Short-term Response to Pro Re Nata Regimen of Aflibercept in Refractory Neovascular Age-related Macular Degeneration with Pigment Epithelial Detachment

Pigment Epitel Dekolmanı Olan Dirençli Neovasküler Yaşa Bağlı Makula Dejenerasyonunun Pro re Nata Uygulanan Aflibersept Tedavisine Kısa Dönem Cevabı

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ABSTRACT

Purpose: To evaluate the short-term visual and anatomic outcomes ofpro re nata (PRN) regimen of Aflibercept (AFL) without a loading phasein refractory neovascular age-related macular degeneration (n-AMD) with pigment epithelial detachment (PED).

Material and Methods: Typical type of n-AMD with PED were only included in this retrospective study. Twenty eyes that met the study criteria were ranibizumab-resistantand switched to pro re nata (PRN) regimen of 2.0 mg aflibercept. Best corrected visual acuity (BCVA), central macular thickness (CMT), changes in pigment epithelium detachments (PED), presence of intraretinal fluid (IRF), and presence of subretinal fluid (SRF) were assessed at 4-8 week intervals.

Results: The mean number of prior injection was 13.3±5.1 during a mean of 44 months of follow-up (15-76).The mean duration after switching was 7.2±1.7 months (5-11) with an average number of 2.5±0.8 (2-5) injections. The mean CMT and maximal PED height improved significantly ($p<0.001$), whereas the mean BCVA remained stable over time. Changes in visual acuity was not associated with reduction in PED height ($R^2= 0.07$, $p=0.73$). Eighty percent of patients remained visually stable, 10% gained two or more lines, and 10% lost two or more lines of visual acuity after switching. Complete resolution of intraretinal or subretinal fluid was observed in 75% of the treated eyes.

Conclusion: The morphological improvements were achieved following PRN regimen of AFL injection in our difficult-to-treat patient population (PED cohort), but there was no concomittant increase in visual acuity.

Key Words: Neovascular age-related macular degeneration, pigment epithelial detachment, ranibizumab, VEGF-Trap eye.

ÖZ

Amaç: Pigment epitel dekolmanına (PED) sahip dirençli neovasküler tip makula dejenerasyonunda (n-YBMD) yükleme fazı olmadan pro re nata (PRN) olarak uygulanan afliberseptin (AFL) kısa dönem görsel ve anatomik sonuçlarının değerlendirilmesi

Gereç ve Yöntemler: Bu retrospektif çalışmaya klasik tip n-YBMD dahil edildi. Çalışma kriterlerini karşılayan 20 göz ranibizumaba dirençli idi ve PRN olarak uygulanan 2.0 mg AFL tedavisine geçildi. En iyi düzeltilmiş görme keskinliği (EİDGK), santral makula kalınlığı (SMK), PED'lerdeki değişimler, intraretinal sıvı (IRS) ve subretinal sıvı (SRS) varlığı 4-8 hafta aralıklarla değerlendirildi.

Bulgular: Ortalama 44 (15-76 aralığında) aylık takip boyunca önceden yapılan ortalama enjeksiyon sayısı 13.3±5.1 idi. İlaç değişimi sonrası ortalama 7.2±1.7 (5-11 aralığında) ayda ortalama 2.5±0.8 (2-5 aralığında) sayıda enjeksiyon yapılmıştır. Ortalama SMK ve

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maksimal PED yükseliğinde anlamlı (p<0.001) değişiklikler olurken, EİDGK zamanla stabil kalmıştır. Görme keskinliğindeki değişimler PED yüksekliğindeki azalma ile ilişkili değildi (R^2= 0.07, p=0.73). Değişim sonrası %80 hastada görme keskinliği korundu, %10 hasta iki sıra ve üzeri kazanç sağladı, %10 hasta ise iki sıra ve üzeri kayıp yaşadı. Tedavi edilen %75 hastada IRS veya SRSnin tamamen çekildiği gözlendi.

Sonuç: Zor tedavi edilen hasta grubumuzda (PED kohortu) PRN olarak uygulanan AFL enjeksiyonu sonrası morfolojik iyileşmeler saptandı, fakat eş zamanlı bir görme keskinliği kazancı olmadı.

Anahtar Kelimeler: Neovasküler yaşa bağlı makula dejenerasyonu, pigment epitel dekolmanı, ranibizumab, VEGF-Tuzak göz.

