The Assessment of Intravitreal Aflibercept in Neovascular Age-related Macular Degeneration with Pigment Epithelium Detachment in Treatment-naive and Switched Patients

Pigment Epitel Dekolmanı ile Birlikte Görülen Neovasküler Tip Yaşa Bağlı Makula Dejenerasyonunda İntravitreal Aflibersептin Naif ve Tedavi Değişimi Hastalarında Değerlendirilmesi

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ABSTRACT

Purpose: To investigate the visual and anatomic outcomes of pro re nata (PRN) regimen of aflibercept (AFL) treatment in naive and switched patients with a diagnosis of neovascular age-related macular degeneration (n-AMD) and pigment epithelium detachment (PED)

Materials and methods: This retrospective study included 30 eyes of 25 patients who presented with typical-type n-AMD with serous or fibrovascular PED. Group 1 included 19 eyes meeting the study criteria who switched therapy while group 2 included 11 treatment-naive eyes. The patients were treated with a PRN regimen of 2.0 mg intravitreal AFL and a loading dose was only given to naive eyes. Best corrected visual acuity (BCVA), central macular thickness (CMT), changes in pigment epithelium detachments (PED), presence of intraretinal fluid (IRF) and subretinal fluid (SRF) were assessed by 4-to-8 week intervals.

Results: After AFL injections, the mean CMT (group 1, p<0.001; group 2, p=0.026) and maximal PED height (group 1, p<0.001; group 2, p=0.004) were improved significantly, whereas the mean BCVA remained stable over time. Serous PEDs showed a significantly better response than fibrovascular PEDs (p=0.037). Changes in visual acuity were not associated with reduction in PED height (R^2=0.002, p= 0.84). There was a resolution of fluid with a range of 64-74% of the treated eyes in two different groups.

Conclusion: Similar morphologic short-term improvements were achieved following a PRN regimen of AFL injection in both the treatment-naive and switched group without change in visual acuity.

Key words: Age-related macular degeneration, Retina, Switch, VEGF-Trap eye.

ÖZ

Amaç: Pigment epitel dekolmanı(PED) ile birlikte görülen neovasküler tip yaşa bağlı makula dejenerasyonunda (n-YBMD) naif ve tedavi değişimi yapılan hastalarda pro re nata (PRN) rejimi ile uygulanan aflibersептin (AFL) görsel ve anatomik sonuçlarının araştırılması

Gereç ve yöntemler: Seröz veya fibrovasküler PED ile birlikte n-YBMD olan 25 hastanın 30 gözü bu retrospektif çalışmaya dahil edilmiştir. 1. grupta çalışma kriterlerine uyan 19 göz tedavi değişimi yapılan, 2. grupta ise 11 göz naif gözlerdir. Bu hastalar PRN rejimi ile 2.0 mg intravitreal AFL ile tedavi edilmiş ve yükleme dozu sadece naif gözlere yapılmıştır. 4-8 hafta aralıklarla en iyi düzeltilmiş görme keskinliği (EİDGK), santral makula kalınlığı (SMK), pigment epitel dekolmanındaki değişiklikler, intraretinal(IRS) ve subretinal sıvı (SRS) varlığı değerlendirildi.

Bulgular: Aflibercept enjeksiyonları sonrası ortalama SMK (grup 1, p<0.001; grup 2, p=0.026) ve maksimum PED yüksekliği (group 1, p<0.001; group 2, p=0.004) anlamlı bir şekilde düzelirken, ortalama EİDGK zaman içerisinde stabil kalmıştır. Seröz ağırlıklı PED yanıtı fibrovasküler PEDlere göre daha iyi olmuştur (p=0.037). Görme keskinliğindeki değişimler PED yüksek-

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Received: 26.02.2019
Accepted: 02.05.2019
Ret-Vit 2019; 28: 368-374

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liği ile ilişkili bulunmamıştır (R2=0.002, p= 0.84). Tedavi edilen her iki grupta da %64-74 oranında sıvılarda gerileme olmuştur. Sonuç: PRN rejimi ile uygulanan AFL enjeksiyonlarını takiben hem değişim hem de naif grupta görme keskinliğinde değişiklik olmadan benzer morfolojik kısa dönem sonuçları elde edilmiştir.

