective data from the IRIS registry provide the most compelling evidence for the presence of long-term IOP elevations after intravitreal injections.[22] However, it is difficult to compare the results from many of the studies that report on long-term IOP elevations: Often there was no control population, varying definitions of IOP elevation were used, and the conclusions depended on the specific time point at which IOP was measured after injection of an anti-VEGF agent. For example, in most studies, the IOP was measured before and after an intravitreal injection but not in between visits or at regular intervals after cessation of injections. In addition, these studies did not include ancillary methods of assessing the onset and progress of glaucoma, such as visual field testing, OCT RNFL thickness measurement, or optic nerve analysis.

Several factors have been suggested as modulating the effect of anti-VEGF agents on IOP in patients. Pretreatment with medications such as brimonidine or acetazolamide, as well as anterior chamber tap, did seem to blunt a postinjection IOP spike; however, whether the level of IOP lowering is helpful in ultimately preventing glaucoma is unknown. Although anterior chamber paracentesis may bear an additional risk of endophthalmitis,[41] this was not reported in the 3 studies that evaluated this intervention.[15,17,35] There was no consistency found in the results from studies of the relationship between IOP and the type of intravitreal injection, the number of intravitreal injections, preexisting glaucoma, and globe decompression before injection. Although vitreous reflux does mitigate an IOP spike, it may also be related to loss of injected medication from the vitreous cavity and does not seem to be a clinically useful modification. There is likely an additional cost associated with implementing some of these interventions in a clinical practice; however, this was not evaluated in any of the studies included in this assessment.

Only 2 studies reported on the long-term effects of multiple injections on glaucoma.[20,40] From these, there is a possibility that RNFL thickness decreases and the odds of receiving glaucoma surgery may increase in patients who receive multiple injections, but additional studies are needed.

Future Research

Initial evidence suggests that there is a strong relationship between intravitreal injections and an immediate elevation of IOP. However, the association with longer-term increased IOP is less certain. Future research is needed to quantify the risk of long-term IOP elevation and the potential association of short- or long-term IOP elevations with incident glaucoma or progression of preexisting glaucoma. Although some interventions (e.g., pretreatment with IOP-lowering medications) may mitigate an IOP spike after injection, the effect of this on an individual's risk of glaucoma or glaucoma progression is unknown. In the future, studies should examine the long-term effects of anti-VEGF injections on measurements related to glaucomatous disease, such as OCT RNFL thickness and visual field loss progression, and they should include evaluations of the optic disc. The risks of progressive damage due to glaucoma, if established, must also be carefully weighed against the benefits of intravitreal injections in at-risk patients. Strategies for identifying patients at risk for glaucoma should also be investigated.

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[1] Ophthalmic Consultants of Boston, Boston, Massachusetts.
[2] Department of Ophthalmology, University of Washington, Seattle, Washington.
[3] Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida.
[4] Miami Veterans Affairs Healthcare System, Miami, Florida.
[5] Byers Eye Institute, Stanford University, Palo Alto, California.
[6] Stein Eye Institute, Los Angeles, California.
[7] Glaucoma Center of San Francisco, Glaucoma Research and Education Group, San Francisco, California.
[8] The Eye Center, Eugene, Oregon, and Casey Eye Institute, Oregon Health & Sciences University, Portland, Oregon.
[9] Harvard Medical School, Department of Ophthalmology, Massachusetts Eye & Ear Infirmary, Glaucoma Service, Boston, Massachusetts.

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Author Contributions:

Conception and design: Hoguet, Mruthyunjaya, P.P. Chen, Junk, Nouri-Mahdavi, Radhakrishnan, Takusagawa, T.C. Chen

Analysis and interpretation: Hoguet, Mruthyunjaya, P.P. Chen, Junk, Nouri-Mahdavi, Radhakrishnan, Takusagawa, T.C. Chen

Data collection: Hoguet, Mruthyunjaya, P.P. Chen, Junk, Nouri-Mahdavi, Radhakrishnan, Takusagawa, T.C. Chen

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Overall responsibility: Hoguet, Mruthyunjaya, P.P. Chen, Junk, Nouri-Mahdavi, Radhakrishnan, Takusagawa, T.C. Chen

Abbreviations and Acronyms:
IOP = intraocular pressure; **IRIS** = Intelligent Research in Sight; **RNFL** = retinal nerve fiber layer; **TM** = trabecular meshwork; **VEGF** = vascular endothelial growth factor.

Correspondence:
Ali Al-Rajhi, PhD, MPH, American Academy of Ophthalmology, Quality and Data Science, P.O. Box 7424, San Francisco, CA 94120-7424. E-mail: aalrajhi@aao.org.