INTRODUCTION

Age-related macular degeneration (AMD) is an acquired degeneration of the retina that leads to severe vision loss over the age of 50 years through a combination of non-neovascular (drusen and retinal pigment epithelium abnormalities), and neovascular disorder (choroidal neovascular membrane formation).The abnormal growth of abnormal vessels induced by vascular endothelial growth factor (VEGF) causes an accumulation of subretinal fluid (SRF), macular edema, intraretinal cysts, and pigment epithelium detachment (PED). There are three available agents that block VEGF: bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), and recently approved aflibercept (Eylea; Regeneron, Inc., Tarrytown, N.Y.). The application of these anti-vascular endothelial growth factor-A (anti-VEGF) pharmaceuticals has radically improved the treatment of neovascular age-related macular degeneration (n-AMD) since the 2000s [1-2] and so the incidence of severe vision loss and blindness has been substantially reduced by 46%–51% in many countries.[3-5]

Because Aflibercept (AFL)binds to VEGF-B and placental growth factor beside VEGF-A in addition to having a stronger binding affinity for VEGF compared with the other agents[6-7], it may be more effective in PEDs and persistent fluid when tachyphylaxis or tolerance occurs due to long-term treatment. The aim of this study was to evaluate a difficult subgroup of n-AMD patients with PED who were treated with pro re nata (PRN) regimen of AFL without a loading phase.

MATERIAL AND METHODS

This retrospective study included 20 eyes of 19 patients with n-AMD treated with AFL injectionsfrom one tertiary vitreoretinal care center between January 2015 and March 2017. Inclusion criteria were age over 50 years, the presence of typical wet AMD with PED, refractoriness to ranibizumab treatment defined as the presence of intraretinal and/or subretinal fluid despite last three regular ranibizumab injections. The retreatment criterion was fluid on optical coherence tomography (OCT). Exclusion criteria were other subtypes of wet AMD, maximal PED height <100 µm measured using OCT at baseline, history or presence of other maculopathies or retinopathies (e.g. retinal vein occlusion, diabetic macular edema, uveitis), patients undergoing any combination therapy.

All patients included in the study underwent a complete ophtalmic examination: BCVA was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a distance of 4 m but converted to logMAR visual acuity for statistical analysis. Macular OCT scan was performed by Topcon 3D OCT-2000 System and maximal PED height was measured from the hyperreflective line of Bruch membrane to the inner magrin of the hyperreflective line of retina pigment epithelium layer. All PEDs were classified as fibrovascular (hyperreflective) and serous (hyporeflective)evidenced by internal reflectivity on OCT. Demographic data, the treatments administered before AFL injections, central macular thickness (CMT), the presence of SRF and/or IRF and the height and presence of PED from baseline to last injection after AFL injections were noted. The main outcomes were the mean changes in BCVA (logMAR), the proportion of eyes with at least 2 lines of BCVA improvement, and the proportion of eyes exhibiting ≥2 lines of BCVA worsening. The correlation between reduction in PED height and visual acuity improvements were also evaluated. The fluid levels and PED were classified: improved (partial or complete), stable or worse. Serious adverse events such as endophthalmitis, retinal detachment or thromboembolic events were investigated.

This study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients before injection. Statistical analysis was performed using SPSS 20. The Shapiro-Wilk test was performed to test the normality for a continuous variable. The paired t-test and Wilcoxon were performed to compare mean differences between pre- and post-injection values of all the parameters evaluated (BCVA, CMT, maximal PED height). Frequencies were compared by using chi-squared or Fisher's exact tests. Linear regression analyses were used to evaluate the relation between PED height reduction and visual acuity. A P<0.05 was considered as a significant clinical result.

