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Original Article

Comparison of intravitreal ranibizumab between phakic and pseudophakic neovascular age-related macular degeneration patients Two-year results

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Abstract

Background and objective: To compare the efficacy of intravitreal ranibizumab (IVR) for the treatment of neovascular age-related macular degeneration (nAMD) between phakic and pseudophakic eyes after a follow-up of two years.
Materials and methods: Data were analyzed retrospectively. The newly diagnosed and treatment naïve nAMD patients were included in the study. The patients were divided into two subgroups: phakic group, and pseudophakic. All patients received 3 consecutive monthly IVR injections, and then the treatment was continued on an as-needed regimen. Patients were examined monthly, and the data at the baseline, at month 6, 12, 18, and 24 were evaluated. The changes in best corrected visual acuity (BCVA), central retinal thickness (CRT), and the number of injections were compared between the two groups.
Results: The study included 92 eyes of 87 patients (58 phakic, 34 pseudophakic). Mean logarithm of the minimal angle of resolution (LogMAR) VA at the baseline, and at month 6, 12, 18, and 24 was 0.89, 0.74, 0.75, 0.73, and 0.75, in the phakic group; and 0.79, 0.71, 0.66, 0.70, and 0.70 in the pseudophakic group, respectively. The change in mean BCVA from the baseline to month 6, 12, 18, and 24 was not statistically different between the two groups ($p = 0.4$, $p = 0.9$, $p = 0.5$, $p = 0.6$, respectively). Mean injection number at month 24 was 7.9 and 8.1 in the phakic and pseudophakic group, respectively ($p = 0.7$).
Conclusion: Intravitreal ranibizumab treatment on an as-needed treatment regimen is effective in preserving vision and improving central retinal thickness in both the phakic and pseudophakic group of nAMD patients. The functional and anatomical outcomes of the treatment, and the number of injections were similar in the phakic and pseudophakic nAMD patients after a follow-up time of 24 months.

Keywords: Age-related macular degeneration, Cataract, Lens, Pseudophakia, Ranibizumab, Visual acuity

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Introduction

Neovascular age-related macular degeneration (nAMD) is the leading cause of severe visual loss among elderly population in developed countries.[1,2] Before the era of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy, only prevention for visual loss might have been achieved in a limited number of nAMD patients with different treatment options.[3–8] The introduction of bevacizumab (full length antibody against VEGF-A) and ranibizumab (Fab part of antibody

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against VEGF-A) has led the vast majority of the patients to preserve the baseline visual acuity (VA) and gave the chance of visual improvement to at least one third of the nAMD patients.[9,10] The multicenter studies showed that ranibizumab was effective to prevent VA loss up to 95% of the patients, and was effective to make an improvement in VA up to 40% of the patients.[10–13] These studies were mainly efficacy and dosing regimen studies, therefore they did not focus on lens status.

Recently, three studies were published about the effect of lens status on the treatment of nAMD with ranibizumab.[14–16] One of these studies was a meta-analysis of the patient data from ANCHOR and MARINA studies,[14] and the two other studies were retrospective single center studies.[15,16] No visual or anatomical differences were found between the phakic and pseudophakic eyes in these three studies.[14–16]

Hereditary factors, environmental factors, and ocular factors such as age-related alterations of the retina, inflammatory reactions, and the effect of free radicals are thought to be responsible for the pathogenesis of AMD.[17] In some experimental studies it was shown that excessive levels of white light exposure may induce the apoptosis of the photoreceptors.[18,19] Therefore the effect of cataract extraction on the progression of AMD is evaluated in many studies.[17,20–25] In most of the studies, it was suggested that cataract surgery may increase the development and progression of AMD.[20–25] This phenomenon was attributed to increased light toxicity, increased inflammation, and postoperative cystoid macular edema after cataract surgery.[17] However, there is still an ongoing debate about whether the cataract surgery has any effect on progression of AMD.[25] Many anatomical and biochemical changes occur in the vitreous after cataract surgery.[26,27] In addition, it is reported that posterior vitreous detachment (PVD) was induced after cataract surgery, and the presence of PVD was found to be related with increased retinal penetration of bevacizumab in rabbit eyes.[28] In regard to these findings we hypothesized that all of these changes after cataract surgery may affect the outcomes of IVR treatment for nAMD in pseudophakic patients and since there is a little amount of data on this topic, we aimed to compare the efficacy of IVR on an as-needed regimen between phakic and pseudophakic nAMD patients.

