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The effect of ranibizumab on eye lens opacity in cases with age-related macular degeneration

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Abstract

Purpose: To evaluate the cataractogenic effect of intravitreal ranibizumab with the use of Lens Opacity Classification System III (LOCS III).

Settings: Cases with a diagnosis of wet Age Related Macular Degeneration (AMD) were included in this university practice based prospective study.

Methods: All cases had monthly injections of intravitreal ranibizumab in the first 3 months; subsequently an OCT-guided pro re nata injection regimen has been adopted. All cases had a comprehensive eye examination and LOCS III evaluation at baseline and 1, 3, 6 and 12 months after the initial injection. Examination outcomes and LOCS III grades were recorded.

Results: Eighteen eyes of 13 cases (7 female, 6 male) were included in this study. The mean age at the baseline was 75,3 ± 6,6 years. A mean of 3,4 ± 0,7 injections was given on each eye. Mean follow-up was 13,83 ± 2,33 months. Baseline mean visual acuity improved from 1,04 ± 0,10 logMAR units to 0,76 ± 0,26 logMAR units after 3 injections ($P < 0.05$). At the 12th month of follow-up mean visual acuity was 0,71 ± 0,27 logMAR units. According to LOCS III grades none of the cases had a prominent change in nuclear color, nuclear opalescence, cortical and posterior subcapsular opacification throughout the follow-up. IOP remained stable at all follow-up points. No complications were recorded throughout the study.

Conclusion: Intravitreal ranibizumab is an efficient treatment in wet AMD. Results of LOCS III assessments in this pilot study suggest that intravitreal ranibizumab has no effect on the progression of lens opacity.

Introduction

In the last decade, significant progress has been made in the treatment of wet AMD. At the present intravitreal anti-VEGF therapy has become the mainstay of treatment. Nevertheless, intravitreal application is a hazardous procedure with a wide range of complications. Endophthalmitis, intraocular pressure (IOP) elevation, retinal detachment, vitreous hemorrhage, and cataract are among the major complications [1].

The current study is focused on the cataractogenic potential of intravitreal ranibizumab. Cataract formation following intravitreal application is frequently associated with an inadvertent trauma at the procedure. However, occasionally the drug -itself- may precipitate cataract formation. Accelerated formation of cataract, has previously been shown as a possible cause of decreased visual acuity, in some cases who received intravitreal injections of triamcinolone [2]. However, no prospective study has, as yet, assessed anti-VEGF agent related cataract progression in cases of AMD. Herein, we have investigated the cataractogenic effect of intravitreal ranibizumab by using the Lens Opacity Classification System III (LOCS III).

Methods and materials

Eighteen eyes of 13 patients (7 female, 6 male) with a diagnosis of wet AMD, were included in this prospective study. All cases were treated with 0.5 mg per 0.05 ml of intravitreal ranibizumab. All eyes had monthly injections of ranibizumab in the first 3 months; subsequently, an OCT-guided, pro re nata injection regimen has been adopted. Throughout the follow-up, a mean of 3, 4 ± 0, 7 [median value: 3, 0 (range: 3-5)] injections were given in each eye.

At the baseline, a comprehensive eye examination was performed on each participant including best corrected visual acuity (BCVA), slit-lamp examination, LOCS III evaluation and fundus examination. BCVA was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart and converted to logarithm of the minimum angle of resolution (logMAR). Initial diagnosis of wet AMD was made with biomicroscopy by using a 90-diopter noncontact lens. Diagnosis is confirmed in all cases on the basis of fluorescein angiography (FA) and optical coherence tomography (OCT) (Carl Zeiss Meditec Inc. Dublin, CA). All injections were performed in the office, in a sterile fashion. History of previous injections of a triamcinolone or anti-VEGF drug was among exclusion criteria. Individuals that had undergone cataract extraction or had other intraocular surgery within 3 months and any other laser treatment within 1 month (including YAG laser iridotomy) were excluded. Again, cases using systemic steroids or anti-glaucomatous drops were not recruited.

