Treatment of Choroidal Neovascularization Secondary to Age-Related Macular Degeneration with Intravitreal Bevacizumab Monotherapy or Combination with Photodynamic Therapy: 12 Month Results

Yaşa Bağlı Maküla Dejenerasyonuna Bağlı Koroidal Neovaskülarizasyon Tedavisinde Tek Başına Bevacizumab veya Fotodinamik Tedavi ile Kombinasyon: 12 Ay Sonuçları

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ABSTRACT

Purpose: To determine the anatomical and visual responses to intravitreal bevacizumab injection (IVB) monotherapy and the combination of IVB with photodynamic therapy (PDT) in neovascular age-related macular degeneration (AMD).

Materials and Methods: This was a prospective study that involved treatment of naive eyes with neovascular AMD. The eyes were divided into 2 groups: the 1st group received only IVB and the 2nd group received IVB+PDT. An activity score (AS) was given to each lesion during all visits. Student's t test and chi-square test were used for the comparison of parameters.

Results: A total of 53 eyes were involved in the study. Mean follow-up time was 12.3 months. There was no significant difference with respect to lesion type, visual acuity, or central foveal thickness between the groups before treatment. After treatment AS decreased significantly in the two groups ($p<0.05$). Visual acuity was the same or increased in 92.5% of the eyes in group 1 and in 88.5% of the eyes in group 2 ($p>0.05$). The mean number of IVB/eye was 2.7 in group 1 and 2.6 in group 2 ($p>0.05$).

Conclusion: IVB+PDT combination therapy seems not to be superior to IVB monotherapy with respect to visual acuity or retreatment needs in neovascular AMD. An activity scoring-guided strategy may help to determine the need for retreatments.

Key Words: Bevacizumab, photodynamic therapy, combination therapy, age-related macular degeneration, anti-VEGF therapy.

ÖZ

Amaç: Neovasküler yaşa bağlı maküla dejenerasyonunda (YBMD), tek başına intravitreal bevacizumab enjeksiyonu (İVB) ile fotodinamik tedavi (FDT) ve İVB kombinasyon tedavisinin anatomik ve görsel sonuçlarının değerlendirilmesi.

Gereç ve Yöntem: Bu geriye dönük çalışmaya daha önce tedavi almamış neovasküler YBMD'li gözler dahil edildi. Çalışma tek başına İVB tedavisi alan 1. grup ve İVB+FDT tedavisi alan 2. grup olmak üzere toplam 2 gruptan oluşturuldu. Tedavi öncesi ve sonrası tüm kontrollerde her lezyona bir aktivite skoru (AS) verildi. Parametrelerin karşılaştırılmasında Student's t testi ve Ki-kare testi kullanıldı.

Bulgular: Çalışmaya toplam 53 göz dahil edildi. Ortalama takip süresi 12.3 ay idi. Tedavi öncesinde gruplar arasında lezyon tipi, görme keskinliği ve santral foveal kalınlık açısında bir fark izlenmedi. Tedavi sonrasında AS her iki grupta da anlamlı olarak azaldı ($p<0.05$). Görme keskinliği 1. gruptaki gözlerin %92.5'inde aynı veya artmış olarak izlenirken bu oran 2.grupta %88.5 idi ($p>0.05$). Ortalama İVB/göz sayısı 1. grupta 2.7, 2. grupta ise 2.6 olarak hesaplandı ($p>0.05$).

Sonuç: İVB+FDT kombinasyon tedavisi tek başına İVB tedavisine göre, görme keskinliği ve tekrar tedavi ihtiyacı açısından üstün görünmemektedir. Tekrar tedavi ihtiyacının belirlenmesinde aktivite skorlama sisteminin kullanılması yardımcı olabilir.

Anahtar Kelimeler: Bevacizumab, fotodinamik tedavi, kombinasyon tedavisi, yaşa bağlı maküla dejenerasyonu, anti-VEGF tedavi.

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INTRODUCTION

Since it has been shown that vascular endothelial growth factor (VEGF) plays a key role in the pathogenesis of neovascular age-related macular degeneration (AMD), direct inhibition of VEGF has become the standard primary treatment for choroidal neovascularization.[1] Pegaptanib, an aptamer that binds VEGF165, was the first intravitreal anti-VEGF agent studied and approved by the Food and Drug Administration (FDA) for use in neovascular AMD.[2,3] Other anti-VEGF agents, ranibizumab and bevacizumab, are humanized monoclonal antibodies directed against all isoforms of VEGF-A. Ranibizumab, a Fab fragment of antibody, was approved by the FDA in 2006 for intravitreal treatment of neovascular AMD and shown to be effective in clinical studies.[4-7] Unlike ranibizumab, the off-label use of intravitreal bevacizumab, a full length antibody, limits the conducting of prospective, controlled clinical studies.