Materials and methods

In this retrospective, comparative study, we reviewed the records of the nAMD patients who had a baseline VA between 1.8 and 0.3 LogMAR and treated with intravitreal ranibizumab injection on an as-needed treatment regimen between January 2009 and January 2011. A written informed consent for the treatment was obtained from all patients before the treatment, and the study adhered to the tenets of the Declaration of Helsinki.

To be included in the study, each patient was required to have all of the following criteria; age $\geqslant$50 years, a best corrected VA (BCVA) between LogMAR 1.8 and 0.3, to be newly diagnosed as nAMD and treatment naive, and a minimum follow-up time of 24 months. Patients were not included in the study if they had a retinal disease other than nAMD, or if they had received previous intravitreal injection, or photodynamic therapy for nAMD, or if they had diagnosed as polypoidal choroidal vasculopathy, or retinal angiomatous proliferation, or if they were treated with other retreatment regimens, or if all of the follow-up data were not available. Also, the phakic patients who underwent cataract surgery during the follow-up time were excluded from the study. The patients were divided into two groups according to their lens state which were phakic and pseudophakic groups at the initial diagnosis. All the pseudophakic patients had undergone uneventful phacoemulsification surgery and had intact posterior capsules. The pseudophakic patients who were included had undergone cataract surgery at least 6 months before the beginning of the IVR treatment.

Data collected from the patients' records included age, gender, choroidal neovascularization (CNV) type (predominantly classic or minimal classic/occult), BCVA and central retinal thickness (CRT) at baseline, month 6, month 12, month 18, and month 24. The total number of injections at month 12 and 24 was also recorded.

The included patients underwent a standardized examination including measurement of BCVA (visual acuity was measured as Snellen lines then converted to LogMAR for statistical analyses), slit-lamp biomicroscopy, intraocular pressure (IOP) measurement via applanation tonometry, and fundus examination. Fundus photography, fluorescein angiography (FA) (HRA-2; Heidelberg Engineering, Heidelberg, Germany), and optical coherence tomography (OCT) imaging (Stratus OCT TM; Carl Zeiss Meditec Inc., Dublin, CA, USA.) were performed before treatment. All examinations were repeated monthly, except FA. Fluorescein angiography was repeated only when the cause of VA deterioration could not be clarified with the other methods. Optical coherence tomography was used for detecting subretinal fluid and measurement of CRT. Central retinal thickness, defined as the mean thickness of the neurosensory retina in a central 1 mm diameter area, was computed using OCT mapping software generated by the device.

All injections were performed under sterile conditions after topical anesthesia, 10% povidone-iodine (Betadine; Purdue Pharma, Stamford, CT) scrub was used on the lids and lashes, and 5% povidone-iodine was administered on the conjunctival sac. Intravitreal ranibizumab (Lucentis; Novartis, Basel, Switzerland) was injected through the pars plana at 3.5 mm posterior to the limbus with a 30-gauge needle. Patients were instructed to return to the hospital if they experienced decreased vision, eye pain, or any new symptoms.

Initially, all patients received a loading dose of three consecutive monthly IVR injections (0.5 mg/0.05 ml). Then the patients were followed monthly, and a single injection of IVR was repeated when the VA decreased by one or more ETDRS lines from the last visit, or newly developed macular hemorrhage, or evidence of subretinal fluid on OCT. The follow-up visits of the patients were performed by two physicians who had the same clinical practice patterns (AO, ATY).

Primary outcome measures of this study included the change in BCVA and OCT defined CRT from baseline to months 6, 12, 18, and 24. Secondary outcome measures were the total number of injections at months 12 and 24, and the complications of intravitreal injections.

Statistical analysis

Visual acuity was converted to the logarithm of the minimum angle of resolution (LogMAR) for statistical analysis.

