Original article

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

Abdullah Ozkaya, Zeynep Alkin, Irfan Perente, Kemal Yuksel, Okkes Baz, Cengiz Alagoz, Ahmet Taylan Yazici, Ahmet Demirok
Beyoglu Eye Training and Research Hospital, and
Medeniyet University, Department of Ophthalmology,
Istanbul, Turkey

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 generation (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

Introduction

Neovascular age-related macular degeneration (nAMD) is the most frequent etiologic factor of severe visual loss among the elderly population in the West (Leveziel et al, 2009; Ferris et al, 1984). 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

Received on: 21.11.2013 Accepted on: 24.03.2014
Address for correspondence
Abdullah Ozkaya, MD
Beyoglu Eye Training and Research Hospital, Bereketzade Camii Sok., 34421, Kuledibi, Beyoglu, Istanbul, Turkey.
Tel: 0090 505 452 92 70
Email: abdozkaya@gmail.com

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 admited 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 ≥ 1 line) (p = 0.4). Seven eyes (17.9 %) in the phakic group and 2 eyes (8.7 %) in the pseudophakic group a had loss of VA by ≥ 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

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

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

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

Month 12 visual acuity, mean mean change from baseline baseline vs month 12 p value	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 mean change from baseline baseline vs most recent p value	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 mean change from baseline baseline vs month 3 p value	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 mean change from baseline baseline vs month 6 p value	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 mean change from baseline baseline vs month 9 p value	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 mean change from baseline baseline vs month 12 p value	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 mean change from baseline baseline vs most recent p value	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, ì : microns.

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).

Although the effect of cataract surgery on the progression of AMD has been studied widely, there are only a few studies which compare the efficacy of intravitreal anti-VEGF agents between phakic and pseudophakic patients (Weinberg et al, 2013; Baek et al, 2013; Ozkaya et al, 2013). In a study by Baek et al. (2013), intravitreal ranibizumab on an as-needed treatment regimen was found to be effective in both the phakic and pseudophakic nAMD patients. In this study, it was reported that the BCVA improved 1.3 LogMAR lines in the phakic patients and 1.2 LogMAR lines in the pseudophakic patients after a mean follow-up period of 18 months; and the authors stated that the difference between the two groups was not statistically significant. They also reported that the mean baseline CRT was 561 μm in the phakic group and 559 μm in the pseudophakic group, and that the decrease in the mean CRT levels at 6, 9, and 12 months, and at the last follow-up was not statistically different between the phakic and pseudophakic groups. The mean number of injections of the phakic and pseudophakic group was reported to be 3.87 and 3.62, respectively, and was reported not to be statistically different. 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 has been announced that the authors were evaluating this relationship in an ongoing study (Baek et al, 2013). The visual and anatomical outcomes of our study are similar to the study by Baek et al (2013). The mean number of injections was very low in the study by Baek et al (2013). This may be due to one of the retreatment criteria of this study which was "visual loss". At the present time, only one line of visual acuity loss is considered as a retreatment criterion; however, in the study by Baek et al. (2013), the visual acuity criterion for retreatment was considered as loss of two or more lines.

The other study about the effect of lens status on the treatment of nAMD with anti-VEGF agents is 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 (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) have 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 BCVA, 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

Leveziel N, Delcourt C, Zerbib J, Dolfius H, Kaplan J, Benlian P et al (2009). [Epidemiology of age related macular degeneration]. J Fr Ophtalmol;32:440-451. [Article in French]

Ferris FL 3rd, Fine SL, Hyman L (1984). Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol; 102:1640-1642.

Manousaridis K, Manjunath V, Talks J (2013). Information used to decide on retreatment of exudative age-related macular degeneration with anti-VEGF in clinical practice. Eur J Ophthalmol;23:108-3.

