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Long-Term Intraocular Pressure Changes in Patients with Neovascular Age-Related Macular Degeneration Treated with Ranibizumab

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Key Words

Age-related macular degeneration · Intraocular pressure · Ranibizumab · Anti-vascular endothelial growth factor

Abstract

Background/Aims: To investigate the long-term effects of multiple intravitreal injections (IVTs) of ranibizumab (Lucentis) on intraocular pressure (IOP) in patients with neovascular age-related macular degeneration. ***Methods:*** In 320 eyes, IOP measurements were performed at baseline prior to injection and compared with IOP measurements of the last visit. Correlations between mean IOP change and total number of IVTs, visual acuity or patient age were tested. ***Results:*** The mean IOP increase was 0.8 ± 3.1 mm Hg ($p < 0.0001$). Seven eyes showed final IOP values between 22 and 25 mm Hg. The mean follow-up was 22.7 ± 14.1 months. No further correlations between IOP change and number of IVTs, visual acuity or patient age have been found. ***Conclusions:*** This study demonstrated a statistically significant IOP increase in patients treated with repeated injections of ranibizumab. However, IOP increase required no glaucoma treatment during the study. Therefore, repeated injections with ranibizumab can be considered safe with regard to long-term IOP changes in patients without ocular hypertension or glaucoma.

Introduction

Age-related macular degeneration (AMD) is the leading cause of visual impairment and irreversible blindness among elderly people over 50 years of age in the Western world [1].

Vascular endothelial growth factor-A (VEGF-A) has been identified as the key factor for the pathogenesis of AMD [2]. Over the last 10 years, a number of new antibodies against VEGF-A emerged for intraocular treatment. These include pegaptanib (Macugen; Eyetech Pharmaceuticals Inc., New York, N.Y., USA), ranibizumab (Lucentis, Novartis Pharma, Basel, Switzerland) and bevacizumab (Avastin, Novartis Pharma) which are widely used as intravitreal injection (IVT) therapy for neovascular AMD [3–5].

Ranibizumab is a recombinant, humanized, monoclonal antibody Fab fragment that inhibits all biologically active VEGF-A isoforms [6]. It is indicated in active neovascular AMD where there is abnormal retinal thickness with evidence of intraretinal or subretinal fluid by optical coherence tomography, intraretinal and subretinal hemorrhage, enlargement of choroidal neovascularization (CNV) size on fluorescence angiography and when there is a new or persistent leakage on fluorescence angiography [7].

The International Retina Expert panel has recommended an evidence-based guideline to optimize treatment outcome with ranibizumab in neovascular AMD [4].

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This recommendation is based on the evidence available from prospective, multicenter studies evaluating different ranibizumab treatment schedules such as ANCHOR [8], MARINA [9], PIER [10], SAILOR [11], SUSTAIN [12] and EXCITE [13].

During the early introduction period of anti-VEGF treatment, there were few reported cases of ocular adverse effect of ranibizumab which included a transient rise of IOP [9–12, 14]. The MARINA study group observed no significant long-term changes in IOP up to 2 years of follow-up [9]. The ANCHOR [8] and PIER [10] study groups reported a transient rise in IOP which reverted back to baseline within hours of injection. Numerous other groups reported transient or even sustained elevation of IOP after intravitreal anti-VEGF therapy [15–23]. Our study aimed to investigate whether there is a long-term effect on IOP in AMD patients who received multiple IVTs at the different points of treatment duration.

Methods

This study was conducted at the Department of Ophthalmology, Inselspital, University of Bern, Switzerland. The charts of all patients with active CNV due to neovascular AMD receiving ranibizumab IVTs between March 2010 and June 2010 were retrospectively reviewed. All patients above 50 years of age with neovascular AMD treated with ranibizumab as single therapy were included. All patients had at least 2 months of follow-up. Patients were excluded if there was documented evidence of ocular hypertension, glaucoma, neovascularization in the anterior segment, uveitis with anterior chamber inflammation, active uveitis intermedia, history of uveitis posterior that might lead to secondary CNV, or any other conditions that might influence IOP. In addition, patients under treatment with steroids, patients who underwent cataract surgery during the follow-up period or patients with previous treatment of neovascular AMD with substances other than ranibizumab were excluded. The study followed the guidelines of the Declaration of Helsinki and was approved by the cantonal ethics committee of Bern. The study was performed with informed consent, following all the guidelines for experimental investigations required by the Institutional Review Board of the Cantonal Ethics Committee of Bern.