RESULTS

A total of 19 patients (13 women) diagnosed with wet AMD

and PED at our retina clinic were analysed and treated with PRN regimen of AFL. The mean age was 76.4±6.1 years (65-87). The mean duration after switching was 7.2 ±1.7 months (5-11) with an average of 2.5±0.8 (2-5) injections for the entire group. The mean number of prior injections was 13.3±5.1 during a mean of 44 months of follow-up (15-76). No significant difference in initial visual acuity (0.56±0.31) was observed in comparison with the recent preinjection values [0.51±0.31 logMAR (p=0.23)]. After AFL treatment, the mean maximal PED height decreased from 264±187µm to 105±100 µm (p<0.001); 80% of eyes showed an improved decrease of PED heights from baseline, 15% of the eyes showed a stable values. There was an increase in PED height greater than baseline (worse) in 5% of eyes. The proportion of complete resolution was 35% (7 eyes). The decreases in PED heights at the initial visits were more variable but then reached a plateau following repeated AFL injections (Figure 1). There was no difference in treatment response to AFL

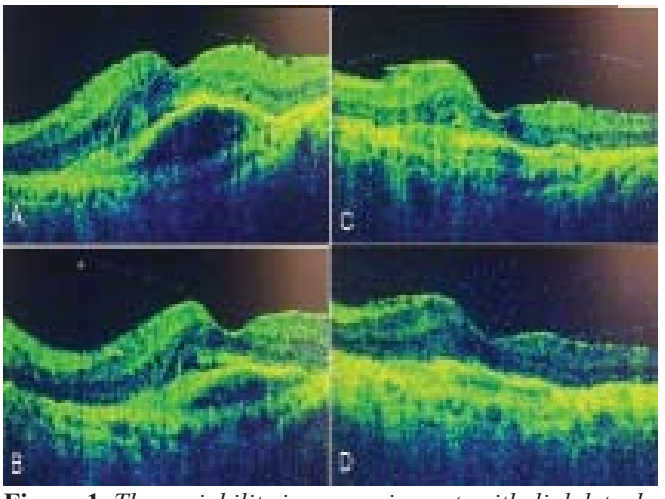
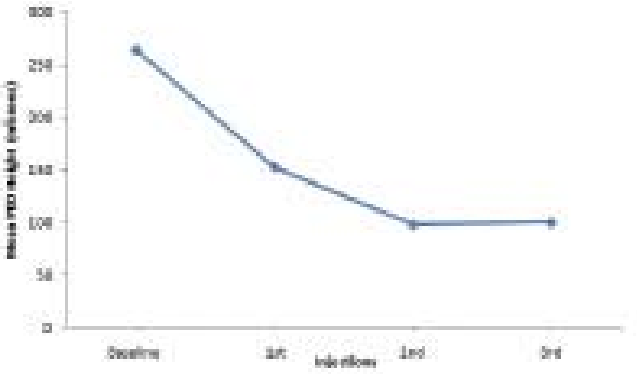


Figure 1. *The variability in mean pigment epithelial detachment heights at the initial visits reached plateau after repeated aflibercept injections.*



between fibrovascular and serous PEDs (p=0.09). The mean BCVA improved from 0.51±0.31 logMAR to 0.47±0.30 logMAR (p=0.23) but not significantly. Eighty percent of patients remained visually stable, 10% gained two or more lines, and 10% lost two or more lines of visual acuity after switching. Improved visual acuity was not associated with reduction in PED height (R^2= 0.07, p=0.73). There were no retina pigment epithelium (RPE) tears on OCT. The mean CMT values before and after AFL injection were 244±103 µm and 155±52 respectively and improved significantly (p<0.001). Table 1 demonstrated the changes and comparison ofpre and pos-injection values.

Before switching, 7 eyes had both persistent intra- and subretinal fluid, 13 eyes had either intra or subretinal fluid in our cohort. Following AFL injections with a PRN regimen,75% of eyes had complete resolution, the remaining eyes had partial resolution in both groups (p=0.40) (Figure 2). There was no deterioration in fluid levels. None of the patients experienced any significant ocular or systemic safety events.

Table 1. The changes and comparison of pre- and post-injection values

Characteristics		Minimum	Maximum	Mean±SD	p value
Mean PED height (µm)	Pre	100	950	264±187	
	Post	0	280	104±106	<0.001
	Change	-57	950	160±207	
Mean CMT(µm)	Pre	91	446	244±103	
	Post	80	247	155±52	<0.001
	Change	-10	348	90±90	
Mean BCVA (logMAR)	Pre	0.10	1.22	0.51±0.31	
	Post	0.10	1.00	0.47±0.30	0.23
	Change	-0.30	0.34	0.04±0.15	
Mean BCVA before AFL injections	Pre	0.16	1.04	0.56±0.31	
	Post	0.10	1.00	0.46±0.29	0.265
	Change	-0.40	0.76	0.09±0.31	
Change in PED height after AFL injections	1st	0	630	153±154	0.006
	2nd	0	250	98±85	<0.001
	3rd	0	280	100±109	0.028

