Ranibizumab Followed by Bevacizumab for Neovascular Age-Related Macular Degeneration: Can Visual Acuity be Maintained?

Eksudatif Tip Yaşa Bağlı Maküla Dejenerasyonunda Tedaviye Ranibizumab ile Başlayıp Bevacizumab ile Devam Edildiğinde Görme Keskinliğindeki Değişim Sürdürülebilir mi?

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ABSTRACT

Purpose: To evaluate the efficacy of a loading dose of ranibizumab for three months followed by a pro re nata (PRN) dosing regimen of bevacizumab for the treatment of neovascular age-related macular degeneration (AMD).

Material and Methods: The medical reports of patients with neovascular AMD treated with 3 monthly ranibizumab injections followed by bevacizumab PRN were reviewed retrospectively. Visual acuity (VA) assessed with an ETDRS chart and central foveal thickness (CFT) determined with optical coherence tomography (OCT) were recorded at baseline and monthly thereafter.

Results: Fifty-four eyes of 53 patients were involved in the study. The mean duration of follow-up was 10 months (range, 7-12 months). The mean VA was 1.07±0.51 logarithm of the minimum angle of resolution (logMAR) before treatment, which increased to 0.91±0.64 logMAR at the 3rd month (p=0.04) and 0.89±0.66 logMAR at the last visit (p=0.034 vs. baseline). VA was the same in 23 eyes (42.6%) and increased by at least 1 line (5 letters) in 25 (46.3%) eyes at the last visit. After switching to bevacizumab, VA was maintained in 39 (72.2%) eyes and increased by at least one line in 8 (14.8%) eyes with respect to values after ranibizumab loading. The mean CFT in OCT was 324.8±93.1 µm before treatment, 256.3±35.4 µm at the 3rd month (p=0.039 vs. baseline), and 242.35±34.13 µm at the last visit (p=0.031 vs. baseline). The mean number of bevacizumab PRN injections was 0.42/eye/month.

Conclusion: The increase in VA obtained by the ranibizumab loading dose could be maintained with bevacizumab PRN treatment in patients with neovascular AMD.

Key Words: Bevacizumab, ranibizumab, visual acuity, macular degeneration.

ÖZ

Amaç: Bu çalışmada eksudatif tip yaşa bağlı makula dejenerasyonu tanısı bulunan ve 3 doz yükleme ranibizumab tedavisi sonrası gerektiğinde bevacizumab tedavisine geçilen hastalarda tedavi sonuçlarını belirlemek amaçlanmıştır.

Gereç ve Yöntem: İlk 3 doz ranibizumab yükleme tedavisi sonrası gerektiğinde bevacizumab tedavisine geçilen hastaların dosyaları retrospektif olarak incelenmiştir. Görme keskinliği ETDRS eşeli ile ve santral foveal kalınlık Optik koherens tomografi (OKT) ile değerlendirilen hastaların kayıtları tedavi öncesi ve takiplerde aylık belirlenmiş ve kaydedilmiştir. İlk 3 ay 3 doz ranibizumab yükleme tedavisi sonrası takiplerde hastalar aylık değerlendirilmiş ve gerektiğinde bevacizumab uygulanmıştır.

Bulgular: Elliüç hastanın 54 gözü çalışmaya dahil edilmiş olup ortalama takip süresi 10 (min:7 max:12) aydır. Başlangıç görme keskinliği 1.07±0.51 logMAR iken, 3.ayda 0.91±0.64 logMAR'a (p=0.04) ve son takipte 0.89±0.66 logMAR' a (p=0.034) arttı. Son takipte başlangıca göre görme keskinliği 23 (%42.6) gözde aynı kalırken 25 (%46.3) gözde artış gösterdi (en az bir sıra, 5 harf). Bevacizumab tedavisine geçildikten sonra ise görme keskinliği yükleme doz uygulandıktan sonraya göre 39 (%72.2) gözde sabit kalırken 8 (%14.8) gözde en az bir sıra arttı. Tedavi öncesinde ortalama Optik Koherens Tomografi (OKT) ile değerlendirilen Santral Foveal Kalınlık (SFK) 324.8±93.1 µm iken, 3. ayda 256.3±35.4 µm olarak (p=0.039 başlangıca göre), son kontrolde 242.35±34.13 µm (p=0.031 başlangıca göre) olarak belirlendi. Gerektiğinde tedavi döneminde ortalama bevacizumab uygulama sayısı 0.42/göz/ay olarak saptanmıştır.

