Reassessment of Treatment-Resistant Exudative Age-Related Macular Degeneration with Indocyanine Green Angiography

Tedaviye Dirençli Eksüdatif Yaşa Bağlı Makula Dejenerasyonunun İndosiyanin Yeşili Anjiyografisi ile Tekrar Değerlendirilmesi

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ABSTRACT

Objective: To evaluate eyes with exudative age-related macular degeneration (AMD) with indocyanine green angiography (ICGA) prior switching from ranibizumab treatment to aflibercept treatment and investigate the effect of findings on visual and anatomic outcomes.

Material and Methods: Fifty-one eyes of 44 patients with exudative AMD diagnosis that are resistant to ranibizumab and switched to aflibercept injections were included in this retrospective study. The primary outcomes were changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) at 3 months and at the last visit following the switch procedure.

Results: Out of 51 eyes, 38 (74%) had polypoidal choroidal vasculopathy (PCV), and 10 (20%) had occult choroidal neovascular membrane (CNV). The mean baseline BCVA of 0.73±0.45 (logMAR) changed to 0.74±0.46 at 3 months and to 0.72±0.43 at the last visit (p=0.77, p=0.55). BCVA was stable in 29 eyes (56.9%), twelve eyes (23.5%) experienced visual improvement while ten eyes (19.6%), all of which were diagnosed with PCV, showed visual loss. Of the 10 eyes with occult CNV, the vision improved in 5 eyes and remained stable in 5 eyes at the last visit. The mean CMT was reduced from 390±103 µm to 326±72 µm at 3 months (p<0.001) and was preserved until the last visit, with similar decreases in the occult CNV and PCV subgroups (p=0.009, p=0.001).

Conclusion: ICGA is a beneficial tool to predict visual and anatomical outcomes in the switch procedure for treatment-resistant AMD cases by detecting the underlying lesions.

Key Words: Indocyanine green angiography, Age-related macular degeneration, Aflibercept, Switch procedure

ÖZ

Amaç: Eksüdatif yaşa bağlı makula dejenerasyonlu (YBMD) gözlerin ranibizumab tedavisinden aflibersept tedavisine geçiş öncesi indosiyanin yeşili anjiyografisi (İSYA) ile değerlendirilmesi ile bulguların görsel ve anatomik sonuçlar üzerindeki etkilerin incelenmesi.

Gereç ve Yöntemler: Ranibizumab tedavisine dirençli olup aflibersept enjeksiyonuna değişiklik yapılan eksüdatif YBMD tanılı 44 hastanın 51 gözü bu retrospektif çalışmaya dahil edildi. Birincil sonuçlar değişiklik prosedürü sonrası 3. ay ve son vizitteki en iyi düzeltilmiş görme keskinliği (EİDGK) ve santral makula kalınlığı (SMK) değişiklikleri idi.

Bulgular: Elli bir gözün 38'inde (%74) polipoidal koroidal vaskülopati (PKV), ve 10'unda (%20) okült koroidal neovasküler membran (KNV) mevcuttu. Ortalama 0,73±0,45 (logMAR) olan bazal EİDGK 3. ayda 0,74±0,46'ya, son vizitte 0,72±0,43'e değişti (p=0,77, p=0,55). EİDGK 29 gözde sabitken (%56,9), 12 gözde (%23,5) görsel iyileşme görüldü ve tamamı PKV tanılı olan 10 göz (%19,6) görmede azalma gösterdi. Son vizitte, okült KNV bulunan 10 gözün 5'inde görme düzelirken 5'inde görme düzeyi sabit kaldı. Ortalama SMK 3 ayda 390±103 µm'den 326±72 µm'ye geriledi (p<0,001) ve son vizite kadar bu düzelme korundu, okült KNV ve PKV alt gruplarında da benzer sonuçlar elde edildi (p=0,009, p=0,001).

Sonuç: İSYA, tedaviye dirençli YBMD olgularında altta yatan lezyonları göstermesi açısından, değişiklik prosedüründeki görsel ve anatomik sonuçların öngörülmesinde yararlı bir yöntemdir.