PED: Pigment Epithelial Detachment, CMT: Central Macular Thickness, BCVA:Best Corrected Visual Acuity, AFL: Aflibercept

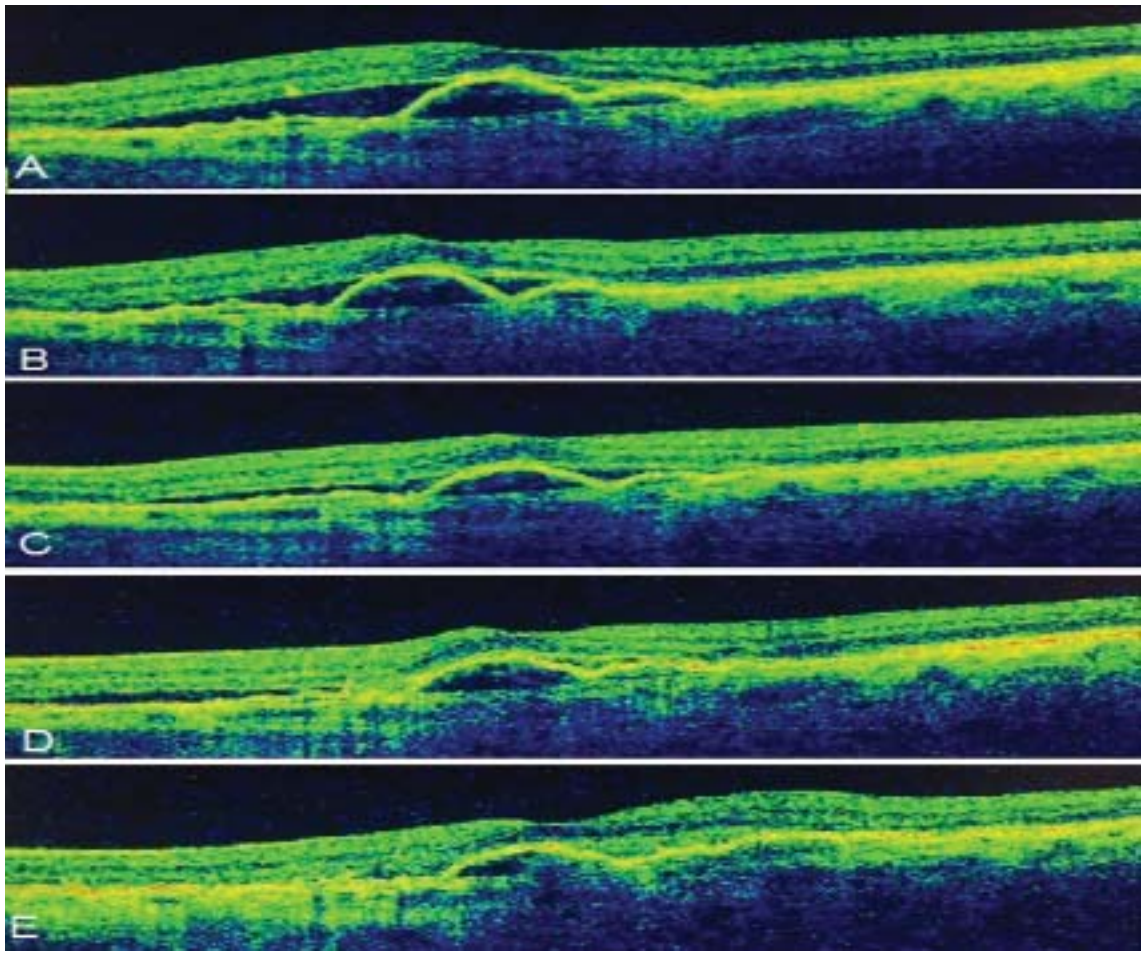


Figure 2. *Good anatomic and visual response to AFL injections in a switch case previous treated with 13 ranibizumab injections* ***A)*** *One month after the last ranibizumab injection, persistent subretinal, intraretinal fluid and subfoveal PED are present on OCT (VA: 0.24 logMAR)* ***B)*** *OCT shows a decrease in PED height and fluid levels after the 1st AFL injection (VA: 0.30 logMAR)* ***C)*** *There is stil minimal intraretinal fluid but no PED on OCT after the 2nd AFL injection (VA: 0.22 logMAR)* ***D)*** *No fluid or PED are seen on OCT at completion of 6 months of treatment with 3rd AFL injection (VA:0.20 logMAR)*