Sonuç: Sonuç olarak ilk üç doz yükleme ranibizumab tedavisi ile elde edilen görme keskinliğindeki artış sonrasındaki takiplerde gerektiğinde bevacizumab uygulaması ile hastaların çoğunda korunabilmiştir.

Anahtar Kelimeler: Bevacizumab, ranibizumab, görme keskinliğ, maküla dejenerasyonu.

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in persons over the age of 50 years in developed countries.[1,2] Treatment options for neovascular AMD are limited, but anti-vascular endothelial growth factor (anti-VEGF) therapies are the latest approach for treating this disease.

The most commonly used VEGF antagonists are ranibizumab (Lucentis®) and bevacizumab (Altuzan®), which are both monoclonal antibodies against VEGF that bind the protein at the same site and neutralize all known biologically active forms.[3]

Ranibizumab, which inhibits all biologically active forms of VEGF, was shown to be safe and highly effective for the treatment of neovascular AMD in two Phase III randomized and controlled clinical trials (MARINA and ANCHOR). The drug was subsequently approved for the treatment of neovascular AMD by the USA Food and Drug Administration (FDA) in 2006 based on the results of those trials.[4,5]

In contrast to ranibizumab, bevacizumab was not originally developed for the treatment of AMD and is currently not approved for this indication. Although bevacizumab received FDA approval in 2004 for the treatment of metastatic colorectal cancer,[3] it has been used as an off-label treatment for neovascular AMD since 2005.[6] Importantly, bevacizumab is much more cost effective than ranibizumab because of lower acquisition costs.[7]

For a period of time in Turkey, the social security system only reimbursed the first three loading doses of ranibizumab for the treatment of neovasular AMD, but not the continued maintenance doses.

Therefore, in order to be cost-effective in practice, patients in our clinic received three loading injections of ranibizumab followed by bevacizumab maintenance therapy pro re nata (PRN). In this study, we evaluated the efficacy of bevacizumab administration PRN after initial loading with ranibizumab in patients with neovascular AMD.

MATERIAL AND METHODS

Study Design and Patients: The medical records of patients who received three ranibizumab injections followed by bevacizumab PRN injections for the treatment of neovascular AMD between May 2008 and January 2010 in our clinic at the Gazi University School of Medicine, Department of Ophthalmology, were reviewed retrospectively.

Inclusion criteria included treatment naïve eyes with a best corrected visual acuity (VA) 20/800 or more, and that had been followed for at least 7 months.

The study was approved by the Institutional Ethics Committee and conducted in accordance with the latest version of the Helsinki Declaration. All patients provided written informed consent for their medical data to be used in the study.

Study Procedures: For the ophthalmological examination, we assessed the VA by determining the best-corrected visual acuity (BCVA) with an ETDRS chart, and the logMAR scale was used for comparisons. In addition, indirect ophthalmoscopy, central foveal thickness (CFT) measurements by optical coherence tomography (OCT; OCT status, Carl ZEISS MEDITEC, Dublin, CA), colored fundus photography, and fluorescein angiography (FA) (before treatment and when needed in subsequent indeterminate cases) were also performed. The examinations were conducted before treatment and monthly thereafter.

