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RETINAL DISORDERS

Persisent ocular hypertension following intravitreal ranibizumab

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Abstract
Background To describe the occurrence of ocular hypertension in four patients following injection of ranibizumab intravitreally.
Methods Case series.
Results Four patients had high intraocular pressure after intravitreal ranibizumab 0.5 mg. Ocular hypertension occurred 1 month after the second ranibizumab injection in patients 1 and 3, and 1 month after the first ranibizumab in patient 2. In patient 4, it occurred several hours after the first ranibizumab injection. In all patients, the IOP increase was sustained across several visits, requiring control with topical glaucoma therapy, and in two cases the addition of a systemic carbonic anhydrase inhibitor. None of the patients had a previous history of glaucoma, ocular hypertension or IOP asymmetry and the IOP was as high as 30, 34, 46, and 50 mmHg in the four patients.
Conclusion Severe and sustained ocular hypertension may occur after intravitreal ranibizumab. Although the mechanism of the pressure rise is unknown, all eyes in our series were controlled with medical therapy.

Keywords Intraocular pressure · Ranibizumab · Intravitreal · Lucentis · Intravitreal · Ocular hypertension · Glaucoma · Pressure increase · Anti-VEGF

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Introduction

Intravitreal ranibizumab (Lucentis, Genentech, San Francisco, CA, USA) is an anti-vascular endothelial growth factor agent (anti-VEGF) that was approved by the Food and Drug Administration (FDA) in June 2006 for the treatment of choroidal neovascularization (CNV) due to age-related macular degeneration (AMD). Reported ocular adverse events are rare and include those specific to the drug, such as intraocular inflammation, and those specific to intravitreal injections, such as retinal tears, vitreous hemorrhage, endophthalmitis, and lens damage.

Intraocular pressure (IOP) increases occur transiently after intravitreal injections. However, within 30 to 60 minutes, the pressures usually return to baseline [1]. Intravitreal steroids, in addition, are known to cause long-term increases in intraocular pressure. In the MARINA [2], and ANCHOR [3] trials, ranibizumab had no long-term effect on intraocular pressure, on average, as assessed by monthly preinjection measurements during the 2-year follow-up. Intraocular pressure was increased on average 1 hour after ranibizumab injections at protocol-mandated intraocular-pressure assessments; however, the absence of corresponding changes in preinjection measurements suggests that the postinjection increases were transient. In the VISION trial [4, 5], there was no evidence of increased mean pre-injection intraocular pressure over 2 years after injection of intravitreal pegaptanib every 6 weeks. Mean values for IOP returned to preinjection levels by 1 week after injection.

The purpose of this study is to report four patients who had longer-term increases in intraocular pressure following intravitreal ranibizumab. Intraocular pressure was measured before dilation in all patients.

Patient 1

A 66-year-old Caucasian female was treated for CNV OD due to AMD. She had no previous or family history of glaucoma, and no steroid use. On presentation, visual acuity was 20/40 OU, and IOPs of 20 mmHg OU. Baseline examination was remarkable for mild cataract OU, CNV OD, early AMD OS, cup to disc ratios of 0.2. Over the following 6 months, she received three intravitreal injections of pegaptanib OD, before treatment was switched to intravitreal ranibizumab. Before the first ranibizumab injection, her IOP was 22 mmHg OD and 17 mmHg OS. Ranibizumab was injected monthly OD. After the second ranibizumab injection, her IOP was 26 mmHg OD and 21 mmHg OS. After eight further ranibizumab injections, her IOP was 30 mmHg OD and 18 mmHg OS. Angles were open 360 degrees on gonioscopy, and Humphrey visual field 24-2 was normal. Cup to disc ratio was 0.2. The patient was treated with timolol 0.5% OD, and 1 month later her IOP was 16 mmHg OD and 18 mmHg OS. Prior to intravitreal ranibizumab she had no IOP asymmetry. The timolol was stopped approximately 1 month later, and the patient had no further IOP increases during the three subsequent ranibizumab injections.