Anahtar kelimeler: Yaşa bağlı makula dejenerasyonu, Retina, değişim, VEGF tuzağı.

INTRODUCTION

Neovascular age-related macular degeneration (n-AMD) is the leading global cause of severe loss of vision in patients aged over 50 years. The abnormal growth of abnormal vessels, choroidal neovascularization (CNV) induced by vascular endothelial growth factor (VEGF) leads accumulation of subretinal fluid (SRF), macular edema, intraretinal cysts, and pigment epithelium detachment (PED). The clinical application of anti-VEGF agents has markedly changed the treatment of n-AMD since the 2000s.[1-2] There are three clinically available agents: ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), a recombinant antibody fragment that binds all active forms of VEGF-A; bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA), a recombinant humanized full-length antibody that also binds all active isoforms of VEGF, and relatively newer agent aflibercept (Eylea; Regeneron, Inc., Tarrytown, NY) approved for the treatment of wet AMD. Aflibercept (AFL) binds to more isoforms of the VEGF-receptor in addition to stronger affinity for VEGF. It also binds to VEGF-B and placental growth factor along with VEGF-A and has a longer half-life compared with the other agents.[3-4]The VEGF Trap-Eye: the Investigation of Efficacy and Safety in Wet (VIEW) 1 and 2 studies were well-controlled, head-to-head trials evaluating the efficacy and safety of AFL when administered monthly, and 2.0 mg every 8 weeks after three initial monthly doses in comparison with monthly ranibizumab.[5] Non-inferiority of AFL to ranibizumab in vision maintenance at 52 weeks as a primary end point was achieved. There was a favorable safety profile for both.

Serous and fibrovascular PEDs are often resistant or incompletely responsive to anti-VEGF treatment; thus, some studies reported that the presence of PED was a poor prognostic factor in AMD.[6] AFL is considered to be more effective in PEDs and persistent fluid, which is attributed to tachyphylaxis or tolerance due to long-term treatment. The aim of this study was to investigate the results of a pro re nata (PRN) regimen of AFL treatment in patients with n-AMD and PED.

MATERIALS AND METHODS

In this interventional, retrospective case series, we reviewed te records of all patients who had typical type of n-AMD with serous or fibrovascular PED and underwent 2.0 mg intravitreal AFL injections between January, 2016 and September, 2017. Inclusion criteria were age over 50 years, the presence of typical wet AMD with PED confirmed using spectral domain optical coherence tomography (SD-OCT), refractoriness to ranibizumab treatment defined as the presence of intraretinal or subretinal fluid despite the last three regular ranibizumab injections, and no previous treatment for the naive group. The retreatment criterion was fluid on SD-OCT, except underneath the PED. Exclusion criteria were maximal PED height <100 μm measured using OCT at baseline, other subtypes of AMD (retinal angiomatous proliferation and polypoidal choroidal vasculopathy) or history or presence of other maculopathies or retinopathies (e.g. retinal vein occlusion, uveitis), patients undergoing any combination therapy, and evidence of end- stage AMD such as disciform scarring at baseline.

All patients included in the study underwent a complete ophthalmic examination: BCVA was assessed either using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a distance of 4 m or Snellen charts, and was converted to logMAR visual acuity for statistical analysis. Macular OCT scans were performed using Topcon 3D OCT-2000 System and CMT measurements were obtained manually at the fovea by placing digital calipers from the outer limit of the Bruch membrane to the internal limiting membrane. Maximal PED height was measured from the hyper-reflective line of the Bruch membrane to the inner margin of the hyper-reflective line of retinal pigment epithelium layer. All PEDs were classified as fibrovascular evidenced by heterogeneous internal reflectivity or serous evidenced by internal hypo-reflectivity on OCT. Demographic data, treatment prior to AFL injections, anterior segment and fundus examination, and possible serious adverse events such as endophthalmitis, retinal detachment or thromboembolic events were collected from the patient files. Patients who were suspected to have other types of n-AMD or were unresponsive to ranibizumab were evaluated with indocyanine green angiography. The primary outcome measures were the mean changes in BCVA (logMAR), CMT, PED, the presence of SRF or IRF from baseline to final AFL injection and the correlation between reduction in PED height and visual acuity improvement.

