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Original Article

Based on the Real-Life Data of Türkiye; Comparison of Anatomical and Functional Outcomes of Phakic and Pseudophakic Patients in Wet Type Age-Related Macular Degeneration

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Abstract

Objectives: The aim of the study was comparison of wet-type age-related macular degeneration in phakic and pseudophakic patients in terms of anatomical and functional success based on the real-life data of Türkiye.

Methods: The multicenter retrospective real-life study data of the. retinal study group were used in this study. Among 867 eyes of 867 patients were included in the study. Patients were divided into two groups according to the status of the lens; phakic group and pseudophakic group. The follow-up period of the two groups, the number of injections at the 1st, 2nd, and 3rd years, and changes in the central macular thickness (CMT, μ) and visual acuity (VA, logMAR) of the patients at the beginning, 6th, 12th, 24th, and 36th months were examined.

Results: In our study, the number of injections in the 1st, 2nd, and 3rd years, respectively, was 4.2±2.0, 1.8±1.9, and 1.0±1.7 in the phakic group, and 3.9±2.0, 1.7±1.9, and 0.8±1.4 in the pseudophakic group. When the two groups were compared in terms of the number of injections, there was a statistically significant difference in the 1st year, but there was no significant difference in the 2nd and 3rd years (p=0.001, p=0.350, and p=0.288, respectively). There was no statistically significant

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difference between the groups in terms of CMT in the baseline, 6th, 12th, 24th, and 36th months (p=0.991, p=0.327, p=0.652, p=0.599, and p=0.873, respectively). Although there was no difference in VA between groups at the beginning (p=0.052), the phakic group showed statistically better VA in controls at 3rd, 6th, 12th, 24th, and 36th months (p=0.001, p=0.001, p=0.000, p=0.000, and p=0.003, respectively).

Conclusion: Differences in the number of injections and visual results between phakic and pseudophakic patients in wet type AMD may necessitate the creation of different treatment and follow-up protocols.

Keywords: Age-related macular degeneration, phakic eye, pseudophakic eye, real-life data

Introduction

Wet type age-related macular degeneration (wAMD) is the leading cause of severe visual loss among the elderly population in developed countries (1,2). wAMD affects only 10-15% of AMD cases but accounts for more than 80–90% of cases of severe visual impairment (1,2). The visual prognosis of wAMD was dramatically improved by the introduction of antivascular endothelial growth factor (anti-VEGF) agents into clinical practice. The efficacy and safety of intravitreal anti-VEGF treatment bevacizumab (Avastin; off-label use; Genentech, Inc, South San Francisco, CA), ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA), and aflibercept (Eylea; Regeneron, Tarrytown, NY)) have been demonstrated in multiple clinical trials and remains the initial treatment option for wAMD (3-8). These studies were mainly efficacy and dosing regimen studies; therefore, they did not focus on lens status. Little attention has been paid to comparing visual acuity (VA) outcomes and anatomical success between phakic and pseudophakic patients.

In most of the studies, it was suggested that cataract surgery may increase the development and progression of AMD (9-14). This phenomenon was attributed to increased light toxicity, increased inflammation, and post-operative cystoid macular edema after cataract surgery (15). However, there is still ongoing debate about whether cataract surgery has any effect on the progression of AMD (14). Many anatomical and biochemical changes occur in the vitreous after cataract surgery (16,17). It is reported that posterior vitreous detachment (PVD) was induced after cataract surgery and the presence of PVD was found to be related to increased retinal penetration of bevacizumab in rabbit eyes (18).

The aim of this multicenter study is to the comparison of wAMD in phakic and pseudophakic patients in terms of anatomical and functional outcomes based on the real-life data of Türkiye.

Methods

This was a retrospective, interventional, and non-comparative real-life experience study conducted in eight tertiary centers and one university faculty of medicine in Türkiye. The records of wAMD patients who were treated with an anti-VEGF agent using a pro-re-nata treatment regimen between January 2013 and December 2015 were reviewed. Written informed consent was obtained from all patients before the treatment and the study adhered to the tenets of the Declaration of Helsinki. Ethical board approval was obtained from University Faculty of Medicine.

Patients who met the following criteria were included in the study were ≥50 years of age, were diagnosed with wAMD, and had a minimum follow-up time of 12 months. Patients who had retinal disease other than wAMD (e.g., diabetic retinopathy, retinal vein occlusion) and those diagnosed with polypoidal choroidal vasculopathy or retinal angiomatous proliferation during follow-up were not included in the study. Furthermore, aphakic and 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 was 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 1 year before the beginning of the intravitreal anti-VEGF treatment.