Categorical variables were presented as numbers and percentages, while numerical variables were expressed as the mean and standard deviation. The baseline characteristics and outcome measures between the groups were compared using the Chi-square test for categorical variables and independent sample test or Mann–Whitney test for numerical variables. The statistical evaluation was performed using SPSS (Version 16.0, SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was considered to be statistically significant.

Results

Ninety-two eyes of 87 patients met the inclusion criteria for the study. The mean age of the patients was 73.5 ± 7.8 years (range 53–89 years). Forty-two patients (48.3%) were male, 45 patients (51.7%) were female. Predominantly classic CNV was present in 21 eyes (22.8%), and occult/minimally classic CNV was present in 71 eyes (77.2%). The mean number of injections at month 12, and 24 was 5.4 ± 1.5 (range 3–8), and 8.0 ± 2.9 (range 3–15). Fifty-eight eyes (63.0%) were phakic, and 34 eyes (37.0%) were pseudophakic. The general characteristics of the two groups were similar (Table 1).

The mean BCVA of the phakic and pseudophakic patients at baseline was 0.89 ± 0.44 and 0.79 ± 0.44 LogMAR, respectively. There was not a significant difference between the mean BCVA levels of the groups at all of the study visits ($p > 0.05$ for all, Table 2, Fig. 1). In addition, the change in mean BCVA from baseline to months 6, 12, 18, and 24 was statistically different in both the groups ($p = 0.004$, $p = 0.01$, $p = 0.009$, $p = 0.02$, respectively for the phakic group; $p = 0.007$, $p = 0.01$, $p = 0.03$, $p = 0.03$, respectively for the pseudophakic group). However, the change in the mean BCVA from baseline to months 6, 12, 18, and 24 was not statistically different between the two groups ($p = 0.4$, $p = 0.9$, $p = 0.5$, $p = 0.6$, respectively).

At month 24, 20 eyes (34.4%) in the phakic group and 13 eyes (38.2%) in the pseudophakic group had gained VA $\geqslant$ 3 lines ($p = 0.2$). Fifty eyes (86.2%) in the phakic group and 28 eyes (82.3%) in the pseudophakic group had stable or improved vision (loss of <3 line, or remained stable, or gained $\geqslant$1 lines) ($p = 0.7$). Eight eyes (13.8%) in the phakic group and 6 eyes (17.6%) in the pseudophakic group had loss of VA $\geqslant$ 3 lines ($p = 0.7$).

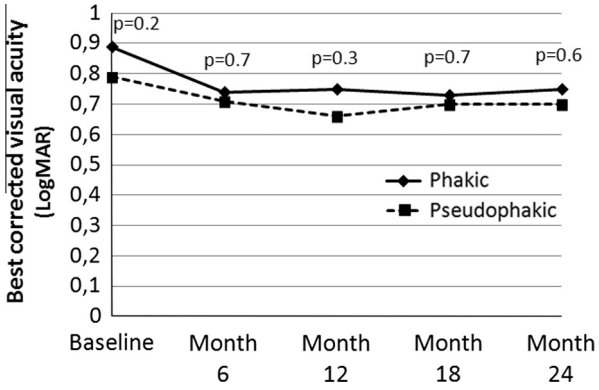

Figure 1. Changes in mean visual acuity in the phakic and pseudophakic groups. The graph shows the mean LogMAR visual acuity levels from baseline to 24 months. The p values for phakic versus pseudophakic groups at each time point.

The mean CRT of the phakic and pseudophakic patients at baseline was 322 ± 99 and 333 ± 89 microns, respectively. There was not a significant difference between the mean CRT levels of the two groups at all of the study visits ($p > 0.05$ for all, Table 2, Fig. 2). In addition, the change in mean CRT from the baseline to months 6, 12, 18, and 24 was statistically different in both the two groups ($p = 0.001$, $p = 0.0001$, $p = 0.0001$, $p = 0.002$, respectively for the phakic group; $p = 0.0001$, $p = 0.0001$, $p = 0.001$, $p = 0.001$, respectively for the pseudophakic group). However, the change in mean CRT from the baseline to months 6, 12, 18, and 24 was not statistically different between the two groups ($p = 0.2$, $p = 0.4$, $p = 0.5$, $p = 0.5$, respectively).

