Comparison of intravitreal bevacizumab treatment between phakic and pseudophakic neovascular age-related macular degeneration patients

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Abstract

Introduction: Before the era of intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment, only prevention for visual loss might have been achieved in a limited number of neovascular age-related macular degeneration (nAMD) patients with different treatment options. Objective: To compare the efficacy of intravitreal bevacizumab (IVB) for the treatment of nAMD between phakic and pseudophakic eyes. Materials and methods: The newly diagnosed nAMD patients were included in this retrospective study. The patients were divided into the phakic and pseudophakic groups. Initially, the patients received three consecutive, monthly, IVB injections, and then the treatment was continued on an as-needed regimen. The patients were examined monthly, and the data at the baseline, at 3, 6, 9, and 12 months and at the last follow-up were evaluated. The changes in the visual acuity (VA), central retinal thickness (CRT) and the number of injections were compared between the two groups. Results: The study included 62 eyes of 62 patients (39 phakic, and 23 pseudophakic patients). The mean follow-up time was 19.7 and 17.2 months in the phakic and pseudophakic groups, respectively (p = 0.06). The mean Log MAR VA at the baseline, 12 months and the last follow-up was 0.82, 0.72 and 0.75 in the phakic group and 0.77, 0.67, and 0.68 in the pseudophakic group, respectively. The change in the mean BCVA from the baseline to 12 months and at the last follow-up was not statistically different between the two groups (p = 0.9 and p = 0.7, respectively). The mean injection number at 12 months was 4.5 and 4.9 in the phakic and pseudophakic group, respectively (p = 0.2). Conclusion: The beneficial effect of IVB is equal 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 two groups.

Keywords: angiogenesis, bevacizumab, cataract, lens, macular degeneration, VEGF
nAMD patients with different treatment options (Manousaridis et al., 2013; Mauget-Faÿsse et al., 2000; Macular photocoagulation study group, 1991; Aslankurt et al., 2013; Özkaya et al., 2010). Intravitreal bevacizumab (IVB, full-length antibody against VEGF-A) and ranibizumab (the fab part of the antibody against VEGF-A) treatments led to the prevention of the VA in about 90 - 95% of the patients and resulted in the visual improvement of at least one third of the nAMD patients (Tao et al., 2010; Brown et al., 2006; Rosenfeld et al., 2006; Lalwani et al., 2009; Martin et al., 2011). The studies showed that ranibizumab and bevacizumab were effective in the prevention of the VA loss in 95% of the patients and were effective in improving the VA in up to 40% of the patients (Brown et al., 2006; Rosenfeld et al., 2006; Lalwani et al., 2009; Martin et al., 2011). These studies were mainly efficacy and dosing regimen studies and comparative studies for the two drugs; therefore, they did not focus on the lens status. Three studies on the effect of the lens status on the treatment of nAMD with ranibizumab have recently been published (Weinberg et al., 2013; Baek et al.; 2013, Ozkaya et al., 2013). The Weinberg et al study was a meta-analysis of the patient data from ANCHOR and MARINA studies and the other two (Baek et al and Ozkaya et al) were retrospective, single-center studies. Since much data on this topic is not available, we in this study aimed to compare the efficacy of IVB on an as-needed regimen between phakic and pseudophakic nAMD patients.

**Materials and methods**

In this retrospective, comparative study, the records of the nAMD patients who had a baseline VA between 1.3 and 0.3 LogMAR and had been treated with intravitreal bevacizumab injection on an as-needed treatment regimen between January 2009 and January 2011 were reviewed. A written informed consent for the treatment was obtained from all the patients, 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 ≥ 50 years, a best corrected VA (BCVA) between LogMAR 1.3 and 0.3, newly diagnosed as nAMD and having had a treatment that was naïve if any, and a minimum follow-up period of 12 months. Patients were not included in the study if they had a retinal disease other than nAMD, or if they had received any kind of treatment for nAMD (intravitreal injection or photodynamic therapy). And the phakic patients who underwent cataract surgery during the follow-up period were also excluded. At the initial diagnosis, the patients were divided into the phakic and pseudophakic groups, according to their lens state. The pseudophakic patients included in the study were chosen on the basis of an uneventful phacoemulsification surgery prior to the study and having an intact posterior capsule.