Anahtar Sözcükler: İndosiyanin yaşili anjiyografisi, Yaşa bağlı makula dejenerasyonu, Aflibersept, Değişiklik prosedürü

INTRODUCTION

Age-related macular degeneration (AMD) remains the leading cause of blindness in developed countries. It is estimated that the prevalence of AMD will continue to increase in the coming decades, affecting up to 288 million people worldwide by the 2040s (1). The exudative form of the disease featuring choroidal neovascularization (CNV) can be treated with recently introduced anti-vascular endothelial growth factor (anti-VEGF) agents, which are now considered the gold standard therapy modalities. There are three currently used agents, consisting of bevacizumab, ranibizumab and aflibercept, which have been proven to improve best-corrected visual acuity (BCVA) and reduce the increase in central macular thickness (CMT) related to intraretinal, subretinal, or sub-RPE fluid leakage (2-5).

However, a considerable proportion of cases are treatment-resistant according to several criteria, such as reduced BCVA, persistent fluid presence and insufficient reduction in CMT, as shown in optical coherence tomography (OCT) despite regular anti-VEGF injections (6). Multiple factors including genetic variations, misdiagnosis, drug tolerance, tachyphylaxis, and other angiogenic factors and pathogenic pathways, are being investigated to elucidate this phenomenon, with each of them suggesting alternative therapy solutions to overcome the issue (7).

At present, regarding the different binding properties of each anti-VEGF agent, combined with the tolerance and tachyphylaxis effects, switching between these drugs has become increasingly popular (8-13). Aflibercept, due to its ability to bind VEGF-A, VEGF-B, and placental growth factor, is usually preferred as the drug of choice for the switching procedure (11,12), whereas there are some authors who rely on the procedure itself rather than the drug (8,10).

Nevertheless, it should be emphasized that the resistance to anti-VEGF therapy might also be related to underlying pathologies, such as polypoidal vascular choroidopathy (PCV) or retinal angiomatous proliferation (RAP), which are considered as diverse subgroups of the broad AMD spectrum of diseases (14,15). Further investigations with imaging tools, such as fundus autofluorescence (FAF) and indocyanine green angiography (ICGA), are being performed in several studies to confirm these diagnoses (16-18), but these investigations have not yet addressed patients that have undergone switching therapy as far as we are aware. This study aims to fill this gap by reassessing the diagnoses of treatment-resistant neovascular AMD cases with ICGA prior to switching the intravitreal injection from ranibizumab/bevacizumab to aflibercept.

MATERIAL and METHODS

This retrospective, observational, non-comparative study was conducted at Beyoglu Eye Research and Training Hospital, Istanbul, among consecutive patients who initially received intravitreal ranibizumab and then switched to aflibercept due to incomplete response to the primary treatment for exudative AMD, between January 2011 and June 2017. The study adhered to the Declarations of Helsinki. The study protocol was approved by the Institutional Ethics Committee (Health Sciences University, Beyoglu Eye Training and Research Hospital, dated: 18.04.2108, nº: 14/E-2). Informed consent was obtained for each patient included in the study.

Ranibizumab administrations consisted of three consecutive monthly ranibizumab injections as a loading dose, followed by injections in a pro re nata regimen in the case of persistence or recurrence of intraretinal fluid (IRF) and subretinal fluid (SRF), new retinal haemorrhages, and a decrease in visual acuity of ≥1 Snellen line. Patients with persisting or increasing IRF/SRF involving the fovea on OCT or presence of retinal haemorrhage related to CNV despite at least three monthly ranibizumab injections were considered to have an incomplete response to treatment. The last three ranibizumab injections had been given monthly in patients with a treatment period of longer than 6 months before the switch. The patients then switched to three monthly injections of 2.0 mg aflibercept and followed with additional aflibercept injections if needed. All patients had to have been followed for at least 6 months after the switch. Occasional injections of bevacizumab were permitted while eyes were being treated with ranibizumab; this was not considered a treatment switch. Patients who had been diagnosed with disease spectra other than AMD such as diabetic retinopathy, cataract and glaucoma, or who received treatment other than anti-VEGF agents such as steroids, photodynamic therapy (PDT), laser photocoagulation or macular surgery were excluded.