However, bevacizumab has been popular in neovascular AMD treatment due to its molecular similarity to ranibizumab and its low cost. Uncontrolled studies and case series support a benefit of intravitreal bevacizumab in neovascular AMD for 3 months to 1 year.[8-20] In several studies combination of intravitreal bevacizumab with photodynamic therapy (PDT) was suggested to be useful in treating neovascular AMD by improving visual acuity and reducing retreatment needs.[21-24] In this study we aimed to determine the anatomical and visual responses to intravitreal bevacizumab injection (IVB) alone or in combination with PDT in patients with choroidal neovascularization secondary to AMD.

MATERIALS AND METHODS

This prospective and comparative study involved patients with neovascular AMD lesions. Inclusion criteria were all types of neovascular AMD (occult lesions with recent disease progression), best corrected visual acuity (VA)>20/800, and no previous treatment. Patients with uncontrolled hypertension and recent thromboembolic events were excluded. A detailed informed consent was obtained from all patients concerning the off-label use and the potential side effects of bevacizumab. The study was conducted in accordance with Good Clinical Practice and Declaration of Helsinki and it received approval from the Republic of Turkey Ministry of Health. The patients were randomized into 2 groups. Eyes treated with only IVB were included in group 1 (IVB group). Those eyes treated with IVB and verteporfin PDT were included in group 2 (IVB+PDT group). The experienced ophthalmologists who performed the efficacy assessment remained blinded during the whole study regarding group allocation. Bevacizumab was administered as needed after the first injection (PRN: Pro Re Nata regimen) in all of the cases. No loading dose was applied.

Each patient underwent a full ophthalmologic examination including VA measurement with a Snellen chart, slit-lamp biomicroscopic examination of the anterior segment, and dilated funduscopic examination of the posterior pole. Additionally, color fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT) were carried out at the baseline visit. VA was measured at each visit along with examination of the anterior segment and fundus. OCT and FA were repeated every month. IVB dose was 2.50 mg/0.1 ml in all eyes. Bevacizumab was administered intravitreally through the pars plana according to the standard procedures.[25] In group 2, IVB injections were performed within 1 week of PDT. PDT with verteporfin was performed according to the recommended standard procedure.[26]

Table 1: Activity Scoring System (Score: 0-14): A score of 7 or more is supposed to indicate an active lesion and deserve treatment.

Parameter	Grading	Score
CLINICAL ASSESSMENT (Amount of hemorrhage associated with the lesion)	No hemorrhage	0
	Decrease	1
	Same amount/baseline	2
	Increase	3
OCT* Subretinal fluid/retinal thickening/PED	None	0
	Decrease	1
	Any amount at beginning/ Stable	2
	Increase	3
FA Staining pattern	No staining/ window defect	0
	Staining of scar tissue/ serous PED	1
	Late leakage/ fibrovascular PED	2
SIZE OF THE LESION* (SOL in FA: mm^2)	Decrease	0
	Beginning size / Stable	1
	Any increase in size	2
VISUAL ASSESSMENT**	OBJECTIVE	
	Increase	0
	Baseline/ No change	1
	Decrease	2
	SUBJECTIVE	
	Increase	0
	Baseline/ No change	1
	Decrease	2

FA; Fluorescein Angiography, SOL; Size Of The Lesion, OCT; Optical Coherence Tomography, PED; Pigment Epithelial Detachment.

* 10% difference is accepted as a change.

** gain or loss of one or more lines in Snellen chart is accepted as a change.

All patients were asked to call promptly in the event of any pain, redness, or significant decrease in vision occurring after injection. Reinjections were given at least 1 month after the previous injection according to a new activity scoring (AS) scheme (Table 1).[27-29] This activity scoring primarily depends on the assessment of the below-mentioned findings:

1- The amount of hemorrhage associated with the lesion (score of 0-3),
2- Central foveal thickness (CFT), as determined by the amount of intra/subretinal fluid in OCT (score of 0-3),
3- FA staining characteristics (score of 0-2),
4- Size of the lesion in FA (size of the lesion; SOL) (score of 0-2),
5- Objective and subjective visual assessments (score of 0-2 for each).