Data collected from the patient's records included age, gender, lens status, best-corrected VA (BCVA), and central macular thickness (CMT) at baseline, month 3, month 6, month 12, month 24, and month 36. The total number of injections and visits number at months 12, months 24, and 36 was also recorded.

All patients underwent a standardized examination including measurement of BCVA through the early treatment diabetic retinopathy study chart or a projection chart at 4 m, slit-lamp biomicroscopy, and fundus examination and measurement of intraocular pressure through Goldman applanation tonometry. The measured BCVA was converted to logMAR units. Fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT) imaging were performed before treatment. As this was a multicenter study, different brands of FA and OCT devices were used to assess the patients. All examinations were planned to be repeated monthly, except FA. FA was repeated only when the cause of VA deterioration could not be clarified with clinical examination and other imaging methods. OCT was used for detecting subretinal, intraretinal fluid, and measurement of CMT. Central macular thickness defined as the mean thickness of the neurosensory retina in the central 1 mm diameter area was computed using OCT mapping software generated by the device.

All injections were performed under sterile conditions in an operating room or an outpatient operating room (clean room). Topical anesthesia and 10% povidone-iodine (Betadine; Purdue Pharma, Stamford, CT, USA) were applied to the lids and lashes, and 5% povidone-iodine was administered to the conjunctival sac. Intravitreal bevacizumab 1.25 mg/0.05 mL, ranibizumab 0.5 mL/ 0.05 mL, or aflibercept 2 mg/0.05 mL was injected through the pars plana 3.5–4 mm posterior to the limbus with a 30-gauge needle. After the injection, an ophthalmic solution of 0.5% moxifloxacin (Vigamox; Alcon Laboratories, Inc., Fort Worth, Texas, USA) was administered 5 times a day for 1 week. Patients were then instructed to consult the hospital if they experienced decreased vision, eye pain, or any new symptoms.

It was planned to call the patients for monthly controls after the first 3 months of the monthly intravitreal anti-VEGF loading dose. A single injection of a first preferred anti-VEGF agent was repeated when VA decreased by one or more lines from the last visit or in the presence of newly developed macular hemorrhage, evidence of subretinal fluid, or persistent intraretinal fluid on OCT.

Primary outcome measures of this study included the change in BCVA from baseline to months 3, 6, 12, 24, and 36 and OCT defined CMT from baseline to months 6, 12, 24, and 36. Secondary outcome measures were the total number of visits and injections at months 12, 24, 36, and the complications of intravitreal injections.

Statistical Analysis

The SPSS 26.0 program was used in the analyses. Mean, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov–Smirnov test. The Mann–Whitney U-test was used in the analysis of quantitative independent data. The Wilcoxon test was used in the analysis of dependent quantitative data. Chi-square testing was used in the analysis of qualitative independent data.

Results

Overall, 867 Turkish patients with wet type AMD, of whom 541 (299 male, 242 female) phakic eyes and 326 (186 male and 140 female) pseudophakic eyes were enrolled in the study. The age of patients in the pseudophakic group was significantly higher than in the phakic group, 77.7±7.7, 70.5±8.4, respectively, (p=0.000). In the phakic and pseudophakic groups, the number of visits at the 1st, 2nd, and 3rd years did not differ significantly (p=0.100, 0.053, and 0.399, respectively). In our study, the number of injections in the 1st, 2nd, and 3rd years, respectively was 4.2±2.0, 1.8±1.9, and 1.0±1.7 in the phakic group, and 3.9±2.0, 1.7±1.9, and 0.8±1.4 in the pseudophakic group. The number of 1st-year injections in the pseudophakic group was significantly lower than in the phakic group (p=0.001). In the phakic and pseudophakic groups, the number of injections in the 2nd and 3rd years did not differ significantly (p=0.288, 0.350, respectively). The mean follow-up period was 23.5±9.9 months in the phakic group and 24.7±9.9 months in the pseudophakic group (range 12–36 months) (p=0.054). The general characteristics except for age and 1st-year injections number of the two groups were similar (Table 1).