All patients underwent ocular examination including visual acuity testing with ETDRS charts, slit lamp examination and fundus examination. In all patients, fluorescein angiography and optical coherence tomography were performed to confirm the diagnosis of neovascular AMD. Charts were reviewed for baseline demographic data, current diagnosis, number of injections, best corrected visual acuity at baseline and during the last visit.

Glaucoma, as exclusion criterion, was defined as a progressive optic nerve disease with loss of optic nerve fiber layer, increased cupping of the disk, and typical visual field defects. Ocular hypertension and family history of glaucoma were also exclusion criteria. In addition, IOP measurements with Goldmann applanation tonometry were performed at baseline prior to injection, and measurements were repeated every time prior to the next planned injection. All measurements were performed by an ophthalmologist with calibrated tonometers approximately at the same time of the day between 10 a.m. and 1 p.m. (due to the rigid clinic schedule). All IOP measurements were done without pupil dilation on the same day before IVT.

A total number of 395 patients was reviewed, and 320 patients with active AMD were included in the analysis. Written consent for IVT was obtained after explaining the procedure and risk/benefit of the procedure before the first IVT. All eyes were treated with an IVT of 0.5 mg ranibizumab following published guidelines under aseptic conditions and local anesthesia. Patients received IVT according to the Bern treatment regimen.

In the Bern treatment regimen, patients received 3 monthly injections during the loading phase. After the loading phase patients were followed and treated pro re nata. Every retreatment due to new disease activity led to 3 additional monthly injections. In case of no disease activity patients received fixed injections every 3 months for a period of 1 year. Patients were closely followed with optical coherence tomography, ETDRS visual acuity testing and fundus biomicroscopy during each follow-up, and in cases of relapse with disease activity, the regimen would start with a reloading phase over again.

Data Analysis

The data was analyzed using StatView software version 5.0. IOP measurement during the last visit was compared to baseline IOP using the paired t test. Pairwise correlation was performed using Spearman's coefficient correlation to test between mean IOP changes and total number of IVT, visual acuity or patient age. A p value of <0.05 was considered to be statistically significant. Repeated measures analysis of variance was used to assess the statistical significance in IOP changes with multiple IVTs.

Results

Demographic and baseline study characteristics for this study are summarized in table 1. The mean baseline IOP (IOP1) and last IOP (IOP2) were 14.2 ± 2.6 and 15.7 ± 3.0 mm Hg, respectively. The mean IOP difference between the last measurement and baseline (IOP2 – IOP1) was 0.8 ± 3.1 mm Hg. Differences between baseline IOP and last IOP were highly significant ($p < 0.0001$). One eye showed an IOP increase of >10 mm Hg (11 mm Hg). In this particular patient, baseline and final IOPs were 10 and 21 mm Hg, respectively. Seven eyes had final IOPs between 21 and 25 mm Hg. All these patients had their baseline IOP between 14 and 18 mm Hg and never had any ocular or family history of glaucoma, suspected glaucoma and ocular hypertension or IOP asymmetry. None of these eyes required treatment with glaucoma medication during the follow-up.

Further analysis found no statistically significant correlations between IOP changes and visual acuity, or the patient's age. In addition, the results showed no statisti-

cally significant correlation between the total number of IVTs and visual acuity improvement.

As shown in table 2, we further categorized the patients into 4 subgroups according to the duration of follow-up: less than 12 months (A), more than 12 months (B), more than 24 months (C) and more than 36 months (D). The IOP increase between all subgroups showed an increasing trend from baseline: 0.46 ± 2.48 mm Hg (A), 1.01 ± 3.38 mm Hg (B), 1.24 ± 3.6 mm Hg (C) and 1.38 ± 3.2 mm Hg (D), respectively. The IOP differences to baseline in all subgroups except subgroup A were statistically significant ($p < 0.0001$). However, there was no significant correlation between mean IOP changes (IOP2 – IOP1) and total number of IVTs in all subgroups.