All of these parameters were evaluated to determine the general activity score of each choroidal neovascularization (CNV) at baseline and at each visit. Retreatments were given in the event of an AS of 7 or more. PDT was repeated at 3-month intervals when needed and IVB alone was applied if there was a need for retreatment within 3 months of the initial combined treatment in group 2. The main outcome measures were AS, VA, and reinjection number. LogMAR equivalent was used for all visual acuity calculations. Blood pressure measurements were routinely done at all visits; any systemic adverse events including new or exacerbated hypertension, stroke, or myocardial infarction were recorded, as well as ocular adverse effects including uveitis, endophthalmitis, vitreous hemorrhage, or retinal pigment epithelial tear. Student's t test and chi-square test were used for the comparison of parameters between the groups. A probability less than 5% ($p<0.05$) was considered statistically significant.

RESULTS

A total of 53 eyes of 53 patients were involved in the study; there were 27 patients in group 1 (IVB group) and 26 patients in group 2 (IVB+PDT group). The mean age was 70.1±7.9 years (54-85 years). All patients were followed up for at least 6 months, with a mean follow-up time of 12.3±3.8 months (6-15 months).

The CNV was predominantly classic in 17 eyes (32.1%), minimally classic in 10 eyes (18.8%), and occult without classic in 26 eyes (49.1%), and the lesion was subfoveal in 41 eyes (77.3%). There was no significant difference with respect to age, lesion type or diameter, VA, or CFT between the groups before the treatments ($p>0.05$, independent t-test), (Table 2). At baseline, the mean logMAR VA was 1.02±0.44 (0.20-1.60) in group 1 and 0.90±0.46 (0.20-1.90) in group 2. After treatment the mean logMAR VA improved to 0.84±0.44 (0.20-1.60), 0.80±0.47 (0.20-1.90), and 0.85±0.44 (0.10-1.60) in group 1 and 0.80±0.33 (0.40-1.90), 0.75±0.42 (0.00-1.90), and 0.67±0.42 (0.00-1.30) in group 2 at the 1, 6, and 12month follow up, respectively.

The increase in VA was statistically significant for the 1st, 3rd, 6th, 9th, and 12th months in group 1 and only for the 12th month in group 2 compared to the baseline ($p<0.05$ paired t-test). At the final follow up, VA was the same or increased in 92.5% of the eyes in group 1 and in 88.5% of the eyes in group 2 ($p>0.05$, chi-square), (Table 3). The median visual acuity improvement was 1 Snellen line in both groups. At baseline, mean AS was 8.05±1.43 (5-10) in group 1 and 8.05±1.00 (7-10) in group 2. At the 1st month follow up, the score decreased significantly to 4.89±1.70 (2-8) in group 1 and 5.00±2.35 (2-10) in group 2 and the values measured at the 3rd, 6th, 9th, and 12th months were significantly lower than the baseline ($p< 0.05$, paired t-test).

Table 2: Baseline characteristics.

Baseline Characteristics	Statistics	Group 1 (IVB)	Group 2 (IVB+PDT)
Age (yrs)	Mean (SD)	69.6 (5.9)	70.7 (9.5)
	(min; max)	(58; 79)	(54; 85)
CNV type			
Predominantly classical	n (%)	8 (29.6)	9 (34.6)
Minimally classical	n (%)	5 (18.5)	5 (19.2)
Occult	n (%)	14 (51.9)	12 (46.2)
CNV localization			
Subfoveal	n (%)	21 (77.8)	20 (77)
Juxtafoveal	n (%)	5 (18.5)	4 (15.4)
Extrafoveal	n (%)	1 (3.7)	2 (7.6)
Size of the lesion in FA (mm^2)	Mean (SD)	4.62 (2.40)	4.25 (2.26)
	(min; max)	(1.17; 9.90)	(1.00; 9.96)
VA (logMAR)	Mean (SD)	1.02 (0.44)	0.90 (0.46)
	(min; max)	(0.20; 1.60)	(0.20; 1.90)

CNV; Choroidal Neovascularization, FA; Fluorescein Angiography, IVB; İntravitreal Bevacizumab İnjection, Min; Minimum, Max; Maximum, PDT; Photodynamic Therapy, SD; Standard Deviation, VA; Visual Acuity.

Table 3: Frequency distribution of changes in visual acuity from baseline to last visit.