Table 1. Demographic data of the two groups

	Phakic		Pseudophakic		p
	Mean±SD./n-%	Median	Mean±SD./n-%	Median	
Age	70.5±8.4	71,0	77.7±7.7	78.0	0.000[m]
Gender					
Male	299±55.3%	186±57.1%			0.608X²
Female	242±44.7%	140±42.9%			
Number of visits					
1st year	7.0±2.5	7,0	6.7±2.4	7.0	0.100[m]
2nd year	5.8±2.8	6,0	5.3±2.8	5.0	0.053[m]
3th year	5.4±2.8	5,0	5.4±3.8	5.0	0.399[m]
Number of injection					
1st year	4.2±2.0	4,0	3.9±2.0	3.0	0.001[m]
2nd year	1.8±1.9	2,0	1.7±1.9	1.0	0.288[m]
3th year	1.0±1.7	0,0	0.8±1.4	0.0	0.350[m]
Follow- up (month)	23.5±9.9	22,0	24.7±9.9	24.0	0.054[m]

[m]Mann–Whitney U-test/X² Ki-kare test; p: inter groups statistical analaysis; SD: Strandard deviation.

The mean BCVA of the phakic and pseudophakic patients at baseline was 0.87±0.65 LogMAR and 0.95±0.63 LogMAR, respectively, p=0.052). There was not a significant difference between the mean BCVA levels, however, the change in the mean BCVA from, the 3rd, 6th,12th, 24th, and 36th months was statistically different between the two groups (p1=0.01, p1=0.001, p1=0.000, p1=0.000, and p1=0.003, respectively). All follow-up time mean BCVA was better in the phakic group (Table 2 and Fig. 1).

VA increased significantly (p2<0.05) compared to baseline in 3rd, 6th, 12th, and 24th month in the phakic group the and 3rd, 6th, and 12th month in pseudophakic group. VA did not change significantly of the phakic group in the 36th month and 24th, 36th, months in the pseudophakic (p2>0.05) (Table 2).

The mean CMT of the phakic and pseudophakic groups at baseline was 391±138 and 400±169 microns, respectively. There was no significant difference between the mean CMT levels of the two groups at all of the study visits (p1>0.05 for all, (Table 3). In addition, the change in the mean CMT from the baseline to 6th, 12th, 24th, and 36th months was statistically different in both the groups (p2<0.05 for all, (Table 3 and Fig. 2).

No serious complications such as endophthalmitis, vitreous hemorrhage, and retinal detachment were observed in any of the patients.

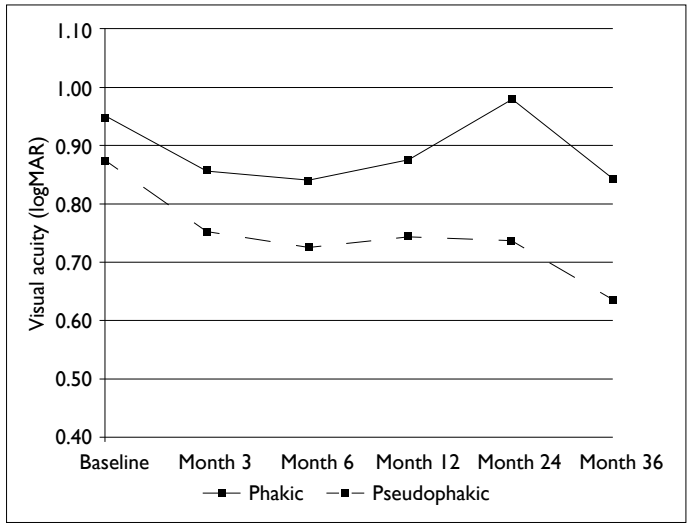

Figure 1. Changes in mean visual acuity level (LogMAR) in the phakic and pseudophakic groups. From baseline to 36 months.

Discussion

Although anti-VEGF therapy has been a breakthrough in the treatment of wAMD, factors underlying the high inter-individual variability of anti-VEGF therapy are yet unknown. Identification of these factors would allow for an individualized adjustment of dosage and injection frequency to avoid overdosing and underdosing. Genetic factors, disease activity, age, retinal molecular characteristics, the ocular volume of the injected eye, and lens status may be expected to impact intraocular pharmacokinetics.

The baseline age is one of the important predictors for final VA outcomes in wAMD. Several studies have shown that younger age is correlated with better clinical outcomes. In the subgroup analysis of the MARINA study, if the average age of one group is younger than another group by 13.7 years at baseline, the change in VA of the younger group will be five letters better than the older group (19). Similarly,

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

	Phakic		Pseudophakic		p1
	Mean±SD	Median	Mean±SD	Median	
Visual acuity (LogMAR)					
Baseline	0.87±0.65	0.70	0.95±0.63	0.82	0.052[m]
3rd month	0.75±0.58	0.52	0.86±0.57	0.70	0.010[m]
p2	0.000	[w]	0.000	[w]	
6th month	0.73±0.58	0.52	0.84±0.56	0.70	0.001[m]
12th month	0.74±0.60	0.52	0.88±0.57	0.70	0.000[m]
p2	0.000	[w]	0.010	[w]	
24th month	0.74±0.60	0.52	0.98±0.66	1.00	0.000[m]
p2	0.037	[w]	0.740	[w]	
36th month	0.64±0.56	0.40	0.85±0.52	0.75	0.003[m]
p2	0.410	[w]	0.089	[w]	

[m]Mann–Whitney u test / [w] Wilcoxon test, LogMAR: Logarithm of the minimum angle of resolutiın, p1: between groups statistical analysis, p2: inter groups statistical analaysis, SD: Standart deviation.