Patient 2

An 88-year-old Caucasian male had previously been treated with 3 monthly intravitreal bevacizumab injections OD for CNV due to AMD. He had no previous or family history of glaucoma, and no steroid use. The patient was pseudophakic, with a PCIOL OU. Pre-injection IOPs at each of those office visits was 18 mmHg OD/19 mmHg OS, 16 mmHg OD /14 mmHg OS, and 16 mmHg OD / 15 mmHg OS. The cup-to-disc ratio was not documented during those office visits, which were performed at an outside institution. On referral to us, vision was 20/200 OD, counting fingers OS, IOPs were 18 mmHg OD, 19 mmHg OS. There was a posterior chamber lens implant OU. Fluorescein angiography and OCT showed CNV OD. The patient was treated with intravitreal ranibizumab 0.5 mg/ 0.05 cc. One month later, vision was counting fingers OU, IOP was 34 mmHg OD and 17 mmHg OS. The patient was prescribed timolol maleate 0.5% OD and brimonidine tartrate 0.2% OS. One week later the IOP was 31 mmHg OD and 18 mmHg OS, and latanoprost 0.005% (Xalatan, Pfizer, New York, NY, USA) was added. Two weeks later, the patient was evaluated by the glaucoma service, and the IOP was 14 mmHg OU. Cup-to-disc ratio was 0.6 OD, 0.4 OS. Angles on gonioscopy were open OU, with 3-4 trabecular pigment; irides were blue. Brimonidine was stopped. One month later vision was 20/400 OD, and counting fingers OS. The IOP was 15 mmHg OU, timolol was stopped and latanoprost continued. No further ranibizumab injections had been given by last followup.

Patient 3

A 78-year-old Caucasian female with AMD and CNV OU had been treated with two intravitreal bevacizumab injections OD, two intravitreal pegaptanib injections OS and 9 intravitreal bevacizumab injections OS. Ocular examination was remarkable for mild nuclear sclerosis OU, cup-to-disc ratios of 0.3 OU, and inferotemporal retinoschisis OU. Intraocular pressures over the past 10 months had been symmetric, with a maximum difference of 2 mmHg between eyes. Prior to the first ranibizumab injection (1 month after the last bevacizumab injection) vision was counting fingers OD and 20/50 OS; IOPs were 14 mmHg OD and 15 mmHg OS. One month later, IOPs were 19 mmHg OD and 22 mmHg OS, and she was retreated with ranibizumab OS. One month after the second ranibizumab injection, vision was stable, but IOPs were 13 mmHg OD and 46 mmHg OS. The patient was prescribed timolol 0.5%, brimonidine tartrate 0.2% and latanoprost OS, and IOP 1 day later was 32 mmHg OS. Four days later, IOP was 22 mmHg OD and 34 mmHg OS and acetazolamide 500 mg po BID was prescribed. One week later, IOP was 20 mmHg OS, but 3 weeks later she had run out of acetazolamide 2 days prior to her visit, and IOP had increased to 40 mmHg. As she was not tolerating acetazolamide well, she was started on methazolamide 50 mg po bid. Over the next month, IOP OS ranged between 18 and 25 mmHg on treatment and vision was stable. No further ranibizumab injections had been given by last follow-up.

Patient 4

A 72-year-old Caucasian female with AMD and CNV OS had vision of 20/20 OD and counting fingers OS. IOPs were 15 mmHg OU. IOPs over the previous 2 years were normal (under 21 mmHg OU); she had one intravitreal triamcinolone injection OS 16 months earlier with no IOP rise. Examination was remarkable for 3 nuclear sclerosis OU, drusen OD and CNV OS. She was treated with intravitreal ranibizumab OS. Several hours later she returned to the emergency room with IOPs of 21 mmHg OD and 50 mmHg OS. She was treated with Cosopt® (dorzolamide hydrochloride-timolol maleate, Merck & Co., Inc., Whitehouse Station, NJ, USA), brimonidine tartrate 0.2%, and acetazolamide 500 mg po BID. The next day her IOP was 12 mmHg OS, and acetazolamide was stopped.