Lesion activity was assessed by changes in VA, CFT in OCT, presence and amount of hemorrhage associated with the lesion, change in lesion size, and FA staining pattern. The eye with active lesion was described as the eye with visual acuity loss (at least 5 letters) with OCT evidence of intraretinal/subretinal fluid in the macula or, an increase in the CFT in OCT or a new macular hemorrhage associated with the lesion, or an increase in the lesion size, or evidence of late leakage of the lesion in FA. All retreatments were performed using bevacizumab.

Study Treatment: Ranibizumab (0.5 mg/0.05 mL) or bevacizumab (1.25 mg/0.05 mL) was administered as an intravitreal injection in a standard aseptic fashion. Topical anesthetic was applied followed by a 5% povidone-iodine scrub to the conjunctiva, lids, and lashes. After placement of an eyelid speculum, a sterile 1 mL tuberculin syringe with a 30-gauge needle was used for the injections. Ranibizumab was injected once per month for a total of 3 doses (0, 1st, and 2nd month), which represented the loading phase. Bevacizumab injections were administered PRN when the lesion was determined to be active during the maintenance period.

Statistical Analyses: The study data were summarized with descriptive statistics (mean±standard deviation, number, and percentage). The mean VA and CFT in OCT before treatment, at the 3rd month (one month after completion of the loading phase), and at the last visit (after maintenance with bevacizumab PRN) were compared by an analysis of variance (ANOVA) followed by a post-hoc test. The number of injections during bevacizumab PRN treatment were determined for each case. A commercially available software package (Statistical Package for Social Sciences, SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. A p value of less than 0.05 was considered to indicate a statistically significant difference.

Table 1: *Basic demografhic and clinic characteristics of patient at baseline.*		
Gender (Male/Female, n)		29/24
Mean age (mean±SD, years)		74.1±8.1
Concomitant diseases (n)	Hypertension	16
	Diabetes mellitus	9
	Cardiovaskuler diseases	8
Gundus fluorescein angiography findings (n)	Occult lesions	19
	Predominantly classic lesions	23
	Minimal classic lesions	23
Optical coherence tomography findings	Fibrovaskuler pigment epithelial detachment	15
	Scrous pigment epithclial detachment	2

Table 2: *Visual acuity and central foveal thickness of patients (53 patients, 54 eyes) before the treatment, at months after the treament (after completion of loading with ranibizumab), and at the last visit (after maintenance with PRN bevacizumab).*

	Pretreatment	**3rd month**	**At the last visit**	**p value[a]**
Visual acuity (logMAR)	1.07±0.51	0.91±0.64	0.89±0.66	p=0.023
Central foveal thickness (µm)	324.8±93.1	256.3±35.4	242.3±4.1	p=0.032

logMAR: logarithm of the minimal angle of resolution.
Data are presented as mean±standart deviation.
[a]p values optained with ANOVA. For visual acuity, p=0.04 for pretreatment vs. 3rd month data and p=0.034 for pretreatment vs. last visit data. For central foveal thicness, p=0.039 for pretreatment vs. 3rd month data and p=0.031 for pretreatment vs. last visit data, and p=0.11 for 3rd month vs. last visit.

