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ARAŞTIRMA MAKALESİ

THE RESULTS OF INTRAVITREAL RANIBIZUMAB TREATMENT FOR CHOROIDAL NEOVASCULARIZATION SECONDARY TO AGE RELATED MACULAR DEGENERATION

YAŞA BAĞLI MAKULA DEJENERASYONUNA SEKONDER KOROİDAL NEOVASKÜLARİZASYONDA İNTRAVİTREAL RANİBİZUMAB TEDAVİSİ SONUÇLARIMIZ

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ABSTRACT

To evaluate the efficacy of intravitreal ranibizumab (IVR) in the treatment of choroidal neovascularization secondary to age related macular degeneration.
In this retrospective study 74 eyes of 67 patients with choroidal neovascularization (CNV) secondary to AMD who had no treatment earlier and treated with repeated Ranibizumab injections, were evaluated. Patients had monthly injections during first three months and repeated injections were given as needed later on. Visits were performed at the first day and four weeks after each injection and monthly after the completion of three injections. Best corrected visual acuity (BCVA) and central foveolar thickness (CFT) were noted in each visit. Flourescein angiography was performed quarterly. Lesions were classified as classic, occult or fibrovascular pigment epithelial detachment (PED).
Mean age was 72.7± 9.3 (48-92) years. Mean follow-up was 10.6± 5,0 (4.0-24.0) months. Lesions were classified as classic CNV in 22(29.7%), occult CNV in 42(56.8%) and fibrovascular PED in 10 (13.5%) eyes. Average injection number was 3.12.
Mean BCVA increased significantly from 1.08±0.47 logMAR to 0.97±0.49 logMAR(p:0.023). Mean CFT decreased from 335.0 µm to 255.1 µm at third month ($p<0.01$) and 275.2 µm at last visit ($p<0.01$). Maximum change in mean CFT was observed in the first three months.
IVR is a safe and effective method in the treatment of neovascular AMD.

Key words: Intravitreal, ranibizumab, AMD, choroidal neovascularization.

ÖZET
Yaşa bağlı makula dejenerasyonuna (YBMD) sekonder koroidal neovaskülarizasyonda (KNV) intravitreal ranibizumab (IVR) tedavisinin sonuçlarını değerlendirmek.
Bu retrospektif çalışmada daha önce hiç tedavi edilmemiş, YBMD'ye sekonder KNV'u olan ve tekrarlayan IVR enjeksiyonları ile tedavi edimiş olan 67 hastanın 74 gözü değerlendirildi. Hastalara ilk 3 ayda aylık ve daha sonra gerekirse enjeksiyon yapıldı. Her enjeksiyondan sonra 1.gün ve 1.ay, üç enjeksiyon

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tamamlandıktan sonra aylık olarak muayene edildi. Her muayenede düzeltilmiş en iyi görme keskinliği (BCVA) ve santral foveolar kalınlık (CFT) kaydedildi. Üç ayda bir fundus floresein anjiografi (FFA) uygulandı. Lezyonlar klasik, okkült ve fibrovasküler pigment epitel dekolmanı (PED) olarak sınıflandırıldı.
Hastaların yaş ortalaması 72.7± 9.3 (48-92) yıl idi. Ortalama izlem süresi 10.6± 5,0 (4.0-24.0) ay idi. Klasik KNV'li 22 (%29.7), okkult KNV'li 42 (%56.8) ve fibrovasküler PED'i olan 10 (%13.5) hasta vardı. Ortalama enjeksiyon sayısı 3.12 idi.
Ortalama BCVA 1.08±0.47 logMAR'dan 0.97±0.49 logMAR'a arttı (p:0.023). Ortalama CFT, üçüncü ayda 335.0 µm'den 255.1 µm'e azaldı (p<0.01) ve son visitte 275.2 µm idi (p<0.01). Ortalama CFT'deki en büyük değişim ilk üç ayda izlendi.
IVR, YBMD'nin tedavisinde etkili ve güvenli bir yöntemdir.

Anahtar kelimeler: İntravitreal, ranibizumab, YBMD, koroidal neovaskülarizasyon

INTRODUCTION

Age-related macula degeneration (AMD) is the most common cause of blindness in developed countries. The prognosis for neovascular AMD has improved dramatically since the introduction of anti–vascular endothelial growth factor (VEGF) treatment (1,2).
AMD is divided in two forms: Non-neovascular (dry or atrophic) form implies drusen, geographic atrophy and retinal pigment epithelium (RPE) anomalies and causes gradual loss of central vision in the long run. Neovascular (wet, exudative) form is responsible for severe visual loss in majority of the patients. Choroidal neovascularization (CNV), detachment of RPE and fibrovascular scar development are distinctive features of this form. Although neovascular form comprises only 10 % of AMD patients, it is responsible for 80 % of legal blindness (3-5). It is estimated that the prevalance of the disease will be double in coming 15 years (6,7). Lesions are defined as extrafoveal, juxtafoveal or subfoveal according to their localization and they are classified as classic, predominantly classic, minimally classic or occult according to their fluorescein angiography (FA) findings (8,9).
Recently, on the base of knowledge about the role of the factors accelerating neovascu larization in the pathogenesis of AMD, the opinion of blocking angiogenesis has been suggested (10). For this purpose, different pharmacological agents blocking angiogenesis, like as steroids, steroid derivatives and VEGF inhibitors, have been used in clinical studies. Pegaptanib, bevacizumab and ranibizumab which are all anti-VEGF drugs are used intra vitreally in AMD patients with CNV. Ranibizumab (Lucentis®, Genentech Inc, San Francisco, CA, USA) is a fragment of humanised murine monoclonal antibody. Because of its large molecule size making it difficult to pass into the subretinal space and retina, antigen binding piece of the anti VEGF monoclonal antibody has been seperated and Fab fragment of 48 Kd size has been acquired. It neutralizes all isoforms and by-products of VEGF-A. Since it has no Fc part to bind complement receptors, it causes no immune reaction. Ranibizumab has a half life of 2-4 days, so that it is safe in terms of systemic side effects. It has been approved by FDA for the treatment of exudative AMD in 2006 (11,12). It has also been used in Turkey since 2008. The objective of this study was to investigate the efficiacy and safety of intravitreal ranibizumab (IVR) treatment for the CNV secondary to AMD.

