

# Persistent Elevation of Intraocular Pressure Following Intravitreal Injection of Bevacizumab

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**ABSTRACT:** **Background:** The number of patients treated with intravitreal injections has increased significantly over the past few years, mainly following the introduction of anti-vascular endothelial growth factor antibody intraocular drugs. Bevacizumab is mostly used in this group of medications.

**Objectives:** To describe persistent elevation of intraocular pressure (IOP) following intravitreal injection of bevacizumab.

**Methods:** We reviewed consecutive cases of persistent IOP elevation after intravitreal bevacizumab injection for exudative age-related macular degeneration (AMD). A total of 424 patients (528 eyes) met the inclusion criteria and received 1796 intravitreal injections of bevacizumab. Persistent IOP elevation was found in 19 eyes (3.6%, 19/528) of 18 patients (4.2%, 18/424) with IOP elevated 30–70 mmHg 3–30 days after injection.

**Results:** Mean IOP was 42.6 mmHg (range 30–70); IOP elevations occurred after an average of 7.8 injections of bevacizumab (range 3–13). Injected eyes (19/528) had a significantly higher incidence of elevated IOP than uninjected eyes (fellow eyes), 1/328,  $P < 0.001$ .

**Conclusions:** Like other anti-vascular endothelial growth factor (VEGF) substances reported in a few recent studies, intravitreal injection of bevacizumab for neovascular AMD may be associated with persistent IOP elevation. Providers should be aware that significant IOP elevation might occur after repeated treatments.

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**KEY WORDS:** age-related macular degeneration (AMD), avastin, bevacizumab, glaucoma, intraocular pressure (IOP), intravitreal injection, anti-vascular endothelial growth factor (VEGF)

The number of patients treated with intravitreal injections has increased significantly over the past few years, mainly following the introduction of new intraocular medications for age-related macular degeneration such as pegaptanib [1], ranibizumab [2] and bevacizumab [3]. An acute short-term intraocular pressure elevation is commonly measured immediately after intravitreal injection [4]. This elevation is related

to the increased intraocular volume following the injection. The volume of the vitreous cavity in the human eye is approximately 4 ml, and the volume of medication injected into the vitreous ranges from 0.05 to 0.1 ml. Therefore, depending on the volume infused, the increase in fluid volume within the vitreous cavity is approximately 1.25%–2.5%. In clinical practice this frequently translates into short-term elevation of IOP [5].

Patients undergoing intravitreal injection of triamcinolone acetonide with no vitreous reflux were found to be at risk of short-term elevated IOP that rapidly normalized over 30 minutes [5]. Clinical trials for currently registered AMD drugs monitored patients for IOP changes for 1 hour after the intravitreal injection. Increased IOP was measured during the first 60 minutes after injection of ranibizumab; however, IOP measured at 60 minutes was only 2–3 mmHg higher than the reported baseline [2]. Similarly, intravitreal injection of pegaptanib caused a mild temporary IOP elevation immediately after injection, with IOP returning close to baseline levels soon after. Some eyes experienced a post-injection IOP elevation greater than 30 mmHg and the IOP returned to baseline within 5 to 7 days [6].

Bevacizumab, a recombinant humanized monoclonal anti-vascular endothelial growth factor antibody originally developed for intravenous therapy for metastatic cancer, is now being used for the treatment of AMD. A recently published study by the CATT research group compared ranibizumab to bevacizumab. The reported rates of serious adverse events were low after anti-VEGF injections [7]. Several small studies reported short-term transient IOP changes following intravitreal injection of bevacizumab. Almost all patients' IOP returned to a safe range ( $< 25$  mmHg) within 30 minutes, although elevated IOP 30 minutes after injection did occur, but rarely [8,9].

Persistent IOP elevation following intraocular injection might occur and is related to the pharmacologic properties of the medication. Intravitreal injection of triamcinolone acetonide induces structural changes in the trabecular meshwork, such as induction of extracellular matrix and deposition of fine fibrils. These changes contribute to obstruction of

IOP = intraocular pressure  
AMD = age-related macular degeneration  
VEGF = vascular endothelial growth factor

fluid outflow and consequent high rate of elevated IOP and secondary glaucoma [10,11].

In this retrospective study we examined whether intravitreal bevacizumab was associated with elevated IOP in a large series of patients with AMD, and assessed the association between the number of injections received and the prevalence of persistent IOP elevation. Demonstrating this phenomenon might further raise awareness of this possible risk factor.

## PATIENTS AND METHODS

We reviewed the medical records of 549 patients who were treated in our clinic with intravitreal bevacizumab for exudative AMD between May 2008 and April 2009. This study included only eyes with AMD. Excluded were eyes with pseudo-exfoliation, ocular hypertension, glaucoma, or a history of periocular or intraocular steroid injection. All patients were required to have a long documented history of stable IOP prior to the sudden IOP elevation. Injections were performed as an office-based procedure, using povidone-iodine, sterile drape, and lid speculum as a part of pre-injection preparation. Conjunctival displacement with a cotton tip was done prior to the injection. Postoperative topical antibiotics were given for 1 week. Follow-up after each injection including IOP measurement was performed at subsequent intravitreal injection visits and as an unscheduled visit according to the patient's complaints.