Evaluation of lens status was assessed according to LOCS III standards. The examination was performed in a masked fashion by a certified ophthalmologist (MB). Pupils were dilated with tropicamide 1% and four attributes of cataract were recorded. Nuclear color (NC), nuclear opalescence (NO), cortical opacity (CO), and posterior

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subcapsular opacity (PSC) were graded for each eye. Nuclear color and opalescence were graded using a thin slit beam of full height at a 45-degree angle. PSC and cortical change gradings were assessed with retroillumination. These illumination techniques were identical to those used for lens photography for the LOCS III system. Grading was based on objective measures of color, density, and area. The grader referred to the LOCS III standard transparency as needed. Each lens was assigned a numeric grade; the degree of NO and NC ranged from 0.1 (clear) to 6.9 (most advanced) in 0.1 increments. Likewise, the degree of CO and PSC ranged from 0.1 to 5.9. The study was carried out with the approval of the local ethics committee and each case provided a written informed consent.

Patients were reevaluated at 1, 3, 6 and 12 months after the initial injection and received a comprehensive ophthalmic history and examination. BCVA, IOP readings, findings of anterior segment examination including evaluation of lens status with LOCS III criteria and fundus examination were recorded. The presence of any adverse events were further investigated. All statistical analyses were performed using SPSS software version–13.0 (SPSS Inc, Chicago, IL) and P values less than 0, 05 were considered statistically significant. Wilcoxon signed ranks test was used to compare the attributes of cataract.

Results

Eighteen eyes of 13 patients (7 female, 6 male) were included in this study. The mean age of the patients was 75, 3 ± 6, 6 years [median age: 78, 5 years (range: 56 to 81 years)]. Mean follow-up was 13, 83 ± 2, 33 [median follow-up: 13 (8-20)] months. A mean of 3, 4 ± 0, 7 [median value: 3, 0 (3-5)] injections were given on each eye.

Mean BCVA was 1, 04 ± 0, 10 [median value: 1, 1 (0, 7-1, 1)] logMAR units at the baseline and at the 1-month follow-up, the mean visual acuity significantly improved to 0, 68 ± 0, 06 [median value: 0, 7 (0, 5-0, 7)] logMAR units ($P < 0.05$). Over the next months, visual acuity remained stable; mean BCVA was 0, 76 ± 0, 26 [median value: 0, 7 (0, 4-1, 1)] logMAR units at 3rd month, 0, 74 ± 0,28 [median value: 0, 7 (0, 4-1, 1)] logMAR units at 6th month and 0, 71 ± 0, 27 [median value: 0, 6 (0, 4-1, 0)] logMAR units at 12th months respectively. Along the follow-up, only one patient had a decrease in the vision which was not related to progression of lens opacity. The distribution of visual acuity outcomes and best-corrected visual acuity change from baseline is shown in Table 1. No significant IOP change was recorded. Mean IOP was 13, 89 ± 1, 79 [median value: 14 (11-17)] mmHg at the baseline whereas it was 13, 89 ± 1, 56 [median value: 13, 5 (11-17)] mmHg, 13, 94 ± 1, 62 [median value: 13, 5 (11-17)] mmHg, 13, 72 ± 1, 23 [median value: 13, 5 (12-16)] mmHg, 13, 83 ± 1, 61 [median value: 14, 0 (12-20)] mmHg at the 1st, 3rd 6th and 12th months respectively.