Table 3. CMT findings in microns in the phakic and pseudophakic groups at different time points

	Phakic		Psodofakik		p1
	Mean±SD	Median	Mean±SD	Median	
Central macular thickness					
Baseline	391.3±138.7	365.0	400.1±169.0	366.0	0.991[m]
6th month	331.7±112.5	310.0	329.5±122.6	304.0	0.327[m]
p2	0.000	[w]	0.000	[w]	
12th month	321.3±110.4	300.0	326.0±123.5	296.0	0.652[m]
p2	0.000	[w]	0,000	[w]	
24th month	318.4±147.4	284.0	311.2±121.6	284.0	0.599[m]
p2	0.000	[w]	0.000	w	
36th month	313.2±146.7	303.5	319.4±133.1	303.0	0.873[m]
p2	0.000	[w]	0.000	[w]	

[m]Mann–Whitney U-test / [w] Wilcoxon test, SD: Standart deviation, p1: between groups statistical analysis, p2: inter groups statistical analaysis, CMT: Central macular thicness.

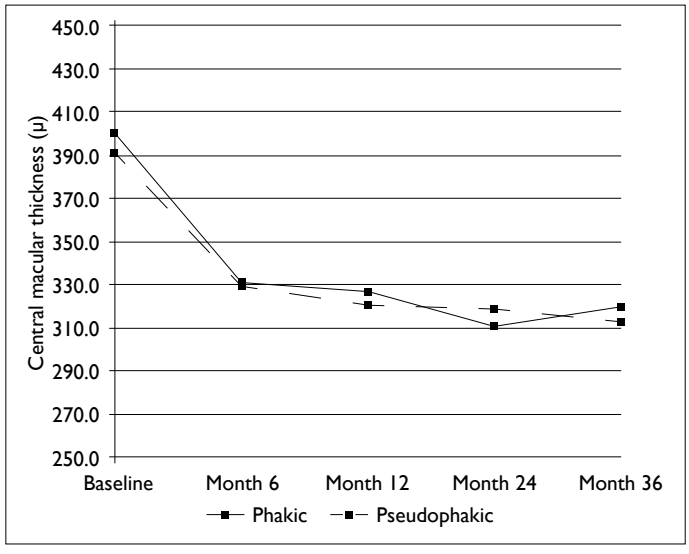

Figure 2. Changes in mean central macular thickness in the phakic and pseudophakic groups from baseline to 36 months.

subgroup analysis of ANCHOR also showed that younger patients gained more compared with the older group (20). CATT study also found that patients <70 years old gained 10.8 letters, while patients 70 years or older only gained 5.6 letters after treatment (21). Zhang and Lai (22) have shown that poorer treatment outcome has been associated with greater age. Our study baseline BCVA was similar in the two groups but in the pseudophakic group 3rd, 6th, 12th, 24th, and 36th months, BCVA was significantly lower than the phakic group. The mean age of the pseudophakic group was higher than that of the phakic group, which may lead to lower functional success (p=0.0001).

There are conflicting data in the literature regarding whether a history of cataract surgery are associated with poorer outcomes in patients with AMD (10). Other study showed a substantially increased incidence of late-stage AMD in pseudophakic eyes compared with phakic eyes (12). Cataract surgery may increase the development and progression of AMD (9,12-14). This phenomenon was attributed to increased inflammation, increased light toxicity, and postoperative cystoid macular edema after cataract surgery (15). However, there is a debate about the relationship between cataract surgery and the progression of AMD (12). In our study, the poor functional success in the pseudophakic group may have been due the retinal structural damage and functional decline related to including light toxicity during the cataract surgery, surgical trauma, or inflammatory factors after surgery, and increased light exposure after removal of the crystalline lens may limit the recovery potential.