Change in Visual Acuity (Snellen)	Group1 (IVB) n (%)	Group 2 (IVB+PDT) n (%)	chi-square
>2 lines increase	8 (29.6%)	8 (30.8%)	(p>0.05)
No change (within 1 line)	17 (63%)	15 (57.7%)	(p>0.05)
>2 lines decrease	2 (7.4%)	3 (11.5%)	(p>0.05)

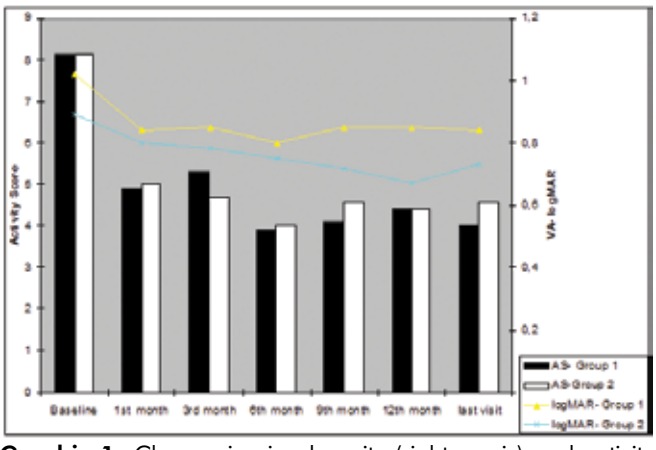
At the last visit, the mean AS was 4.00±1.00 (2-6) in group 1 and 4.64±1.89 (2-10) in group 2, which did not differ significantly between the two groups (p>0.05, independent t-test). A graphical representation of visual acuity and activity score over time is shown in Graphic 1.

The mean CFT at baseline was 356±132 μm (150-623 μm) in group 1 and 390±165 μm (187-800 μm) in group 2. At the 1st month after treatment, the mean CFT decreased to 254±87 μm (150-449 μm) in group 1 and 198±83 μm (80-431 μm) in group 2.

At the 6th and 12th month follow-up, the mean CFT values were lower than baseline and at the final visit the mean CFT was 177±52 μm (80-331 μm) and 202±82 μm (100-414 μm) in groups 1 and 2, respectively (p< 0.05, paired t-test). A graphical representation of CFT and visual acuity over time is shown in Graphic 2.

The mean number of IVB/eye was 2.7±1.1 (1-4) in group 1 and 2.6±1.8 (1-7) in group 2, which did not differ significantly between the two groups (p>0.05, independent t-test). The mean number of PDT/eye was 1.2±0.4 (1-2) in group 2.

The number of eyes that needed only one single injection was 6 (22.2%) in group 1 and 9 (34.6%) in group 2 during a mean follow-up of 12.3 months, but the difference was not statistically significant (p>0.05, chi-square).



Graphic 1: Change in visual acuity (right y-axis) and activity score (left y-axis) from baseline to the last follow-up (mean, 12.3 months) after treatment in group1 and group 2.

Safety; pigment epithelial tear in two eyes (one in each group), newly diagnosed systemic hypertension in 2 patients (Group 1), and a newly diagnosed cerebrovascular accident in 1 patient (Group 2) were recorded during the study. The patient with the cerebrovascular accident recovered without any sequela. No inflammation, infection, or ocular toxicity sign was seen.

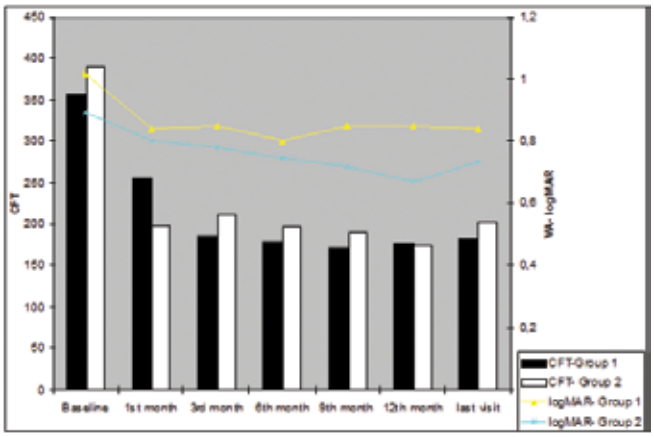
DISCUSSION

Bevacizumab has been reported to lead to improvement in visual acuity and/or decrease in subretinal/intraretinal fluid in patients with neovascular AMD as well as in other neovascular eye diseases.[8-20,30-32] However, as there is an insufficient number of prospective studies and a lack of published dose-ranging studies, the dosage and frequency of intravitreal bevacizumab treatment remain uncertain. The most common intravitreal dose for neovascular AMD is 1.25 mg and injections have been administered at every 4-6 weeks according to signs of progression or investigator's discretion.[9,10,12,13] Several studies also used fixed-dosing regimens.[11,17-19]

Furthermore, 1.25 mg of bevacizumab is approximately equivalent to the amount of ranibizumab used for phase III clinical trials.[4,5,10] However, as bevacizumab is a larger molecule, it might have lower concentrations in the subretinal space.