The 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, at 3, 6, 9 and 12 months and at the most recent follow-up. The total number of injections given was also recorded at 12 months.

The patients included in the study underwent a standardized examination including measurement of BCVA via the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 meters, 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 the treatment. All examinations except FA were repeated monthly. 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 in the operation room. 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 bevacizumab (Avastin; Genentech, South San Francisco, CA, USA) was injected through the pars plana with a 30-gauge needle at a point 3.5 mm posterior to the limbus. The patients were instructed to be admitted 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, IVB injections (1.25 mg/0.05 ml). The patients then were followed-up monthly, and a single IVB injection was repeated when the VA decreased by one or more ETDRS lines from the last visit, or when a newly developed macular hemorrhage or evidence of subretinal fluid on OCT was present.

The primary outcome measures of this study included the change in BCVA and CRT from the baseline to 3, 6, 9, and 12 months and to the most recent follow-up. The secondary outcome measures were the total number of injections at 12 months 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. The categorical variables were presented as numbers and percentages, while the numerical 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 the independent sample test or Mann-Whitney test for the 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
Sixty-two eyes of 62 patients met the inclusion criteria for the study. The mean age of the patients was 72.0 ± 8.5 years (range 52 - 88 years). Twenty-nine patients (46.8 %) were male and 33 (53.2 %) were female. Predominantly classic CNV was present in 12 (62.9 %) eyes and occult/minimally classic CNV was present in 50 (80.6 %) eyes. The mean follow-up period was 18.7 ± 4.8 months (range 12 - 24 months). The mean number of injections at 12 months was 4.6 ± 1.2 (range 3 - 7). Thirty-nine eyes (62.9 %) were phakic, and 23 eyes (37.1 %) 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 0.82 ± 0.25 and 0.77 ± 0.28 LogMAR, respectively. There was no significant difference between the mean BCVA levels of the two groups at all of the study visits (p > 0.05 for all, Table 2). In addition, the changes in the mean BCVA from the baseline to 3, 6, 9, and 12 months and to the most recent follow-up were statistically different in both the two groups (p < 0.05 for all, Table 2). However, the change in the mean BCVA from the baseline to 3, 6, 9, and 12 months and to the most recent follow-up was not statistically different between the two groups (p = 0.8, p = 0.8, p = 0.8, p = 0.9, and p = 0.7, respectively).

At 12 months, 15 eyes (38.4 %) in the phakic group and 8 eyes (34.7 %) in the pseudophakic group had gained VA by ≥3 lines (p=0.7). Thirty-two eyes (82.1 %) in the phakic group and 21 eyes (91.7 %) in the pseudophakic group had a stable or improved vision (loss of < 3 lines, or
had remained stable, or gained by \( \geq 1 \) line) 
\((p = 0.4)\). Seven eyes (17.9 \%) in the phakic group and 2 eyes (8.7 \%) in the pseudophakic group had loss of VA by \( \geq 3 \) lines \((p = 0.4)\).

The mean CRT of the phakic and pseudophakic patients at baseline was 328 ± 104 and 311 ± 97 microns, respectively. There was no significant difference between the mean CRT levels of the two groups at all of the study visits \((p > 0.05\) for all, Table 2\). In addition, the change in the mean CRT from the baseline to 3, 6, 9, and 12 months and to the most recent follow-up was statistically different in both the groups \((p > 0.05\) for all, Table 2\). However, the change in the mean CRT from the baseline to 3, 6, 9, and 12 months and to the most recent follow-up was not statistically different between the two groups \((p = 0.6, p = 0.7, p = 0.9, p = 0.4,\) and \(p = 0.4,\) respectively).