All patients underwent AFL injections in the operating room under topical anesthesia. They received topical moxifloxacin eye drops four times during the week after injections and were examined on post-operative day 1 for visual acuity,

anterior chamber reaction, intraocular pressure (IOP), and fundus evaluation using indirect ophthalmoscopy.

Informed consent was obtained from all patients before the injections. This study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. Statistical analysis was performed using SPSS 20. The Shapiro-Wilk test was performed to assess the normality of continuous variables. The paired t-test and Wilcoxon signed-rank test were performed to compare mean differences between pre- and post-injection values of all evaluated parameters (BCVA, CMT, maximal PED height). Mann Whitney U test was used for comparisons between groups. Chi-square, Fisher's exact or McNemar tests were used to compare frequencies between groups. Linear regression analysis was used to evaluate the correlation between PED height reduction and visual acuity. A p value<0.05 was considered as statistically significant.

RESULTS

This study included 30 eyes of 25 patients: 19 switched eyes in group 1 and 11 treatment-naive eyes in group 2. The mean age of the patients was 76.1±6.5 years (range, 61-87 years) and the mean duration of follow-up after AFL injections was 7.4 ±1.9 months (range, 5-11 months) with an average of 3.0±1.1 injections (range, 2-6). The initial demographic characteristics were comparable between the two groups (p>0.05). In group 2, the mean number of AFL injections was 3.8±1.1 (range, 3-6) over an average of 7.6±2.4 months. Table 1 shows the characteristics of injections for group 1.

After AFL treatment, the mean maximal PED height decreased from 286±203µm to 124±129 µm (p<0.001); 16 eyes (53%) showed a more than 50% decrease in PED heights compared to baseline while 12 eyes (40%) showed a less than 50% decrease in PED heights compared to baseline. There was an increase in PED height greater than baseline (deterioration) in 2 (7%) eyes. The complete resolution rate was 37% (11 eyes).

Serous PEDs showed a significantly better (p=0.037) response than fibrovascular PEDs (Fig 1). Eight percent of PEDs were extra-foveal. The mean BCVA improved from 0.49±0.33 logMAR to 0.45±0.33 logMAR (p=0.15) but the difference did not reach statistical significance. The reduction of PED height was not associated with improved visual acuity (R^2=0.002, p= 0.84). There were no retina pigment epithelium (RPE) rips on OCT. The mean CMT values before and after AFL injection were 256±96 µm and 164±52 respectively (p=0.001). Both groups had a similar trend: the anatomic response was better than the visual outcomes, and BCVA remained stable during the follow-up period. Table 2 compares the changes in the two groups. Similarly, no significant difference in initial visual acuity (0.54±0.28) was observed in the switch group [before AFL injection; 0.46±0.27 logMAR (p=0.29)] while administering ranibizumab injections.

Before switching, 6 eyes had both persistent intra- and subretinal fluid, and 13 eyes had either intra or subretinal fluid. In group 2, 1 eye had both intra- and subretinal fluid, and 10 eyes had either intra or subretinal fluid (Fig 2). Following aflibercept injections with a PRN regimen, approximately 74% of eyes in group 1 and 64% of eyes in group 2 had

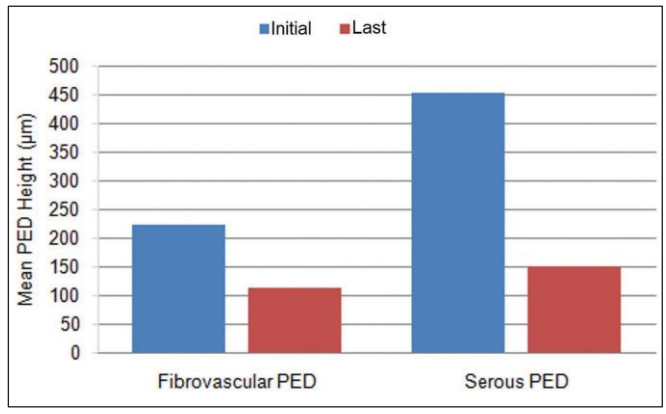

Figure 1: *The reduction of PED height after aflibercept injection was more significant in serous than in fibrovascular PED.*