Patients underwent ICGA (Spectralis, Heidelberg Engineering, Heidelberg, Germany) imaging at the time the switch decision was made. The lesions were classified as occult CNV, predominantly/minimally classic CNV, PCV, or RAP by the treating physician according to the ICGA features. Clinical examinations including BCVA, slit lamp biomicroscopy, applanation tonometry, fundus examination and OCT imaging (Spectralis, Heidelberg Engineering, Heidelberg, Germany) were performed at each visit. BCVA and CMT measurements along with the number of anti-VEGF injections at baseline prior to aflibercept treatment, at the 3-month visit after the switch, and at the last visit were noted.

Primary outcome measures were defined as BCVA and CMT changes between the baseline and 3 months and the last visit after the switch. Improvement or decrease in vision was defined as a change by one line on the Snellen chart compared to baseline visual acuity.

Statistics were analysed with IBM SPSS version 20.0 (IBM Corp., Armonk, USA). BCVA was recorded at each visit using the logarithm of the minimum angle of resolution (logMAR) letter score. The Friedman test was used to compare BCVA and CMT values before and 3 months after the switch, and at the last visit. The Wilcoxon signed rank test was performed to confirm differences between each group separately.

RESULTS

Fifty-one eyes of 44 patients considered treatment-resistant exudative AMD with persistent active CNV were recruited to the study. Given that 7 patients had bilateral involvement, our study was eye-based. Twenty-five of the 44 patients were male and slightly younger than the females, although this did not reach statistical significance (mean age: 71 versus 72 years, p=0.63).

The baseline characteristics of the patients are presented in Table I. Following ICGA, 38 eyes were found to have PCV, while 10 eyes had occult CNV and 2 eyes were with RAP. Only 1 eye was diagnosed with predominantly classic CNV. The mean number of intravitreal aflibercept injections after the switch was 4.9±1.7 (range: 1-8) by the end of the follow-up. The mean duration of follow-up was 8.9±2.1 months after the switch. After confirming the diagnosis of PCV, PDT with verteporfin was administered in 8 eyes with PCV at standard fluence when IRF/SRF was detected on OCT despite 3-monthly aflibercept injections. There was no statistically significant difference in best-corrected visual acuity between baseline and 3 months and the last visit following the switch (p=0.77 and 0.55, respectively). Visual acuity was found to be stable in 29 eyes (56.9%) at both 3 months and the last visit after the switch. Eight eyes (15.7%) experienced visual acuity improvement at 3 months and 12 (23.5%) eyes at the last visit. Eleven eyes (21.6%) demonstrated visual acuity loss at 3 months and 10 eyes (19.6%) at the last visit after the switch. Among all patients, the most efficient therapeutic effect regarding the visual acuity improvement was observed in the occult CNV subgroup at 3 months and the last visit. Of the 10 eyes with occult CNV, 5 eyes showed visual acuity improvement, and 5 eyes remained stable at 3 months and the last visit. However, 11 of 38 eyes with PCV experienced visual acuity loss at 3 months and 10 eyes at the last visit. Additionally, 1 eye with RAP lesion and 1 eye with classic CNV maintained their visual acuity, and 1 eye with RAP lesion showed improvement during follow-up.

Differences between the BCVA and CMT values during the follow-up are shown in Table II. Before switching to aflibercept, the mean baseline CMT was 390±103 µm. At 3 months and the last visit following switching, mean CMT values were calculated as 326±72 µm and 330±88 µm, respectively. The difference between baseline and 3 months and the last visit mean CMT values were statistically significant (p<0.001). The decreases in CMT values for occult CNV and PCV subgroups were also significant when comparing the baseline and the last visit (p=0.009 and 0.001, respectively).

DISCUSSION

Given that there is a growing preference for the use of aflibercept for switching procedures concerning treatment-resistant exudative AMD cases, multiple studies have been published addressing the topic (11-13, 19-22). Accordingly, several meta-analyses that highlight the main outcomes of these trials are available (23, 24). In a measure of visual and anatomical changes, our data are in line with this literature. Various explanations that have been proposed by the authors of these studies are discussed below.

The meta-analysis performed by Spooner et al. evaluated 28 articles, which were mostly retrospective studies and excluded studies with PCV cases (23). These authors concluded that BCVA remained stable and CMT levels decreased significantly following the switch procedure. They also emphasized that prospective studies, case groups which received less than 12 injections prior to switching,

Table I: Baseline demographic and clinical characteristics of switch procedure patients.