DISCUSSION

There is a high rate of patients between 53 to 71% who continue to have persistent fluid on OCT despite receiving monthly injections of ranibizumab or bevacizumab.[8,9] We evaluated the visual and anatomic response of patients with refractory neovascular AMD after switching to AFL injection. In the comparison of AMD Treatments Trials (CATT), sustained vision loss of > 15 letters (3 lines) was observed in 6.9% of patients, and they had a large visual decline with a mean loss of33 letters by 2 years.[10] The subgroup analysis of them showed that not only retinal thinning and more geographic atrophy but also more intraretinal fluid and retinal thickening may have been associated with visual decline. Thus,we may regain the efficacy following switching that results in clearing of retinal fluid and reduction in retinal thickness.

A great deal of studies showed better anatomic[11-14] and sometimes functional outcomes when switching to AFL in eyes previously treated with the other anti-VEGF agents.[15,16] In the current study, we found a significant change of the maximal PED height and central retinal thickness, whereas visual acuity preserved with a mean duration of 7.2±1.7 months.[5-11] Indeed, the lack of a concomitant gain in visual function may be relevant to an accumulating effect of long term neovascularization, such as development of retinal gliosis, and progression of retinal atrophic changes that have been documented to occur in neovascular AMD eyes treated with anti-VEGF injections.[17-19] Yonekawa and colleagues revealed the outcomes of 102 eyes with chronic n-AMD where they found stabilized vision and improved anatomic outcomes with a lenghtened injection interval of 1-2 weeks, on average, after switching from ranibizumab to AFL. They found that 91% of eyes with refractory AMD showed improvement on OCT, while %9 were stable and no eyes worsened.[20] Similarly, we demonstrated anatomic improvement-

sapproximately in all eyes following AFL injections. There was no deterioration in fluid levels. Ho and et al. analyzed 96 eyes treated with 3 monthly injections of AFL followed by a fourth injection within 2 months.[12] Eighty-five percent of patients remained stable in visual acuity, 7% gained two or more lines, and 7% lost two or more lines with a close rate of our results.

The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (Views 1 and 2) compared monthly and every other month intravitreal injections (after three montly loading doses) of various doses of AFL to monthly injections of 0.5 mg of ranibizumab. Monthly and every other month, intravitreal injections of 2 mg AFL were shown to have non-inferior results compared to monthly injections of ranibizumab in the first year. The number of retreatments in the PRN period was also lower for the 2 mg dose of AFL - 4.2 for aflibercept vs 4.7 for ranibizumab. Administering fewer injections and reducing the burden is a common issue that causes trying different regimen of injections, particularly in developing countries. Approximately one injection performed once every three months through the lack of loading doses with PRN regimen and it worked as well as prior reports that had a loading phase. As a result, if we trust in our optimal treatment with previous anti-VEGF agents, we suppose that an induction phase is controversial for switching cases.

In our case series, 80% of eyes showed an improved decrease of PED heights from baseline, 15% of eyes showed a stable values after AFL injections. There was an increase in PED height greater than baseline (worse) in 5% of eyes. The decreases in PED heights at the initial visits were more variable but then reached a plateau following repeated AFL injections. In this study, improved visual acuity was not associated with reduction in PED height (p= 0.86) in accordance with the most previous studies that have shown little to no correlation between them.[21-22]In contrast to mechanical obstacle theory that complicates PED flattening by growth of an occult choroidal neovascular membrane in fibrovascular PED,there was no difference in treatment response to AFL between fibrovascular and serous PEDs.

CONCLUSION

The retrospective design, limited number of cases with a short-term results are limitations of our study. Even though the functional importance of PED flattening is unclear, we know that PEDs are often weakly responsive to anti-VEGF therapies and associated vision loss in some cases.[23]We achieved morphological improvements with a stable visual acuity in the treatment of selected PED cohortof n-AMD patients resistant to ranibizumab using a PRN regimen of AFL.

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