Table 1. *Baseline characteristics of group 1 for injections.*

	Minimum	Maximum	Mean	Std. Deviation
Number of AFL injections	2.00	5.00	2.50	0.80
Number of previous RAN injections	7.00	24.00	13.70	5.60
Total follow-up time (month)	15.00	76.00	41.0	18.00
Follow-up time for AFL (month)	5.00	11.00	7.60	1.70
BCVA values (logMAR) before RAN injections	1.04	0.20	0.55	0.29
BCVA values (logMAR) before AFL injections	1.00	0.10	0.46	0.27

BCVA: Best corrected visual acuity; **AFL:** Aflibercept; **RAN:** Ranibizumab.

Table 2. *Comparison of the two groups.*			
	Group 1	Group 2	p value
	Mean± SD	Mean± SD	
CMT (μm)			
Preop	254±99	261±94	0.851
Postop	156±46	179±60	0.235
Change (median)	98±90 (64)	76±112 (45)	0.654
Preop-postop p value	<0.001	0.026	
PED height (μm)			
Preop	266±192	321±225	0.333
Postop	110±106	150±165	0.426
Change (median)	164±211(114)	172±156 (120)	0.667
Preop-postop p value	<0.001	0.004	
BCVA (LogMAR)			
Preop (median)	0.46±0.27 (0.40)	0.54±0.42 (0.46)	0.544
Postop (median)	0.43±0.28 (0.30)	0.47±0.41 (0.30)	0.774
Change (median)	0.03±0.15 (0.02)	0.07±0.18 (0)	0.491
Preop-postop p value	0.443	0.205	
Fluid type (%)			
Preop			
IRF	3 (15.8%)	2 (18.2%)	0.367
SRF	10 (52.6%)	8 (72.7%)	
SRF+IRF	6 (31.6%)	1 (9.1%)	
Postop			
No fluid	14 73.7%)	7 (63.6%)	0.400
IRF	0%	1 (9.1%)	
SRF	5 (26.3%)	3 (27.3%)	
Preop-Postop p value	0.047	0.016	

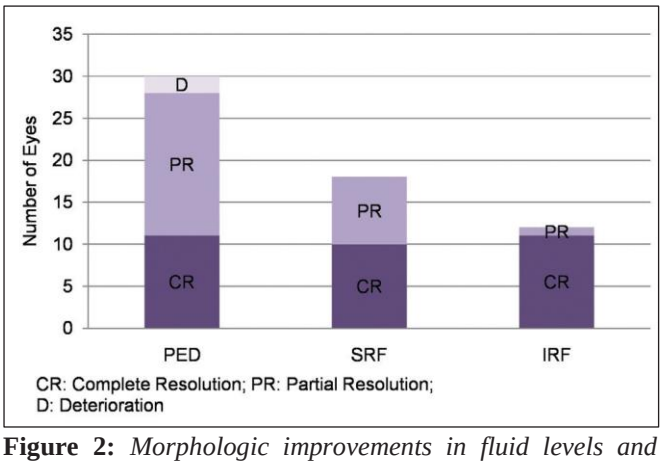

Figure 2: *Morphologic improvements in fluid levels and pigment epithelial detachment at the final control visit compared to baseline are seen.*

complete resolution, reaching 70% in total; the remaining eyes had partial resolution in both groups (p=0.40) and there was no deterioration in fluid levels. None of the patients experienced any significant ocular or systemic safety events.