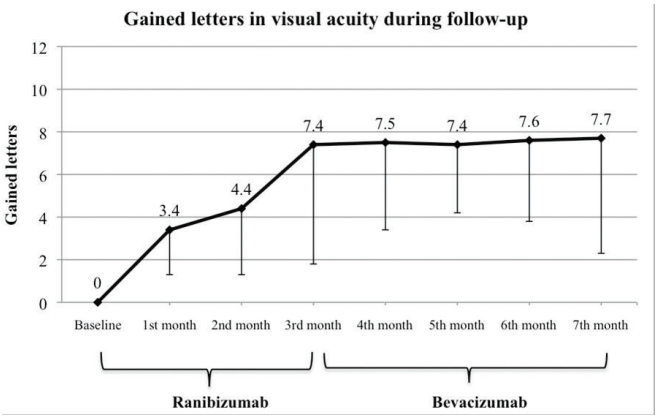
RESULTS

Fifty-four eyes from 53 patients were analysed in the study. Basic demographic and clinical characteristics of patients at baseline are summarized (Table 1). The mean VA before the treatment was 1.07±0.51 logMAR, which increased to 0.91±0.64 logMAR (p=0.04 vs. baseline) at the 3rd month and to 0.89±0.66 logMAR (p=0.034 vs. baseline) at the last visit. Similarly, the mean CFT decreased steadily during follow-up from 324.80±93.12 µm at baseline to 256.34±35.40 µm at the 3rd month (p=0.039 vs. baseline) and 242.35±34.13 µm at the last visit (p=0.031 vs. baseline), (Table 2).

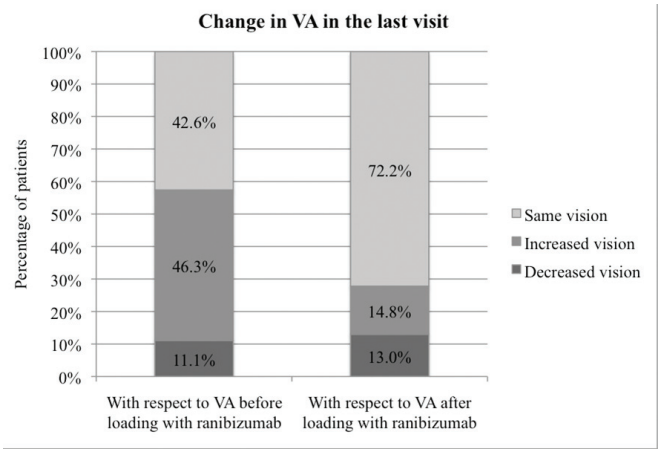
After three months of loading with ranibizumab, bevacizumab was administered for a mean duration of 7 months (range, 4-9 months). The social security system of Turkey only paid for the first three loading doses of ranibizumab for a period of time, but at the end of this period, the system began paying for ranibizumab as a maintainence therapy. Therefore, we were unable to extend the follow-up time for ranibizumab maintenance therapy. The mean number of bevacizumab injections was 0.42/eye/month at the end of follow-up.

The mean number of gained letters in VA was 7.4±5.6 letters at the end of the 3rd month and 7.7±5.4 letters at the last visit (Graphic 1).

Compared to the VA at baseline, the VA was the same in 23 (42.6%) eyes, increased by at least one line (5 letters) in 25 (46.3%) eyes, and decreased by at least one line in 6 (11.1%) eyes at the last visit. After switching to bevacizumab therapy, the VA was maintained in 39 (72.2%) eyes, decreased by at least one line in 7 (13.0%) eyes, and increased by at least one line in 8 (14.8%) of the eyes at the last visit (Graphic 2).



Graphic 1: *Mean number of gained letters in visual acuity (VA) during 7 months of follow-up, of which the first 3 months were the loading phase with ranibizumab followed by 4 months of a bevacizumab maintenance phase. Increased vision is defined as a minimum of 5 letters of increase in VA. Minus error bars show the standard deviation.*



Graphic 2: *Change in visual acuity (VA) in the last visit (as a percentage of patients) with respect to VA before or after loading with ranibizumab. Increased vision denotes an increase in VA by at least one line (5 letters), and decreased vision denotes a decrease in VA by at least one line.*

DISCUSSION

In this retrospective study, we evaluated the efficacy of a loading phase of three monthly injections of ranibizumab followed by a PRN bevacizumab protocol for the treatment of neovascular AMD. The results showed that the initial increase in VA following the loading phase with ranibizumab could at least be maintained with bevacizumab PRN treatment.