This study was performed in accordance with the ethical standards of the Helsinki declaration and was approved by the institutional review board of Meir Medical Center.

## RESULTS

Between May 2008 and April 2009, 549 patients (677 eyes) received 2202 intravitreal bevacizumab injections at a single practice in Israel at a dosage of 1.25/0.05 mg/ml. A total of 424 patients (528 eyes) met the inclusion criteria and received 1796 intravitreal injections of bevacizumab. Of these injections, 24 eyes of 23 patients were associated with IOP elevation of 24–70 mmHg.

To further strengthen the assumption that the IOP elevation was caused by the intraocular injection, we included in our study eyes that had an IOP above 29 mmHg. We had 19/528 eyes (3.6%) among 18/424 patients (4.2%) that met this criterion and were associated with IOP elevation between 30 and 70 mmHg measured 3–30 days after the intraocular injection of bevacizumab. The patients' demographic and clinical information are listed in Table 1. We found one patient, who had IOP elevation (36 mmHg) 1 week after injection to the fellow eye (not treated with intravitreal injections), with no history of ocular hypertension, glaucoma or pseudo-exfoliation. We found a statistically significant difference in the incidence of

elevated IOP between the uninjected eyes (fellow eyes), 1/328, and the injected eyes, 19/528 ( $P < 0.001$ ). Mean peak IOP was 42.6 mmHg (range 30–70), and all patients had an open angle. IOP elevation occurred after an average of 7.8 prior injections of bevacizumab (range 3–13) [Table 1].

IOP elevations were treated with standard of care medications. In all but one eye this treatment resulted in normalization of the IOP to less than 21 mmHg. One patient required a trabeculectomy to gain normal IOP. In eyes that required additional bevacizumab treatments, the IOP before the next injection was in the normal range, but elevation of IOP recurred with maximal pressure values similar to those measured in the previous episode, even though some patients continued treatment with IOP-lowering agents.

## DISCUSSION

We report a series of 19 eyes with IOP levels ranging from 30 to 70 mmHg, measured 3–30 days after intravitreal bevacizumab, in a single clinical practice in Israel. This series suggests that persistent IOP elevation might be a complication of intravitreal bevacizumab. To strengthen the assumption that the elevated IOP was caused by the intraocular bevacizumab injection, we included in our study only eyes that had IOP above 29 mmHg. We found only one fellow eye 1/328 (not treated with intravitreal injections) that had IOP above the normal range (36 mmHg) in a patient with no history of glaucoma, ocular hypertension or pseudo-exfoliation. We speculate that the IOP rise in the fellow eye without injection is a first sign of primary ocular hypertension. We found a statistically significant difference in the incidence of elevated IOP between the uninjected eyes (fellow eyes) and the injected eyes ( $P < 0.001$ ).

The mechanism by which intraocular bevacizumab might cause persistent IOP elevation is not clear; however, we suggest one hypothesis: IOP elevation may be triggered by an inflammatory process. In patients with anterior uveitis, inflammatory cells may occlude the trabecular meshwork and obstruct aqueous flow. Such a mechanism was described in patients with herpes simplex uveitis [12]. As bevacizumab is a full-length antibody, it has a crystallizable fragment (Fc) portion. The Fc fragment is involved in the binding of immune molecules such as complement factors. Bevacizumab, therefore, has the potential to trigger an immune response, leading to complement-mediated cytotoxicity. Although one should expect to see a concomitant inflammatory reaction and there was no inflammatory reaction in any of the eyes in our study, we cannot rule out the possibility of small particles (immunocomplexes) occluding the trabecular meshwork and obstructing aqueous flow. Perhaps after each injection more and more immunocomplexes accumulate, aggravating the obstruction of aqueous flow. Supporting this idea is the fact that symptoms appeared

**Table 1.** Demographics and clinical presentation of 18 patients with persistent IOP > 29 mmHg after intravitreal injection of bevacizumab for AMD

Patient no.	Age (yr)	Gender	Eye	Lens status	No. of avastin injections prior to IOP elevation	Baseline IOP of case eye (mmHg)	Highest IOP of case eye (mmHg)	Presenting symptoms
1	83	Male	Left	Phakia	3	17	33	None
2	80	Female	Left	Pseudophakia	11	18	50	Deterioration of vision, headache
3	88	Male	Left	Phakia	7	16	35	None
4	78	Female	Left	Phakia	8	18	42	Headaches, pain around left eye
5	77	Male	Right	Pseudophakia	8	20	48	None
6	91	Male	Right	Pseudophakia	13	10	42	None
7	69	Male	Right	Phakia	10	13	36	None
8	82	Female	Right	Phakia	6	19	48	None
8	82	Female	Left	Phakia	7	20	70	Deterioration of vision, left eye pain radiating to the head
9	77	Male	Right	Phakia	9	19	35	None
10	73	Female	Left	Phakia	3	16	43	None
11	93	Male	Right	Pseudophakia	7	16	42	None
12	73	Female	Right	Phakia	3	20	30	None
13	74	Male	Right	Phakia	5	19	40	None
14	91	Female	Right	Pseudophakia	10	18	50	None
15	86	Female	Left	Phakia	10	20	42	Decreased vision
16	80	Male	Left	Pseudophakia	11	12	50	None
17	77	Male	Right	Phakia	10	13	38	None
18	86	Female	Right	Pseudophakia	8	20	35	None

only a few days after the intravitreal injection, and the fact that the patients in our series were all treated with bevacizumab several times before the persistent IOP elevation occurred.