Baseline LOCS III scores for the main attributes of cataract were 0, 2 ± 0, 07 [median value: 0, 2 (0, 1-0, 3)] for NC, 0, 12 ± 0, 04 [median value: 0, 1 (0, 1-0, 2)] for NO, 1, 0 ± 0, 13 [median value: 1, 0 (0, 8-1, 3)] for CO and 0, 90 ± 0, 09 [median value: 0, 9 (0, 7-1, 0)] for PSC. The change from baseline in all LOCS III attributes were small throughout the follow-up. NC grades were 0, 2 ± 0, 07 [median value: 0, 2 (0, 1-0, 3)] at the 1st month and it did not improve significantly over the next months; it was 0, 2 ± 0, 08 [median value: 0, 2 (0, 1-0, 3)] at 3rd, 0, 2 ± 0, 08 [median value: 0, 2 (0, 1-0, 3)] at 6th months and 0, 2 ± 0, 08 [median value: 0, 2 (0, 1-0, 3)] at 12th months. NO grades were 0, 12 ± 0, 04 [median value: 0, 1 (0, 1-0, 2)] at the 1st month, 0, 12 ± 0, 04 [median value: 0, 1 (0, 1-0, 2)] at the 3rd month, 0, 12 ± 0, 04 [median value: 0, 1 (0, 1-0, 2)] at the 6th month and it remained as 0, 12 ± 0, 04 [median value: 0, 1 (0, 1-0, 2)] at 12 month. Likewise CO grades remained stable over the course (1, 0 ± 0, 13 [median value: 1, 0 (0, 8-1, 3)] at 1st month, 1, 0 ± 0, 12 [median value: 1, 0 (0, 8-1, 3)] at 3rd month, 1, 0 ± 0, 12 [median value: 1, 0 (0, 8-1, 3)] at 6th month and 1, 0 ± 0, 12 [median value: 1, 0 (0, 8-1, 3)] at 12th month follow-up). Also, PSC was not effected from intravitreal injections of ranibizumab; (0, 90 ± 0, 09 [median value: 0, 9 (0, 7-1, 0)] at 1st month, 0, 90 ± 0, 09 [median value: 0, 9 (0, 7-1, 0)]at 3rd month, 0, 90 ± 0, 09 [median value: 0, 9 (0, 7-1, 0)] at 6th month and 0, 90 ± 0, 09 [median value: 0, 9 (0, 7-1, 0)] at 12th months). The grades of LOCS III assesments is summarized in Table 2.

Table 1. Best-corrected visual acuity change throughout the study.

	Mean BCVA (logMAR)	Median BCVA (logMAR)
Baseline	1, 04 ± 0, 10	1, 1 (0, 7-1, 1)
First month	0, 68 ± 0. 06	0, 7 (0, 5-0, 7)
Third month	0, 76 ± 0, 26	0, 7 (0, 4-1, 1)
Sixth month	0, 74 ± 0, 28	0, 7 (0, 4-1, 1)
Twelfth month	0, 71 ± 0, 27	0, 6 (0, 4-1, 0)

Wilcoxon signed ranks test was used to compare the 4 indicators of cataract. There was no significant difference in between ($p=1.000$). A within group analysis of all 4 attributes, showed that none of attributes had a progression throughout the study ($p=1.000$). No other adverse events were noted in this series. There were no cases of ptosis, inadvertent intraocular penetration or any ocular infections.

Discussion

The introduction of intravitreal anti-VEGF agents has revolutionized the treatment of AMD [3]. The favorable results in AMD have encouraged physicians in using anti-VEGF agents in different fields of ophthalmology. Still several studies are investigating the use of anti-VEGF agents in; diabetic retinopathy, retinopathy of prematurity, retinal vein occlusions, cystoid macular edeme and neovascular glaucoma [4-8]. However, there are still some questions that need to be addressed. Namely, the potential complications and adverse events of intravitreal anti-VEGF agents have not been fully explored. Herein we intend to investigate particularly the cataractogenic effect of ranibizumab in AMD patients.

Eighteen eyes of 13 cases were included in this study with a mean follow-up of 13, 83 ± 2, 33 months. A mean of 3, 4 ± 0, 7 injections were given on average in each eye. The results of this pilot study suggest that ranibizumab has no effect on the attributes of cataract. Assesments of nuclear color, nuclear opalescence, cortical opacity, and posterior subcapsular opacity, in accordance to LOCS III standarts, have clearly shown that neither of these attributes progress after intravitreal ranibizumab injections. Along the follow-up only one patient had a decrease in the vision. It was attributed to the gradual loss of foveal structure and the RPE in that case. Injections of ranibizumab did not alter the status of lens in any subject.