DISCUSSION

The long duration of disease course in n-AMD and repeated injections induce phenomena of tachyphylaxis and tolerance. Tachyphylaxis is a sudden decrease in response to a drug after an initial dose or a series of small doses. Increasing the interval between doses or interrupting treatment for a short time may be useful to regain efficacy. The mechanism of tachyphylaxis during anti-VEGF therapies for n-AMD is still unclear. Tolerance is the lacking of efficacy when

drugs are used repeatedly over time, and the patient no longer responds to the drug in the way they preliminarily responded. Increasing the dosage, using shorter dosing time intervals, and switching can achieve the desired effect when tolerance occurs in ophthalmology.[7] Up-regulated expression of VEGF due to chronic inhibition, changes in signal transduction, systemic and local immune response that leads to the development of neutralizing antibodies, and increased clearance of the drug from the eye may all result in tolerance. Based on two pivotal Phase III trials, ANCHOR and MARINA, which reported 1-year data, the baseline incidence of immunoreactivity to ranibizumab was 0–3%, and reached up to ~1–6% after monthly dosing with ranibizumab for 12-24 months.[8]

Several studies showed better anatomic[9-12] and sometimes functional outcomes when switching to AFL in eyes previously treated with other anti-VEGF agents.[13-14]In the current study, we reported a significant change of maximal PED height and central retinal thickness, whereas visual acuity could only be stabilized. At the final visit, 26% of eyes had subretinal fluid compared with more than 83% at baseline; less than 5% of eyes had intraretinal fluid compared with 40% of eyes at baseline, and there was no deterioration in fluid levels. Naive eyes are probably more prone to gain visual acuity than those of patients who are resistant to anti-VGEF due to the lack of long-term presence of chronic fluid and the development of scar tissue. For example, Cho et al. analyzed the clinical outcomes of 202 treatment-naive n-AMD eyes with PED who were treated with anti-VEGF (ranibizumab and aflibercept) injections on an ‘as-needed’ basis after a loading phase. They achieved significant improvement of visual acuity from 0.71 to 0.60 approximately 5 letters together with anatomic success in PED resolution and macular thickness after 12 months of follow-up.[15] However, improvement of visual acuity in our treatment-naive patient group was not statistically significant over 7.5 months; the relatively high rate (36% of eyes) with partial fluid resolutions might have been the reason in these difficult-to-treat n-AMD patients with PED, and maybe more time is needed to achieve better visual results.

Most previous studies about switching contained a loading dose of three monthly injections followed by a bimonthly regime while a minority used a PRN regimen. A report of 86 eyes (comprising 17 treatment-naive patients and 69 patients who had previously received ranibizumab) found that aflibercept with a PRN regimen gained an improvement in visual acuity and central retinal thickness in all treated groups with fewer injections than advocated at a 12-month follow-up.[16] The VIEW1 and VIEW2 trials demonstrated that intravitreal AFL 2 mg every 2 months produced similarly favorable efficacy results as monthly ranibizumab. The number of re-treatments in the PRN period (second year) was smaller for the 2 mg dose of AFL (4.2 for aflibercept vs. 4.7 for ranibizumab) and this seems to be due to the fact that fewer patients needed more intensive therapy with aflibercept.[5,17]Reducing the burden of monthly intravitreal injections is a common goal that has given rise to the necessity to try different injection regimens, particularly in developing countries. Considering the financial burden and risks of frequent intravitreal injections, we chose the PRN regimen of AFL with close follow-up for both groups and administered a loading dose only to treatment-naive patients. If switching is performed between drugs with a similar target (VEGF), we believe that an induction phase is controversial. On the other hand, AFL is assumed to be a broad-spectrum anti-VEGF agent binding VEGF-B and placental growth factor in addition to its stronger affinity for VEGF, and so better visual results might be possible with a loading dose in the event of switching. Further studies are needed to determine the necessity of a loading dose in switching between anti-VEGF drugs.

It is widely claimed that growth of an occult choroidal neovascular membrane and extravasation of fluid leads to RPE elevation in fibrovascular PED, which, in turn, becomes a mechanical obstacle that complicates PED flattening. On the contrary, the space between the RPE and Bruch’s membrane mainly constitutes fluid in serous PED, which seems optically empty on OCT. Hence, the treatment response of serous PEDs is expected to be better than those with fibrovascular PEDs. Furthermore, the mechanism of PED formation may be different between n-AMD subtypes. A recent study demonstrated that the flattening of PED was more frequent in PCV and RAP than in typical AMD.[15] In our retrospective case series, we determined strict inclusion criteria and excluded patients with PCV and RAP in order to prevent effects of confounding factors. Serous PEDs showed a significantly better (p=0.037) response than fibrovascular PEDs, similar to previous studies.[18-19] Although the maximal PED height significantly reduced and there were no RPE rips, visual acuity was not associated with a reduction in PED height. Lacking of correlation between PED reduction and visual outcomes makes PED height a less useful method as a clinical indicator of treatment.[19] PED flattening was also attributed to decreased activity of the choroidal neovascular membrane or a toxic effect by the drug, which has been claimed in some animal and in vitro studies.[20-21] We think that our findings support the former theory because the PEDs in the present study seemed to have a seesaw pattern in accordance with the advent of subretinal or intraretinal fluids (Fig 3).