Mauget-Faÿsse M, Cougard R, Français-Maury C, Milea D, Chiquet C, Martin P, et al (2000). [Radiotherapy for age-related macular degeneration: risk factors of complications, prevention and treatment side-effects]. J Fr Ophtalmol;23:127-136. [Article in French]

Macular Photocoagulation Study Group (1991). Laser photocoagulation of subfoveal neovascular lesions in age-related macular degeneration. Results of a randomized clinical trial. Arch Ophthalmol;109:1220-1231

Aslankurt M, Aslan L, Aksoy A, Erden B, Cekiç O (2013). The results of switching between 2 anti-VEGF drugs, bevacizumab and ranibizumab, in the treatment of neovascular age related macular degeneration. Eur J Ophthalmol;23:553-7.

Özkaya A, Gürcan Z, Yiðit U, Elmastaþ Gültekin Ö, Özkaya HM (2010). Photodynamic therapy results in age related macular degeneration. Ret-Vit; 4:289-96.

Tao Y, Libondi T, Jonas JB (2010). Long-term follow-up after multiple intravitreal bevacizumab injections for exudative age-related macular degeneration. J Ocul Pharmacol Ther.;26:79-83.

Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group (2006). Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med;355:1432-1444.

Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group (2006). Ranibizumab for neovascular age-related macular degeneration. N Engl J Med;355:1419-1431.

Lalwani GA, Rosenfeld PJ, Fung AE, et al (2009). A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol;148:43-58.

CATT Research Group; Martin DF, Maguire MG, Ying GS, et al (2011). Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med.;364;1897-1908.

Weinberg DV, Shapiro H, Ehrlich JS (2013). Ranibizumab treatment outcomes in phakic versus pseudophakic eyes an individual patient data analysis of 2 phase 3 trials. Ophthalmology; 120:1278-1282.

Baek JS, Cho HJ, Cho SW, Kim CG, Kim JW (2013). Intravitreal ranibizumab injection for neovascular age-related macular degeneration in phakic versus pseudophakic eyes. Retina;33:467-473.

Ozkaya A, Alkin Z, Yazici AT, Demirok A. Comparision of intravitreal ranibizumab in

phakic and pseudophakic neovascular age-related macular degeneration patients with good baseline visual acuity. Retina; October 17. [Epub ahead of print]

Algvere PV, Marshall J, Seregard S (2006). Age-related maculopathy and the impact of blue light hazard. Acta Ophthalmol Scand;84:4-15.

Grimm C, Reme CE, Rol PO, Williams TP (2000). Blue light's effects on rhodopsin: photoreversal of bleaching in living rat eyes. Invest Ophthalmol Vis Sci;41:3984-3990.

Hafezi F, Marti A, Munz K, Remé CE (1997). Light-induced apoptosis: differential timing in the retina and pigment epithelium. Exp Eye Res;64:963-970.

Pollack A, Marcovich A, Bukelman A, Oliver M (1996). Age-related macular degeneration after extracapsular cataract extraction with intraocular lens implantation. Ophthalmology;103:1546-1554

Wang JJ, Klein R, Smith W, Klein BE, Tomany S, Mitchell P (2003). Cataract surgery and the 5-year incidence of late-stage age-related maculopathy: pooled findings from the Beaver Dam and Blue Mountains eye studies. Ophthalmology;110:1960-1967.

van der Schaft TL, Mooy CM, de Bruijn WC, Mulder PG, Pameyer JH, de Jong PT (1994). Increased prevalence of disciform macular degeneration after cataract extraction with implantation of an intraocular lens. Br J Ophthalmol; 78:441-445.

Wang JJ, Fong CS, Rochtchina E, et al (2012). Risk of age-related macular degeneration 3 years after cataract surgery: paired eye comparisons. Ophthalmology;119:2298-2303

Üney GÖ, Ünlü N, Acar MA, et al (2013). Role of posterior vitreous detachment on outcome of anti-vascular endothelial growth factor treatment in age-related macular degeneration. Retina June 6. [Epub ahead of print].

Source of support: nil. Conflict of interest: none