The total number of injections at month 12 was 5.4 ± 1.3 (range 3–8) in the phakic group and 5.4 ± 1.7 (range 3–8) in the pseudophakic group ($p = 0.8$), and the total number of injections at month 24 was 7.9 ± 2.5 (range 3–14) in the

Table 1. Baseline characteristics of the two groups.

	Phakic group	Pseudophakic group	P value
Mean age	72.4 ± 7.1 years (range 53–85 years)	75.4 ± 8.6 years (range 54–89 years)	0.08
Gender (F/M)	21/32	21/13	0.06
CNV type (O/C)	11/47	10/24	0.3

F, female; M, male; R: right eye; L, left eye; CNV, choroidal neovascularization; O, occult; C, classic.

Table 2. LogMAR visual acuity values and CRT findings in microns in the phakic and pseudophakic groups at different time points.

Variables	Phakic	Pseudophakic	Phakic vs pseudophakic p values
Baseline visual acuity, mean	0.89 ± 0.44 (range 0.3–1.8)	0.79 ± 0.44 (range 0.4–1.8)	0.2
Month 6 visual acuity, mean	0.74 ± 0.37 (range 0.1–1.5)	0.71 ± 0.52 (range 0.1–2.1)	0.7
Month 12 visual acuity, mean	0.75 ± 0.42 (range 0.1–1.7)	0.66 ± 0.52 (range 0.0–2.1)	0.3
Month 18 visual acuity, mean	0.73 ± 0.44 (range 0.2–2.1)	0.70 ± 0.57 (range 0.0–2.1)	0.7
Month 24 visual acuity, mean	0.75 ± 0.45 (range 0.2–2.1)	0.70 ± 0.56 (range 0.0–2.1)	0.6
Baseline CRT, mean	322 ± 99 μ (range 198–681)	333 ± 89 μ (range 174–516)	0.6
Month 6 CRT, mean	272 ± 83 μ (range 155–553)	253 ± 63 μ (range 165–463)	0.2
Month 12 CRT, mean	258 ± 65 μ (range 150–443)	250 ± 58 μ (range 178–414)	0.5
Month 18 CRT, mean	257 ± 61 μ (range 156–403)	251 ± 67 μ (range 151–483)	0.6
Month 24 CRT, mean	264 ± 73 μ (range 146–429)	258 ± 69 (range 139–425)	0.6

CRT: central retinal thickness, LogMAR: logarithm of the minimum angle of resolution, vs: versus, μ: microns.

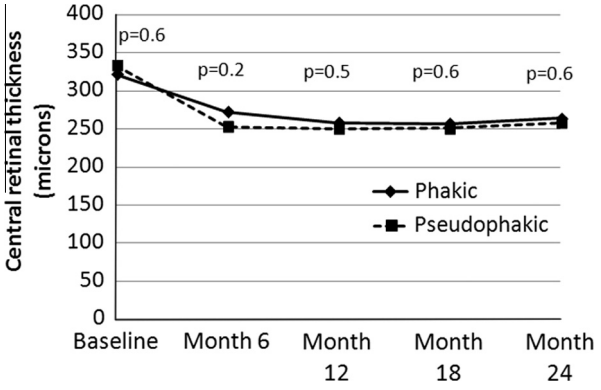

Figure 2. Changes in mean central retinal thickness in the phakic and pseudophakic groups. The graph shows the mean central retinal thickness levels from baseline to 24 months. The p values for phakic versus pseudophakic groups at each time point.

phakic group and 8.1 ± 3.5 (range 3–15) in the pseudophakic group ($p = 0.7$).

No serious complications such as endophthalmitis, vitreous hemorrhage, and retinal detachment were observed in any of the patients. Only mild complications such as punctuate keratitis (10.5% in phakic group, 15% in pseudophakic group, $p = 0.2$) subconjunctival hemorrhage (8.7% in phakic group, 7.5% in pseudophakic group, $p = 0.7$), transient mild anterior uveitis (3.5% in phakic group, 5.0% in pseudophakic group, $p = 0.6$) were detected.