Additionally, it has lower affinity towards VEGF receptor and it is thought to be less immunogenic. Therefore, it may be more suitable to use a dose of 2.5 mg to allow an adequate subretinal concentration of bevacizumab, which was the dose used in the present study.

The need for retreatment is another challenge in bevacizumab treatment. In some studies retreatments were given in cases of persistent intraretinal or subretinal fluid on OCT as a PRN regimen without a loading dose after the 1st injection [9,10,12-15] while in others 3-monthly injections (loading dose) were used.[11,17-19]



Graphic 2: Change in log MAR visual acuity (VA) (right y-axis) and central foveal thickness (CFT) in OCT (left y-axis) from baseline to the last follow-up (mean, 12.3 months) after treatment in group 1 and group 2.

In a prospective study, Arias et al., compared these two IVB treatment protocols and reported that the loading dose protocol yielded better visual acuity results than the PRN protocol in neovascular AMD during 6 months' follow-up.[20] In the present study, an activity scoring scheme was used for evaluating the need for retreatment. We use this scheme in our practice to determine recurrence or reactivation of the lesion and so the need for retreatment. We have modified the scheme over the years and arrived at the present scheme.[27-29]

As presented in table 1, presence of hemorrhage associated with the lesion, presence of intra/subretinal fluid in OCT, FA staining pattern, change in lesion size (in FA), and change in both objective and subjective visual acuity (patient's feeling of visual change) are all taken into account to get an activity score. An activity score of 7 or more is considered to indicate an active lesion and given retreatment. During a mean of 12 months' follow-up the mean number of IVB injection/eye was 2.7 in patients who received IVB alone.

This finding may be interpreted as showing that a larger dose (2.5 mg vs. 1.25 mg) and activity scoring-guided strategy may reduce the need for retreatments. The multifactorial pathogenesis of neovascular AMD encouraged researchers to use combination therapy protocols, which act through different pathways to inhibit CNV and might have the potential for greater efficacy and/or better safety.

The goal of combination therapy would be to inhibit continued neovascularization and to destroy existing CNV while reducing the frequency of retreatment. PDT alone eradicates existing CNV and eliminates the source of VA deterioration; on the other hand, it up-regulates VEGF expression, which may lead to recurrences and may limit VA benefits. The addition of anti-VEGF therapy blocks the effect of VEGF, which could be over-expressed by the pathogenesis of CNV and by the effect of PDT.

Based on this idea, several studies evaluated the efficacy and safety of PDT combined with IVB in CNV secondary to AMD. In a study by Dhalla et al., a single combined therapy with PDT and IVB was suggested to be sufficient for 63% of eyes within 7-month follow-up.[21]

In another study, PDT and IVB combination therapy was compared with IVB monotherapy prospectively and it was suggested that a single administration of combination therapy led to significantly higher improvement and maintenance in visual acuity over a 3-month period than IVB monotherapy.[22]

Recently Smith et al., reported that 83% of eyes had stabilization of visual acuity and 65% of eyes received a single PDT and IVB combination therapy during a mean 9.5 months of follow-up.[23] In a prospective study by Ladewig et al, a single dose combination therapy was suggested to support a benefit for the decrease of intraretinal and subretinal fluid secondary to neovascular AMD; however, visual acuity improvement did not correlate with the anatomical restoration.[24]

In the present study, PDT and IVB combination therapy was found not to be superior to IVB monotherapy with respect to visual acuity or retreatment needs in neovascular AMD, which is in contrast to the results of the above-mentioned studies.

Most of the patients (68%) had occult and minimally classic lesions, which might be the reason for the greater number of reinjections or lower visual acuity improvement. Similarly, Lazic et al. reported that 64% of eyes with occult CNV secondary to AMD had positive results after two to three IVB injections as a mean for short term follow-up.[13]

In conclusion, IVB monotherapy seems to be an effective, safe, and cheap treatment for CNVs secondary to AMD. Our 1-year results do not support the addition of PDT to IVB treatment; however, long term results with higher numbers of patients will give more reliable results.

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