Table 1. Demographic data and study characteristics split by CNV lesion types, number of injections, IOP characteristics and follow-up

Gender, n	320
Male, %	27.19
Female, %	72.81
Age, years	
Mean ± SD	79.8±8.2
Range	56–96
Age group, n	320
50–64 years, %	6.56
65–74 years, %	17.19
75–84 years, %	43.75
≥85 years, %	32.5
CNV lesion subtype, n	320
Predominantly classic, %	21.25
Occult, %	63.13
Minimally classic, %	2.81
Cannot classify, %	12.81
Number of injections per eye	
Mean ± SD	13.0±8.0
Range	2–35
Baseline IOP (IOP1), mm Hg	
Mean ± SD	14.2±2.6
Range	7–21
Last IOP (IOP2), mm Hg	
Mean ± SD	15.7±3.0
Range	7–25
IOP change (IOP2 – IOP1), mm Hg	
Mean ± SD	0.8±3.1
Range	–10 to 11
Follow-up, months	
Mean ± SD	22.7±14.1
Range	2–51

Discussion

Based on our results, there is a statistically significant long-term IOP increase (0.8 ± 3.1 mm Hg, $p < 0.0001$, table 2) in patients treated with IVT with ranibizumab for neovascular AMD. The incidence of transient raised IOP has been reported in few articles earlier [15–17]. The main reasons are most likely due to sudden volume raised after the intravitreal injection, and fortunately the IOP returned back to normal within 30–60 min after the injection without any intervention. Other factors which have been found to influence the temporary increase in IOP include size of the eyeball, volume of the drug and the technique of injection. Knecht et al. [18] reported a significant rise in IOP with tunneled IVT as compared to a straight intravitreal technique immediately after the injection; however, there was no significant difference in IOP 15 min after injection.

PubMed database search showed 3 previous reports on sustained ocular hypertension (OHT) following intravitreal injections with ranibizumab or bevacizumab. Bakri et al. [19] reported persistent OHT after intravitreal ranibizumab in 4 patients who had no ocular or family history of glaucoma, suspected glaucoma, OHT or asymmetry IOP. Kahook et al. [20] reported 6 cases of sustained elevation of IOP following single or multiple intravitreal bevacizumab for treating various CNV diseases. Three out of the 6 patients did not have any particular history of glaucoma, suspected glaucoma or OHT, received IVT of bevacizumab for treatment of CNV due to high myopia and unspecific cause. Adelman et al. [21] reported that 4 out of 116 patients with AMD (3.45%) developed sustained elevation IOP following multiple IVTs of bevacizumab and/or ranibizumab in AMD patients who had no ocular or family history of glaucoma, suspected glaucoma, OHT or asymmetric IOP. Choi et al. [22] investigated 127 patients treated with bevacizumab, ranibizumab or pegaptanib and found 9.4% of the patients who devolved IOPs of >25 mm Hg. In another study, Tseng et al. [23] present a series of 25 eyes of 23 patients who developed increased IOP due to repeated anti-VEGF therapy.

The reason for this sustained elevation of IOP is not fully understood.

One possible mechanism might be due to a disrupted anterior hyaloid or disrupted zonules which may allow access for high-molecular-weight proteins to enter the anterior chamber. Multiple doses of these proteins may disrupt mechanically and/or physiologically the normal aqueous outflow in the trabecular meshwork [19]. From pharmacokinetic studies it is known that bevacizumab, a 149-kDa full-length antibody, diffuses into the anterior chamber and clears slowly from the vitreous cavity [24].

Table 2. IOP increase from baseline in 4 patient groups with increasing treatment duration

Treatment duration	Eyes n	Mean IOP2 – IOP1 ± SD mm Hg	Paired t test p value
Less than 12 months (A)	100	0.46±2.48	0.0712
More than 12 months (B)	220	1.01±3.38	<0.0001
More than 24 months (C)	149	1.24±3.55	<0.0001
More than 36 months (D)	79	1.38±3.22	0.0003

Jalil et al. [25] hypothesized that bevacizumab may accumulate in the trabecular meshwork, thereby blocking the aqueous outflow and leading to increased IOP.