Previous studies show tahat posterior vitreous detachment (PVD) was induced after cataract surgery (17,23,24). Neudorfer et al. found no difference in functional or anatomic outcomes related to the PVD status for eyes with exudative AMD treated with intravitreal bevacizumab (25). The presence of PVD was not evaluated in our study when different brands of OCT devices were used to assess the patients. In regard to these findings, we hypothesized that all of these changes after cataract surgery may affect the outcomes of intravitreal injection treatment for wAMD in pseudophakic patients since there is a little amount of data on this topic.

Pseudophakia is known to alter the anatomic features and biochemical profile of the vitreous (17,23). With the replacement of the native lens with an artificial implant of

lesser volume, the volume of the vitreous, and therefore the volume of distribution of drug, increases. Finally, the replacement of the native lens may affect the transit and exit of intravitreally injected drugs through the anterior chamber. Laude et al. suggest that cataract-operated patients could have a faster clearance of vitreous drugs (26). Krohne et al. (27) investigated the impact of lens status on VEGF inhibitor pharmacokinetics. In pseudophakic eyes, diffusion of intravitreal drugs into the anterior chamber and subsequent elimination from the eye through Schlemm's canal may be accelerated as compared with that in phakic eyes. They tested both hypotheses by measuring the time course of drug concentrations and VEGF suppression in aqueous humor samples from patients at different time points after intravitreal injection of ranibizumab and bevacizumab. However, Krohne et al. (27) did not detect a difference in the duration of action between the groups, indicating that lens status does not impact the intraocular pharmacokinetics of VEGF inhibitors to a relevant degree. Although the number of visits in the 1st year was the same as the two groups in our study, the injection of an average of 3.9 in the pseudophakic group and 4.2 in the phakic group did not support the hypothesis anti-VEGF was eliminated faster in the pseudophakic group (p=0.001).

There are only a few studies that compare the efficacy of intravitreal anti-VEGF agents between phakic and pseudophakic patients. In a study by Baek et al., (28) 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. Ozkaya et al., (29,30) the treatment outcomes of ranibizumab and bevacizumab were compared between the phakic and pseudophakic groups of nAMD patients. The results of the studies were that no difference was found between the two groups in regard to visual and anatomical outcomes (29,30). 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 (34). In 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 (31). Although the anatomical results of our study are consistent with these previous studies; functional outcomes are different from the previous studies. This does not seem surprising as in older patients and had cataract surgery, the retinal structural damage and functional decline related to age may limit the recovery potential.

In our study based on real life data, anatomical success in the pseudophakic group diagnosed with wAMD was found to be similar to the phakic group, while functional success was significantly lower in the pseudophakic group. Retinal damage at the microscopic level of the photoreceptor and retinal pigment epithelium as a result of delayed diagnosis and treatment of possible age-related macular degeneration due to lens opacity in the pseudophakic group. Or, it may be due to light toxicity, inflammatory process, or ultraviolet toxicity that occurs during or after cataract surgery. For this reason, every patient in whom we are planning to have cataract surgery should be followed closely for the development or progression of AMD before and after surgery. In addition, it may be recommended that experienced surgeons perform cataract surgery in patients, especially to reduce the light toxicity during surgery and the inflammatory process that may occur afterward as much as possible.

The main limitation of this study was its retrospective design. Furthermore, different OCT devices were used in different centers which contributed to this study and the resolutions of these devices might affect the clinical decision of the physicians. We did not evaluate the status of posterior hyaloid detachment in the present study which might affect the clinical outcome. However, this is a very important national study regarding the demographics and injection characteristics which are major strengths.

Conclusion

This was the first national broad-based wAMD research conducted by the retinal specialists from nine referral centers, reflecting the real-life treatment outcomes in the Turkish population. In this study, we revealed that anatomical outcome is not parallel with the functional outcome in the pseudophakic subgroup of our study. This phenomenon might be secondary to late diagnosis, increased age, or light toxicity during cataract surgery. Of course, these factors are only proposals, and all need to be clarified with further studies.

Disclosures

Ethics Committee Approval: Written informed consent was obtained from all patients before the treatment and the study adhered to the tenets of the Declaration of Helsinki. Ethical board approval was obtained from University Faculty of Medicine.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept: L.K.; Design: L.K.; Data collection and/or processing: H.E.K., A.O., L.K., C.A., Z.A., O.A., S.E.B., S.B., G.D., M.D., A.D., B.E., G.E., M.E., E.E., I.U.O., O.A.O., S.O.E., M.O., F.S., I.P., K.S., N.S., D.Y., I.Y., Z.Y.A.; Analysis and/or interpretation: L.K.; Literature search: H.E.K.; Writing: H.E.K.; Critical reviews: H.E.K., L.K.

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