Ranibizumab was the first therapy shown by several clinical trials to improve vision in patients with wet AMD.[3,4,8] Bevacizumab has been commonly used as an off-label drug for the management of AMD because of its lower cost and equivalent effectiveness.[9,11] Previous comparative studies have shown similar efficacy of bevacizumab and ranibizumab in the treatment of AMD.[12,17] In a prospective, double-blind, single-center, controlled trial in 20 patients with AMD, bevacizumab and ranibizumab showed similar improvement in VA. In that study, the mean vision increased from 31.6 to 46.4 letters in the bevacizumab group and from 30.4 to 37.4 letters in the ranibizumab group at the 6th month compared to baseline, respectively ($p>0.05$ for comparison between groups).[13]

In addition, at the 1-year follow-up, there were no differences between the study groups; however, the ranibizumab group received a significantly lower mean number of injections than the bevacizumab group (4 vs. 8 injections, respectively; $p=0.001$).[14]

In another comparative study from India in 104 eyes with choroidal neovascular membrane secondary to AMD, both ranibizumab and bevacizumab significantly increased VA without any difference between the treatment groups with respect to changes in VA and CMT at the 18th month follow-up.[16]

Moreover, a recent systemic review based on randomized and controlled trials of the two drugs concluded that both agents improved VA.[15] The most recently published head-to-head, randomized clinical trial by the CATT Research Group, ranibizumab and bevacizumab were compared in 1208 patients with neovascular AMD and a 1-year follow-up. In that study, monthly injection of bevacizumab was found to be equivalent to monthly injection of ranibizumab, with 8.0 and 8.5 letters gained in VA, respectively. Bevacizumab administered PRN was also found to be equivalent to ranibizumab PRN, with 5.9 and 6.8 letters gained in VA, respectively. Thus, this large comparative study showed that bevacizumab and ranibizumab had equivalent effects on VA at 1 year follow-up when administered according to the same schedule.[12]

Although there are numerous head-to-head randomized studies comparing the effects of ranibizumab and bevacizumab in AMD, data on the sequential use of ranibizumab and bevacizumab are limited. Stepien et al.,[18] retrospectively evaluated 84 eyes with neovascular AMD switched from bevacizumab (mean duration, 7.1 months) to ranibizumab (mean duration, 7.3 months) therapy and found no apparent differences in VA or injection rates after switching therapy.

In the present study, we started treatment with a loading phase of 3 monthly injections of ranibizumab followed by a maintenance phase of bevacizumab PRN for an average of 7 months thereafter. This treatment schedule was based on the fact that the social security system in Turkey only covered the cost for the first three monthly injections of ranibizumab at the time the patients were treated.

Since most of the patients could not afford the cost of ranibizumab for maintenance therapy, we practically switched to bevacizumab PRN, which has a lower cost for maintenance. Our results showed that VA increased and CFT decreased significantly with 3 doses of ranibizumab loading therapy, while bevacizumab PRN treatment maintained the respective VA increase and CFT decrease. Thus, loading with ranibizumab and maintenance with bevacizumab PRN may be an alternative to ranibizumab monotherapy while providing the same efficacy and a lower cost.

This study has some limitations, including its retrospective nature and lack of a systemic safety assessment of the drugs. Although numerous studies reported clinical non-inferiority between bevacizumab and ranibizumab,[12-17] emerging data have suggested that bevacizumab may have an unfavourable ocular and systemic safety profile compared to ranibizumab.[9,15,19] Therefore, this incremental risk for both ocular and systemic adverse events may have an impact on the cost-effectiveness of bevacizumab.

In conclusion, bevacizumab PRN, which has a much lower cost than ranibizumab, can be administered to maintain the increased VA obtained by ranibizumab loading in patients with neovascular AMD. Therefore, ranibizumab followed by a bevacizumab regimen may be a good alternative that provides a lower cost than ranibizumab monotherapy. To the best of our knowledge, this is one of the first studies to report on a ranibizumab loading regimen followed by a bevacizumab maintenance regimen in neovascular AMD. Based on these findings, further prospective studies with a larger sample size evaluating the efficacy, safety, and cost-effectiveness of the sequential use of ranibizumab and bevacizumab in the treatment of neovascular AMD are warranted.

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