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Original article

Intraocular pressure changes after repeated intravitreal antivascular endothelial growth factor injections in patients with neovascular age-related macular degeneration with or without glaucoma

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ABSTRACT

Purpose: To investigate the long-term effects of multiple intravitreal injections on intraocular pressure (IOP) in patients with exudative age-related macular degeneration, and to determine whether this is related to a pre-existing diagnosis of glaucoma.

Methods: A retrospective study was carried out on 209 eyes in 173 patients with neovascular age-related macular degeneration who received at least three intravitreal injections of bevacizumab or ranibizumab, or both, from January 2006 to December 2012 at Shin Kong Wu Ho-Su Memorial Hospital. Sequential changes in IOP following the intravitreal injections were documented and the incidence and characteristics of the patients diagnosed with glaucoma were recorded and analyzed.

Results: Two hundred and nine eyes in 173 patients were included in this study. The mean number of injections was 10.1 (range 3–23). No significant change was found in IOP ($p = 0.41$, paired t test) and none of the patients experienced delayed ocular hypertension during the treatment course. No correlation was found between differences in IOP and the number of injections (correlation coefficient −0.086) and no significant change in IOP was found in patients with or without glaucoma ($p = 0.42$ and 0.37, respectively, paired t test). In addition, the use of drugs to lower IOP did not increase with repeated intravitreal injections in patients with glaucoma [single drug, 24 (63.2%) patients; two drugs 14 (36.8%) patients].

Conclusion: Repeated intravitreal antivascular endothelial growth factor injections of bevacizumab or ranibizumab, or both, did not increase the risk of increasing IOP in patients with exudative age-related macular degeneration, with or without glaucoma.

1. Introduction

Exudative age-related macular degeneration (AMD), which is characterized by the occurrence of a choroidal neovascular membrane in the macular area, has become one of the most common causes of severe impairment of visual function in elderly patients, including those in Asia and Taiwan. For years, intravitreal injections of antivascular endothelial growth factors (anti-VEGFs), such as bevacizumab and ranibizumab, were the main treatment regimen for exudative AMD. As exudative AMD often runs a chronic, prolonged course with frequent recurrences of choroidal neovascular membranes, multiple injections of anti-VEGFs are necessary for the care of these patients. Aside from common ocular complications such as postoperative infections, or inflammation and hemorrhage in the vitreous or conjunctiva, the possibility of prolonged ocular hypertension (OHT) has also been postulated to induce glaucoma.

Changes in intraocular pressure (IOP) after repeated intravitreal injections of anti-VEGF have been thoroughly studied since anti-VEGF treatment for exudative AMD was introduced. A transient increase in IOP has been noted after anti-VEGF treatment for exudative AMD; however, it is seldom sustained after a few weeks of observation.[1–7] The MARINA study observed no significant long-term changes in IOP after up to 2 years of follow-up.[1] The ANCHOR[2,3] and PIER[4] study groups reported a transient increase in IOP in some patients; however, it returned to baseline within a few

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hours of the injection in all cases. Nevertheless, several studies have reported a short-term[8–10] or even sustained increase[11–20] in IOP after intravitreal anti-VEGF treatment. Therefore, whether sustained OHT is a delayed complication of intravitreal anti-VEGF treatment has yet to be confirmed.

The aim of this study was to investigate whether there was a long-term effect on IOP in patients with exudative AMD who received multiple intravitreal injections at different points during treatment. We also investigated whether this was related to a pre-existing diagnosis of glaucoma.

2. Methods

This was a retrospective study conducted at Shin Kong Wu Ho-Su Memorial Hospital from January 2006 to December 2012. All the patients receiving intravitreal injections of bevacizumab or ranibizumab, or both, were informed about the drugs, including the off-label use of bevacizumab, and all agreed to the treatment. This study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Shin Kong Wu Ho-Su Memorial Hospital.

Data on 209 eyes in 173 patients with neovascular AMD who received at least three intravitreal injections of bevacizumab or ranibizumab, or both, were collected, together with the treatment course. Demographic information, systemic comorbidities, lens status, ocular surgery, number of injections, use of drugs to lower IOP, and IOP at baseline and at each visit were recorded. The endpoint was the last visit during this study period.

The patients were diagnosed with neovascular AMD based on clinical symptoms, optical coherence tomography (OCT), fluorescein angiography, and indocyanine green findings. The exclusion criteria were: glaucoma that was not well controlled before the first injection (baseline IOP >21 mmHg); previous ocular surgery complicated with OHT; polypoidal choroidal vasculopathy as diagnosed by indocyanine green angiography (ICGA) and other ocular disease including proliferative diabetic retinopathy, retinal vein or artery occlusion, uveitis and other ocular inflammatory diseases; and intraocular surgery during the course of treatment.