Ten days later, IOP was 23 mmHg OD and 14 mmHg OS. Gonioscopy showed extensive peripheral anterior synechiae (PAS) with increased pigment inferiorly, OU. Six weeks later, IOP was 18 mmHg OD and 32 mmHg OS, and the patient had not used drops in 2 days. Cup-to-disc ratio remained 0.1 OU throughout followup. Three months later, IOP was 20 mmHg OD, and 33 mmHg OS and the patient had not used drops in 2 days. She was treated with intravitreal bevacizumab OS. Several hours later she had pain from a corneal abrasion OS, IOP was 34 mmHg OS, and acetazolamide 500 mg po BID was added. One day later, IOP was 24 mmHg OS, acetazolamide was stopped and latanoprost was started. Two months later, IOP was 18 mmHg OD and 14 mmHg OS. She was treated with verteporfin PDT OS. Two months later IOP was 26 mmHg OD and 17 mmHg OS, on all three drops OS. She was started on Cosopt OD for the ocular hypertension OD. Visual fields showed a nasal step and superior arcuate defect OD, and a nasal step OS.

Gonioscopy was not performed on patient 3, was normal in patient 1, showed increased pigment in the trabecular meshwork in patient 2, and PAS in patient 4.

Discussion

Ocular hypertension was diagnosed 1 month after the second ranibizumab injection in patients 1 and 3, and 1 month after the first ranibizumab in patient 2. Interestingly in patient 4, it occurred several hours after the first ranibizumab injection. In all cases, the IOP increase was sustained across several visits, requiring treatment with topical glaucoma medication and in some the addition of a systemic carbonic anhydrase inhibitor. Patient 1 was retreated with ranibizumab and had no further IOP increases with three subsequent injections. The other three patients were not retreated with ranibizumab.

Ocular hypertension is very rare after intravitreal ranibizumab, and while the exact incidence is not known, reports from the ANCHOR and MARINA trials show that there was no evidence of increasing IOP over time. However, we have not been able to gain access to data from individual patients in the anti-VEGF medication trials to know how many had an IOP spike. None of the authors have had patients present with similarly high IOPs after intravitreal bevacizumab. This paper is not intended as an incidence study, and we are systematically reviewing our patient charts to better define the incidence of high IOPs after anti-VEGF agents.

Possible mechanisms for the IOP rise following intravitreal ranibizumab include a direct effect of the drug on the aqueous outflow channels including the trabecular meshwork or Schlemm's canal. It is known that glucocorticoids affect extracellular matrix deposition in the trabecular meshwork [6], and alter aqueous proteomics [7] and gene expression. [8, 9] There are no such studies on the effect of anti-VEGF agents. The patients may have experienced low-grade inflammation after the injection, which could not be detected clinically. In the MARINA trial, serious uveitis occurred in 1.3% of patients. Another explanation, and a possible cause in patient 4, is that the patient had a predisposition to ocular hypertension, due to underlying undiagnosed glaucoma. The sudden increase in intraocular volume in such an eye and the additional presence of pre-existing peripheral anterior synechiae (PAS) precipitated the severe and sustained IOP elevation. In patient 4, approximately 10 months after the IOP spike in the injected eye, the IOP started to increase slowly in the fellow uninjected eye, which also had PAS. Intraocular pressure is known to spike and return exponentially to baseline after a rapid change in ocular volume; thus, the increased volume of 50 ul could not explain the pressure rises beyond several hours [1]. Thus, we would hypothesize, based on the immediate reaction in one patient and the persistent IOP rise in all patients, that the drug may block immediate outflow from the eye for several weeks to months. Because of the idiosyncratic nature of this reaction, the mechanism of this is not known.

To our knowledge, this is the first report of delayed and sustained ocular hypertension after intravitreal ranibizumab injection. It is important to recognize that this entity exists, and to follow and treat it over the long term. Further studies are needed to define and understand the molecular, genetic, and protein changes that occur in the anterior chamber and trabecular meshwork after intravitreal ranibizumab.

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