Patient Characteristics	Value
Eye (n)	51
Gender (f/m, %)	19/25 (43%/57%)
Previous treatment	
Mean duration (months±SD, range)	30.2±2.33 (6-96)
Injection type (n)	Ranibizumab: 47 Bevacizumab: 4
Mean amount of injection (n±SD)	10.9±0.64 (3-24)
ICG angiography findings	
Classic CNV (n,%)	1 (2%)
Occult CNV (n,%)	10 (20%)
PCV (n,%)	38 (74%)
RAP (n,%)	2 (4%)

Table II: Primary visual and anatomical outcomes of patients following switch procedure.

	Baseline	3 months	Last visit
BCVA			
Overall (logMAR±SD)	0.73±0.45	0.74±0.46	0.72±0.43
Occult CNV	0.61±0.42	0.48±0.35	0.46±0.34
PCV	0.75±0.46	0.79±0.46	0.79±0.44
RAP	0.90±0.56	0.80±0.70	0.80±0.70
CMT			
Overall (µm±SD)	390±103	326±72	330±88
Occult CNV	399±131	307±58	279±46
PCV	390±98	339±75	345±92
RAP	334±127	263±10	272±49

and cases that received the pro re nata (PRN) treatment protocol for aflibercept presented better results than retrospective studies, case groups that received more than 24 injections, and those that received the treat and extend protocol for aflibercept. Another meta-analysis conducted by Seguin-Greenstein et al. reviewed seven studies, finding similar visual and anatomical outcomes to Spooner et al. (23,24). These authors also concluded that studies with a prospective nature obtained results showing significant visual improvement with better accuracy.

Curry et al. investigated 19 eyes in their vTAS study and reported that BCVA was maintained in 16 eyes and that the median CMT decreased from 313 µm to 258 µm (19). These authors executed a stratified analysis upon fluid location and concluded that the cases with intraretinal fluid (IRF) prior to switching responded significantly better to treatment in both visual and anatomical measures. Waizel et al. compared two treatment-switching procedures from bevacizumab to either ranibizumab or aflibercept (20). Although the latter had better anatomical response, it should be noted that the former group had poorer baseline response with an increase in CMT thickness from 396 µm to 499 µm following initial bevacizumab treatment prior to switching to ranibizumab, compared with the latter which responded to bevacizumab with slight decrease of CMT from 430 µm to 419 µm prior to switching to aflibercept.

Our study differs from those in the literature because it is based on reassessment of the diagnosis with ICGA prior to switching to aflibercept. Among the clinical studies included in the meta-analyses mentioned above (23,24), none had performed ICGA for further investigation. Although ICG angiography findings were presented by Ricci et al. and Massamba et al., in which PCV and RAP subtypes were noted, no clinical observation was mentioned regarding any possible differences between these subgroups (13,21). On the other hand, we were able to demonstrate an improvement in visual acuity in the occult CNV subgroup despite including eyes with PCV.

Eyes with occult CNV that demonstrated persistent IRF or SRF during ranibizumab treatment might suggest possible tachyphylaxis, which was defined as decreasing therapeutic response to a pharmacological agent following repeated administration (25,26). Tachyphylaxis was demonstrated to occur in 2% of recurrent CNV patients. It is suggested that many such eyes show an increased response to a change in the anti-VEGF agent used (27,28).

Furthermore, the anatomical success due to the aflibercept switching treatment might be related to the majority of cases being PCV. It has been reported that aflibercept has a greater effect over polypoidal lesions than other anti-VEGF drugs (29,30).

The limitations of this study include its retrospective nature, small sized subgroups, and the lack of a control group. The predominance of PCV cases might raise suspicion about the correlation of our results with other switching studies but this finding might have implications for the presumed effects of aflibercept in treatment-resistant cases. Also, the maintenance of vision and anatomical improvement remains widely accepted as the outcome of the switching procedure concerning cases belonging to any subtype of the AMD disease spectrum.

CONCLUSION

To our knowledge, this is the first study that re-evaluates treatment-resistant exudative AMD cases with ICGA prior to the decision to switch treatment to aflibercept injections.

Based on our findings, we conclude that disclosure of possible AMD subgroups (e.g., PCV and RAP) prior to switching treatment, with the aid of ICGA, might deserve consideration. Further studies with larger groups are now required to determine the implications of these findings and to uncover correlated findings, thereby improving treatment efficiency.

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