The intravitreal injections were performed under local anesthesia with 0.5% proparacaine hydrochloride eye drops. Before injection, the periocular skin was disinfected with 5% povidone–iodine solution and draped as per standard procedures. The intravitreal injections were performed at 3.5–4.0 mm posterior to the limbus in phakic eyes, or 3.2–3.5 mm posterior to the limbus in pseudophakic and aphakic eyes with a 30-gauge needle, with intravitreal injections of bevacizumab 2.5 mg/0.1 mL after anterior chamber tapping for 0.05 mL or intravitreal injections of ranibizumab 0.5 mg/0.05 mL after anterior chamber tapping for 0.05 mL, or both.

After the procedure, topical 0.25% chloramphenicol and 1% prednisolone were given four times a day, and Codemycin ointment (Oasis, Taipei, Taiwan; hydrocortisone acetate 0.1% + neomycin sulfate 0.05%) was given before bed for 3 days for the prophylaxis of infection and inflammation. The patients were then instructed to visit our clinic 1 week after the procedure and were followed monthly to decide whether reinjection of the anti-VEGF was necessary. The decision to reinject was based on an "as-needed" principle and the patients were advised to receive a reinjection if: (1) any subretinal fluid or cystic changes were persistent or reappeared in OCT examinations; (2) there was a marked increase in serous or hemorrhagic pigment epithelial detachment on OCT examinations; or (3) any hemorrhagic complications were noted on fundus examinations. Complete ocular examinations, including best corrected visual acuity, IOP, slit-lamp biomicroscopy, fundus ophthalmoscopy, and OCT, were performed at each follow-up visit.

IOP was recorded with a non-contact tonometer (NIDEK NT-530, NIDEK Inc., Tokyo, Japan) without local anesthesia and before the application of a mydriatic agent. Changes in IOP were identified as the difference between the IOP before and 1 week after each injection. Delayed OHT was defined as either an IOP ≥22 mmHg at two consecutive visits with an increase from baseline >6 mmHg, or a single IOP increase of >26 mmHg with concomitant initiation or increase in the use of IOP-lowering treatment. Changes in IOP were analyzed with paired *t* tests.

The patients were then divided into subgroups of those with glaucoma and those without glaucoma. Glaucoma was diagnosed based on funduscopy and OCT evidence of optic disc or retinal nerve fiber layer (RNFL) structural abnormalities or visual field damage consistent with retinal nerve fiber layer damage, or both. Only eyes with neovascular AMD that received intravitreal injections were taken into consideration. Changes in IOP between the patients with and without glaucoma were analyzed with independent *t* tests. The incidence and characteristics of the patients diagnosed with glaucoma, demographic data, and sequential IOP changes following the intravitreal injections were analyzed.

3. Results

Two hundred and nine eyes in 173 patients were included in this study. In total, 2132 injections of anti-VEGF were performed, including 2071 injections of bevacizumab and 61 injections of ranibizumab. One hundred and eighty eyes received intravitreal injections of bevacizumab monotherapy, and 29 eyes received both intravitreal injections of bevacizumab and ranibizumab sequentially. The mean age of the patients was 65.3 years (range 58–82 years) and 73 (34.9%) were men. A total of 70.3% of eyes were in patients with hypertension and 26.8% were in patients with diabetes mellitus. The mean number of injections was 10.1 (range 3–23). Table 1 summarizes the demographic data for the patients. There was no significant change in IOP ($p = 0.41$, paired *t* test) and none of the patients experienced delayed OHT during the treatment course. There was no correlation between the difference in IOP and the number of injections (Fig. 1; correlation coefficient −0.086).

Thirty-eight of the 209 (18.2%) eyes were diagnosed with open angle glaucoma. The pre-injection mean ± standard deviation IOP was 15.3 ± 2.43 mmHg in the patients with glaucoma, and 13.2 ± 3.47 mmHg in the patients without glaucoma. The mean numbers of injections were 9.1 and 10.3 in the patients with and without glaucoma, respectively. The changes in IOP were +0.28 ± 0.74 mmHg in the patients with glaucoma, and +0.26 ± 0.81 mmHg in the patients without glaucoma. No significant change in IOP was found in either group (glaucoma group $p = 0.42$; without glaucoma group $p = 0.37$; paired *t* test).

The use of IOP-lowering drugs did not increase with repeated intravitreal injections. An increase in IOP was not found in both

Table 1
Demographic data for all 209 eyes in this study.

Characteristic	Patients ($n = 173$)	Eyes ($n = 209$)
Age (y), mean (range)	65.3 (58–82)	64.8 (58–82)
Male sex, *n* (%)	62 (35.8)	73 (34.9)
Comorbidity, *n* (%)		
Hypertension	124 (71.7)	147 (70.3)
Diabetes mellitus	44 (25.4)	56 (26.8)
Lens status, *n* (%)		
Phakic		102 (47.7)
Pseudophakic		112 (52.3)
Glaucoma, *n* (%)	27 (15.6)	39 (18.2)
No. of injections, mean (range)		10.2 (3–23)