Discussion

Although the effect of cataract surgery on the progression of AMD is widely studied, there are only three studies which compare the efficacy of intravitreal anti-VEGF agents between phakic and pseudophakic patients.[14–16] The results of our study are consistent with these previous studies; there are a few differences in regard to visual acuity cut-off points and treatment protocol details.[14–16]

In a study by Baek et al.,[15] intravitreal ranibizumab on an as-needed treatment regimen was found to be effective in both phakic and pseudophakic patients. In the study it was reported that, the anatomical and visual outcomes were similar between the two groups after a mean follow-up period of 18 months. The mean injection number of the phakic and pseudophakic group was reported to be 3.87 and 3.62, respectively and was reported not to be statistically different. Also the possible effect of posterior vitreous detachment on the intravitreal ranibizumab treatment was mentioned in the study. However, this relationship was not evaluated, and it is announced that the authors were evaluating this relationship in an ongoing study.[15] The visual and anatomical outcomes of our study are similar to the study by Baek et al. The mean injection number was very low in the study by Baek et al. This may be due to one of the retreatment criteria of this study which was ''visual loss''. At the present, only one line of visual acuity loss is considered as a retreatment criterion, however in the study by Baek et al., the visual acuity criterion for retreatment was considered as loss of two or more lines.

In a meta-analysis of individual patient data from the ANCHOR and MARINA studies, the outcomes of monthly ranibizumab treatment were compared between the phakic and pseudophakic patients.[14] In the study 243 phakic and 179 pseudophakic eyes from the ANCHOR study, and 385 phakic and 330 pseudophakic eyes from the MARINA study were evaluated. No visual or anatomical differences were found between the phakic and pseudophakic eyes in the study.[14]

In a more recent study by Ozkaya et al.,[16] the treatment outcomes of as-needed ranibizumab treatment were compared between the phakic and pseudophakic groups of nAMD patients with a good baseline visual acuity. The results of the study were similar to our study and no difference was found between the two groups in regard to visual and anatomical outcomes.

Although the results of our study are consistent with the previous three studies; there are a few differences in regard to visual acuity cut-off points and treatment protocol details.

In a more recent study, the effect of posterior vitreous detachment on the intravitreal bevacizumab or ranibizumab treatment was evaluated by Üney et al.[29] They reported that the patients with posterior vitreous detachment had better visual outcomes than the patients with attached posterior vitreous.

In this study, intravitreal ranibizumab on as-needed treatment regimen was found to be effective in both phakic and pseudophakic group of patients. There was not a statistically significant difference in improvement of BCVA and CRT, and the mean injection numbers between the two groups. These results may show that the therapeutic effect of intravitreal ranibizumab treatment does not change after cataract extraction in this subgroup of patients, and both phakic and pseudophakic patients may equally benefit from this therapy. This may be attributable to different mechanisms. It is conventionally thought that the presence of cataract has a protective effect on the progression of nAMD and it is a known fact that PVD is induced after cataract surgery in up to 60% of the patients, on the other hand in some studies it is reported that the therapeutic effects of intravitreal injections were better in the presence of PVD.[27,29] The results of our study may be explained by the combination of these data and it may be proposed that the presence of PVD may offset the negative effects of cataract surgery on the progression of nAMD.

The main limitation of the study was the retrospective design. Also we used a time domain OCT device and the incidence of posterior vitreous detachment was not evaluated in the patients. The time domain OCT guided as-needed treatment regimens may not be as effective as spectral domain OCT guided as-needed treatment regimens because of the difference between the resolutions of the devices, therefore this was a limitation. The powerful sides were the relatively long follow-up time and the similarity of baseline characteristics in the two groups. Randomized controlled studies including the other variables such as the presence of posterior vitreous detachment, and the factors that may affect the final visual outcomes would be necessary in this subgroup of patients.

In conclusion, the results of this study imply that the therapeutic effects of IVR treatment were similar in both of the pseudophakic and phakic group of nAMD patients.

Conflict of interest

The authors declared that there is no conflict of interest.

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