The total number of injections at 12 months 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 12 months was 4.5 ± 1.2 \((range 3 - 7)\) in the phakic group and 4.9 ± 1.3 \((range 3 - 7)\) in the pseudophakic group \((p = 0.2)\).

No serious complications like endophthalmitis, vitreous hemorrhage or retinal detachment were observed in any of the patients in the two groups. Only mild complications like punctuate keratitis \((12.8 \% in the phakic group and 18.1 \% in the pseudophakic group, p = 0.2)\) subconjunctival hemorrhage \((15.3 \% in the phakic group, 9.0 \% in pseudophakic group, p = 0.1)\), transient mild anterior uveitis \((7.6 \% in the phakic group, 4.5 \% in the pseudophakic group, p = 0.6)\) were detected.

### Table 1: General characteristics of the phakic and pseudophakic patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Phakic Group</th>
<th>Pseudophakic Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>71.2 ± 8.4 years (range 52 - 86 years)</td>
<td>73.2 ± 8.6 years (range 54 - 88 years)</td>
<td>0.3</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>16/23</td>
<td>13/10</td>
<td>0.3</td>
</tr>
<tr>
<td>CNV type (O/C)</td>
<td>7/32</td>
<td>5/18</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean follow-up time</td>
<td>19.7 ± 4.7 months (range 12-24 months)</td>
<td>17.2 ± 8.4 months (range 12-24 months)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Abbreviations: F: female; M: male; RE: right eye; LE: left eye; CNV: choroidal neovascularization; O: occult; C: classic; GLD: greatest linear dimension; DD: disc diameter; p: P value.

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Phakic</th>
<th>Pseudophakic</th>
<th>Phakic vs Pseudophakic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline visual acuity, mean</td>
<td>0.82 ± 0.25 (range 0.3-1.3)</td>
<td>0.77 ± 0.28 (range 0.3-1.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>Month 3 visual acuity, mean mean change from baseline baseline vs month 3 p value</td>
<td>0.76 ± 0.38 (range 0.3-1.8) +0.6 LogMAR line 0.3</td>
<td>0.74 ± 0.37 (range 0.2-1.5) +0.3 LogMAR line 0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Month 6 visual acuity, mean mean change from baseline baseline vs month 6 p value</td>
<td>0.73 ± 0.37 (range 0.3-1.8) +0.9 LogMAR line 0.1</td>
<td>0.67 ± 0.33 (range 0.2-1.3) +1.0 LogMAR line 0.09</td>
<td>0.4</td>
</tr>
<tr>
<td>Month 9 visual acuity, mean mean change from baseline baseline vs month 9 p value</td>
<td>0.72 ± 0.37 (range 0.3-1.8) +1.0 LogMAR line 0.04</td>
<td>0.66 ± 0.27 (range 0.2-1.3) +1.1 LogMAR line 0.02</td>
<td>0.4</td>
</tr>
</tbody>
</table>
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Discussion

Environmental factors, hereditary factors, and various ocular factors like age-related alterations of the retina, inflammatory reactions, and the effect of free radicals are thought to be responsible for the pathogenesis of AMD (Algvere et al, 2006). In some studies, it was shown that high levels of white light exposure may induce the apoptosis of the photoreceptors (Grimm et al, 2000; Hafezi et al, 1997). Therefore the effect of cataract extraction on the progression of AMD has been evaluated in many studies (Algvere et al, 2006; Pollack A et al, 1996; Wang et al, 2003; Van der Schaft TL et al, 1994; Wang et al, 2012). It was suggested in most of the studies that cataract surgery may increase the development and progression of AMD (Pollack A et al, 1996; Wang et al, 2003; van der Schaft TL et al, 1994; Wang et al, 2012). This phenomenon was attributed to increased inflammation, increased light toxicity, and postoperative cystoid macular edema after cataract surgery (Algvere et al, 2006). However, there is a debate about the relationship between cataract surgery and the progression of AMD (Wang et al, 2003).