The limitations of this study are its retrospective nature, short-term results, and limited number of cases, which was caused by specifying strict inclusion criteria. Even though the functional importance of a reduction in PED height is

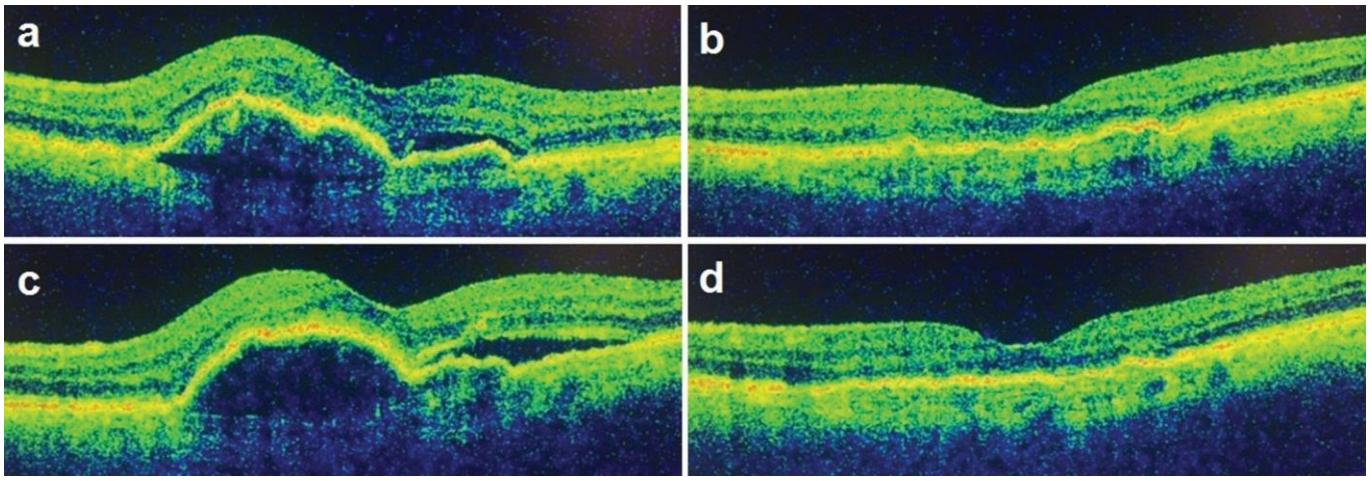

Figure 3: *Good anatomic and stable visual response to AFL injections in a treatment-naive patient with n-AMD.* **a.** *Representative case showing PED and subretinal fluid on OCT at baseline (VA:0.20 logMAR)* **b.** *The fluid and PED completely disappeared after the loading phase (VA:0.20 logMAR)* **c.** *Subretinal fluid and serous PED are present again at month 5 confirming a seesaw pattern (VA:0.24 logMAR)* **d.** *No subretinal fluid or PED is seen after the fourth AFL injection on OCT (VA:0.22 logMAR).*

unclear, we know that PEDs, which are often incompletely responsive to anti-VEGF therapies, can cause macular architectural distortion and associated vision loss in some cases.[22] Our real-world data using a conventional PRN regimen of AFL over 7.5 months presented morphologic improvements with stable visual acuity, in both treatment-naive and switched groups and even in the treatment of the selected PED cohort.

ACKNOWLEDGEMENTS

All the listed authors agree with the submission of this article and none have any related conflicting financial interests. The authors also declare no research funding. The English language was checked by a professional native English editor.

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