From this small case series it seems that intraocular bevacizumab may cause a persistent elevation in IOP after multiple injections. In our study the elevated IOP occurred after an average of 7.8 injections of bevacizumab. We found a few reports regarding IOP measurement after repeated intraocular bevacizumab injections. Lee et al. [13] measured intraocular pressure before, and 30 minutes, 1 day, 1 week, 3 weeks and then every month after the bevacizumab injection and found no IOP elevation. However, the study included only 14 patients, most of whom received two intravitreal bevacizumab injections in the same eye over an average interval of 2 months. The remaining patients had only one injection or one in each eye. Good et al. [14] reported on patients with AMD who received single or multiple injections of anti-VEGF agents, both bevacizumab and ranibizumab. In the bevacizumab subgroup, they found that 9.9% developed increased IOP, while 3.1% of those who received ranibizumab experienced increased IOP. This recently published study adds to several case series reports describing sustained intraocular pressure elevation following recurrent intravitreal injections of bevacizumab [14]. Six cases were described by Kahook and team [15], and a case of acute

angle-closure glaucoma complicating an intravitreal injection of bevacizumab was described by Semoun et al. [16].

Three articles with the same conclusion as our own were recently published. Tseng et al. [17] found 25 eyes of 23 patients with neovascular AMD who had increased IOP while receiving interval doses of intravitreal ranibizumab and/or bevacizumab. Choi and collaborators [18] described 5.5% of eyes that developed sustained elevated IOP after anti-VEGF injections requiring glaucoma medication or surgery. Adelman et al. [19] observed 3.45% of eyes that developed sustained elevated IOP after multiple anti-VEGF injections. These studies further substantiate the possibility of persistent IOP elevation after intravitreal anti-VEGF injections. To the best of our knowledge, the present series contains the highest reported number of patients treated with bevacizumab injections who had persistent IOP elevation.

In our study 18/424 patients (4.2%) had IOP of  $\geq 30$  mmHg in at least one eye. The low awareness of this phenomenon might partially be a result of under-diagnosis. IOP elevation is often attributed to primary open-angle glaucoma or primary ocular hypertension. Larger prospective studies are needed so that physicians will realize the full extent of this phenomenon and understand the risk factors and the possible etiologies.

In conclusion, this study adds to the available published data by showing that persistent IOP elevation might occur after repeated treatments with intravitreal bevacizumab.

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**Capsule**

**Innate lymphoid cells regulate CD4+ T cell responses to intestinal commensal bacteria**

Innate lymphoid cells (ILCs) are a recently characterized family of immune cells that have critical roles in cytokine-mediated regulation of intestinal epithelial cell barrier integrity. Alterations in ILC responses are associated with multiple chronic human diseases, including inflammatory bowel disease, implicating a role for ILCs in disease pathogenesis. Owing to an inability to target ILCs selectively, experimental studies assessing ILC function have predominantly used mice lacking adaptive immune cells. However, in lymphocyte-sufficient hosts ILCs are vastly outnumbered by CD4+ T cells, which express similar profiles of effector cytokines. Therefore, the function of ILCs in the presence of adaptive immunity and their potential to influence adaptive immune cell responses remain unknown. To test this, Hepworth and group used genetic or antibody-mediated depletion strategies to target murine ILCs in the presence of an adaptive immune system. The authors show that loss of retinoic-acid-receptor-related orphan receptor- $\gamma$ -positive (ROR $\gamma$ t+) ILCs was associated

with dysregulated adaptive immune cell responses against commensal bacteria and low-grade systemic inflammation. Remarkably, ILC-mediated regulation of adaptive immune cells occurred independently of interleukin (IL)-17A, IL-22 or IL-23. Genome-wide transcriptional profiling and functional analyses revealed that ROR $\gamma$ t+ ILCs express major histocompatibility complex class II (MHCII) and can process and present antigen. However, rather than inducing T cell proliferation, ILCs acted to limit commensal bacteria-specific CD4+ T cell responses. Consistent with this, selective deletion of MHCII in murine ROR $\gamma$ t+ ILCs resulted in dysregulated commensal bacteria-dependent CD4+ T cell responses that promoted spontaneous intestinal inflammation. These data confirm that ILCs maintain intestinal homeostasis through MHCII-dependent interactions with CD4+ T cells that limit pathological adaptive immune cell responses to commensal bacteria.

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Eitan Israeli

“Common sense is the fountainhead of Justice”

Ronald W. Stone, American judge