| Month 12 visual acuity, mean change from baseline vs month 12 | 0.72 ± 0.35 (range 0.3-1.8) +1.0 LogMAR line 0.04 | 0.67 ± 0.30 (range 0.3-1.3) +1.0 LogMAR line 0.04 | 0.6 |
| Most recent visual acuity, mean change from baseline vs most recent | 0.75 ± 0.44 (range 0.3-2.1) +0.7 LogMAR line 0.3 | 0.68 ± 0.30 (range 0.3-1.5) +0.9 LogMAR line 0.1 | 0.4 |
| Baseline CRT, mean | 328 ± 104 μ (range 211-598) | 311±97 μ (range 186-598) | 0.5 |
| Month 3 CRT, mean change from baseline vs month 3 | 273±82 μ (range 169-477) -55 μ 0.002 | 272±108 μ (range 178-676) -39 μ 0.02 | 0.9 |
| Month 6 CRT, mean change from baseline vs month 6 | 262±79 μ (range 140-477) -66 μ 0.0001 | 253±70 μ (range 140-463) -58 μ 0.01 | 0.6 |
| Month 9 CRT, mean change from baseline vs month 9 | 252±65 μ (range 149-414) -76 μ 0.0001 | 238±54 μ (range 148-365) -73 μ 0.0001 | 0.3 |
| Month 12 CRT, mean change from baseline vs month 12 | 250±74 μ (range 150-443) -78 μ 0.0001 | 256±64 (range 180-444) -54 μ 0.02 | 0.7 |
| Most recent CRT, mean change from baseline vs most recent | 236±69 μ (range 136-449) -92 μ 0.0001 | 244±76 (range 136-444) -67 μ 0.02 | 0.7 |

* p values for phakic vs pseudophakic groups; the other p values are for the change achieved with the two groups relative to the baseline values.

CRT: central retinal thickness, LogMAR: logarithm of the minimum angle of resolution, vs: versus, μ: microns.
Several studies have investigated the efficacy of intravitreal anti-VEGF agents between phakic and pseudophakic patients. A meta-analysis of individual patient data from the ANCHOR and MARINA studies showed that the outcomes of monthly ranibizumab treatment were compared between the phakic and pseudophakic patients (Weinberg et al., 2013). 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 (Weinberg et al., 2013).

Üney et al. (2013) evaluated the effect of posterior vitreous detachment on the intravitreal bevacizumab or ranibizumab treatment in a more recent study. The authors report that the patients with posterior vitreous detachment had better visual outcomes than did the patients with attached posterior vitreous. In this study, IVB on a as-needed treatment regimen was found to be effective in both the phakic and pseudophakic group of nAMD patients. There was no statistically significant difference in improvement of the BCV A, CRT and the mean number of injections between the two groups. These results may show that the therapeutic effect of IVB treatment does not change after cataract surgery in this subgroup of patients, and that both phakic and pseudophakic patients may equally benefit from intravitreal anti-VEGF therapy.

To our knowledge, this is the first study that compares the efficacy of IVB between the phakic and pseudophakic group of nAMD patients (from a PubMed search). The main limitations of this study were the retrospective design and the number of patients. Also, we used a time domain OCT device and the incidence of posterior vitreous detachment was not evaluated in the patients. The stronger points of this study were the relatively long follow-up period and the similarity of the baseline characteristics in the two groups. Randomized controlled studies including the other variables like presence of
posterior vitreous detachment and the factors that may affect the final visual outcomes would be necessary in this subgroup of nAMD patients.

Conclusion
Although it is believed that cataract surgery has an unfavorable effect on AMD progression and has a negative effect on the vitreous in many aspects, no difference was found in the efficacy of IVB between the phakic and pseudophakic group of the nAMD patients.

References


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