Ranibizumab is a genetically manipulated Fab fragment with a molecular weight of approximately 48 kDa and therefore it is much smaller compared to bevacizumab. Further investigation is needed to clarify if the same mechanism accounts for IOP elevation in IVT with ranibizumab. In particular, possible changes in the trabecular meshwork of such patients might be of interest. For example, it is completely unknown if repeated, transient IOP elevations associated with IVTs might also induce chronic damage to the trabecular meshwork.

A number of other possible mechanisms may contribute to sustained IOP elevation following intravitreal anti-VEGF injections. Inflammation has been described after intravitreal anti-VEGF injections [5]. One can also hypothesize that repeated intravitreal injections might induce an undetectable low-grade inflammation that leads to changes in the trabecular meshwork (scar formation, fibroblast proliferation). In addition, drug-induced trabeculitis, uveitis or endophthalmitis could be one of the contributing factors as well. Kahook et al. [26] found significant differences in IgG concentration measured in repackaged bevacizumab. In addition, Liu et al. [27] found silicone oil microdroplets and high-molecular-weight aggregates in repackaged bevacizumab and ranibizumab as effects of long-term storage and product mishandling. These observations might explain some cases of sustained IOP elevation after injection of repackaged drugs. However, in our study no repackaged drugs have been used and therefore other underlying causes must be responsible for the IOP elevation.

There is a possibility that other factors such as age, blood pressure, body mass index and central corneal thickness might have influenced the rise in IOP which cannot be tested in the current study. Several studies have found a statistically significant increase in IOP with age. The Beaver Dam Eye Study, the Egna-Neumarkt Study and the Blue Mountain Eye Study reported a trend of increasing IOP with age of 0.5, 0.4 and 0.3 mm Hg, respectively [28–30]. Interestingly in the Black Barbados Eye Study, a larger age-related increase in IOP (2 mm Hg) was observed as compared to a Caucasian population [31].

As shown in table 2, our data showed a clear tendency of increasing IOP with treatment duration. These findings indicate that multiple IVTs with ranibizumab might lead to slow changes either in the trabecular meshwork or changes in aqueous fluid production. Our analysis was unable to demonstrate any significant correlation between IOP changes, visual acuity and patient age.

In contrast to our findings, Rosenfeld et al. [9] in the MARINA study group trial reported no long-term changes in IOP up to 2 years of follow-up. The same study recorded a temporary rise in IOP within the first hour after injection and dropped down to only 2–3 mm Hg higher than the recorded baseline after 1 h. They also reported no changes in IOP after escalating the dose of IVT up to 4 months in the follow-up period. However, up to this point no long-term data of patients who have been followed over more than 2 years regarding IOP changes has been published yet.

In the present study, the longest interval between first and last injection documented was 51 months, and the maximum number of injections received was 35. To our knowledge, this study has currently the longest follow-up on IOP changes in AMD patients who received multiple IVTs with ranibizumab.

In addition to IOP changes, the current study documented a statistically significant improvement of mean best corrected visual acuity (4.51 ± 15.8 letters) compared to baseline. These findings are comparable to the results of various major studies which reported general stabilization and/or improvement of visual acuity after IVT [7–14].

As a limitation of this study no other IOP-influencing factors such as blood pressure, body mass index or central corneal thickness were tested. In addition, the lens status (pseudophakic, phakic, grade of cataract) was not assessed in this retrospective analysis, knowing that cataract surgery tends to lower the IOP.

In conclusion, this study demonstrated a small but statistically significant IOP increase associated with repeated injections of intravitreal ranibizumab. Our data showed that ranibizumab can be considered safe with regard to long-term IOP changes in patients without ocular hypertension or glaucoma. However, there was a clear tendency to increased IOP in eyes with longer treatment duration which might become problematic in patients who have to be treated for many years to come and espe-

cially in patients who have both AMD and glaucoma. Further studies are needed to define and understand the long-term cellular and molecular effects of anti-VEGF antibodies on intraocular tissue, especially the trabecular meshwork system.

Disclosure Statement

None of the authors has a conflict of interest with the submission.

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