Cataract progression with ranibizumab has been reported before in ANCHOR trial [9]. Actually, both ranibizumab treated eyes and PDT treated eyes had a progression of cataract in this trial. However the rate of cataract progression in ranibizumab treatment group did not increase in either MARINA or PIER trials [10,11]. Actually, these results are contradictory. To the best of our knowledge, LOCS III standarts have not been used yet, to monitor the progression of cataract in ranibizumab treated AMD cases.

It is well known that iatrogenic cataract formation may occur following intravitreal injections. It is generally caused by an inadvertent trauma at the procedure. On the other hand, the drug-

Table 2. Outcomes of LOCS III assesments.

	NC	NO	CO	PSC
Baseline	Mean: 0, 2 ± 0, 07	Mean: 0, 12 ± 0, 04	Mean: 1, 0 ± 0, 13	Mean: 0, 90 ± 0, 09
	Median: 0, 2 (0, 1-0, 3)	Median: 0, 1 (0, 1-0, 2)	Median: 1, 0 (0, 8-1, 3)	Median: 0, 9 (0, 7-1, 0)
First month	Mean: 0, 2 ± 0, 07	Mean: 0, 12 ± 0, 04	Mean: 1, 0 ± 0, 13	Mean: 0, 90 ± 0, 09
	Median: 0, 2 (0, 1-0, 3)	Median: 0, 1 (0, 1-0, 2)	Median: 1, 0 (0, 8-1, 3)	Median: 0, 9 (0, 7-1, 0)
Third month	Mean: 0, 2 ± 0, 08	Mean: 0, 12 ± 0, 04	Mean: 1, 0 ± 0, 12	Mean: 0, 90 ± 0, 09
	Median: 0, 2 (0, 1-0, 3)	Median: 0, 1 (0, 1-0, 2)	Median: 1, 0 (0, 8-1, 3)	Median: 0, 9 (0, 7-1, 0)
Sixth month	Mean: 0, 2 ± 0, 08	Mean: 0, 12 ± 0, 04	Mean: 1, 0 ± 0, 12	Mean: 0, 90 ± 0, 09
	Median: 0, 2 (0, 1-0, 3)	Median: 0, 1 (0, 1-0, 2)	Median: 1, 0 (0, 8-1, 3)	Median: 0, 9 (0, 7-1, 0)
Twelfth month	Mean: 0, 2 ± 0, 08	Mean: 0, 12 ± 0, 04	Mean: 1, 0 ± 0, 12	Mean: 0, 90 ± 0, 09
	Median: 0, 2 (0, 1-0, 3)	Median: 0, 1 (0, 1-0, 2)	Median: 1, 0 (0, 8-1, 3)	Median: 0, 9 (0, 7-1, 0)

itself- may provoke cataract formation as well. Following intravitreal triamcinolone acetonide injection, progression of cataract has been reported in 0 to 57% [12]. Jonas *et al.* [13] has shown that cataract progression could be associated with increased IOP. Again, in asthmatic patients treatment with ciclesonide or beclomethasone dipropionate has been reported to have a minimal impact on lenticular opacities development and/or progression [14]. Herman *et al.* [15] have found an increased rate of cataract extraction and combined cataract/filtering surgery in cases treated with anti-glaucomatous drops and there was a borderline higher LOCS III grading for posterior subcapsular opacity in those cases. In the present study none of the cases experienced IOP elevation and cataract progression after ranibizumab injections.

Limitations of our study are the the lack of a placebo control, small number of subjects and a relatively short follow-up. Actually, treating a AMD patient with placebo would have introduced some ethical considerations hereby we have preffered a masked fashion. This small pilot study is designed to investigate and give an insight on the cataractogenic effect of ranibizumab. In conclusion, the early results of our study suggest that ranibizumab has no impact on the development and/or progression of lenticular opacification in AMD cases over a 12-month follow-up. We strongly believe that further studies, with a longer follow-up and larger scale, are required to validate this initial observation.

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