MATERIALS AND METHODS

In this retrospective study, data of 100 AMD patients who had IVR injection between January 2011 and August 2012 were reviewed. 74 eyes of 67 patients having CNV secondary to AMD, who had no treatment earlier and who were treated with repeated Ranibizumab injections, were included into the study. 35% of patients had hypertension, 20% diabetes and 5% had both. Majority of the patients had three monthly injections during first three months. Repeated injections were given as needed during follow-up. Patients who could not attend to regular follow-up visits and patients who received less than two injections in the first three months were excluded.
During baseline visit, all the patients had through ophthalmic examination including refraction, biomicroscopy, Goldmann app lanation tonometry and fundus biomicroscopy with a 90 D lens. Best corrected visual acuities (BCVA) were measured with a Snellen chart at 6 meters. BCVA values were converted into logarithm of minimum angle of resolution (LogMAR) for statistical analysis. Colour fundus photography, FA (Canon CX-1 Digital Retinal Camera, Canon Inc, Tokyo, Japan) and spectral domain optical coherence tomography (SD OCT) imaging (Cirrus HD 4000, Carl Zeiss Meditec Inc, Dublin, CA, USA) were performed. Central foveolar thickness (CFT) was noted. Lesion types were classified as classic, occult or fibrovascular pigment epithelial detachment (PED).
Follow-up visits were performed at the first day and four weeks after each injection and monthly after the completion of three injections. BCVA measurement, anterior seg ment biomicroscopy, tonometry and fundus biomicroscopy with 90D examinations were repeated in each visit. Patients were checked for any sign of inflammation, lens damage or retinal detachment. Whilst OCT imaging was acquired in every follow-up visit, FA was repeated three monthly. All the patients were examined by at least two retina specialist during follow-up visits. Additional injection criteria were as follows: 1. If CFT is the same or

increased as compared to the baseline OCT. 2. If there is any sign of leakage, enlargement or recurrence of CNV at FA. 3. Lesions developing subretinal fluid or cystic maculopathy subsequently which were initially dryat OCT, 4. Presence of any new hemorrhage or exudation, 5. One or more line decrease in BCVA.

Before IVR, all the patients were informed about the benefits and side effects of the treatment and written permission were taken. IVRs were injected in operating room. After local anesthesia with proparacain HCl and local desinfection with 10% Betadine, eye lashes were draped and a lid speculum placed. 5 % betadine was instilled. 0.05ml (0,5mg) Ranibizumab was injected slowly into the vitreous cavity through the lower temporal pars plana 3.5mm posteriorly from the limbus with a 30G needle. Injection site was supported with a cotton tip applicator during removal of the needle. After the injection, patients were instructed to use local antibiotics four times a day for one week. Patients were informed about symptoms of endophthalmitis.

NCSS 2007&PASS 2008 Statistical Software (Utah, USA) was used for analysis of the data. Kruskal-Wallis test was used to compare parameters (without normal distrubution) between groups. Mann Whitney U test was used to define the group triggering the difference. Student t test was used for comparison of the two groups in terms of parameters with normal distrubution. Paired samples t test was used for comparison of parameters with normal distrubution within the group. Wilcoxon signed rank test was used for for comparison of parameters without normal distrubution within the group. Spearman's rho correlation test was used to assess interactions between parameters. Results were given in 95 % confidence interval, and statistical significance was defined as $p<0.05$.

RESULTS

Mean age of 34 female (50.7%) and 33 male (49.3%) patients was 72.7± 9.3 (48-92) years. Mean follow-up was 10.6± 5,0 (4.0-24.0) months. Involved eye was right in 48.6% of the cases and left in 51.4%. Lesions classified as classic CNV in 22 eyes (29.7%), occult CNV in 42 eyes (56.8%) and fibrovascular PED in 10 (13.5%). During study period two injections were done in 10 eyes (13.5%), 3 injections in 43 eyes (66.2%), 4 in 12 eyes (16.2%) and 5 in 3 eyes (4.2%). Totaly 230 injections have been performed and average injection number per eye was 3.12.

A statistically significant decrease was observed in mean LogMAR value after the treatment ($p<0.05$). Mean LogMAR visual acuity was 1.08±0.47 at baseline. It decreased to 0.91±0.41 at the end of the third month. This decrease was statistically significant ($p=0.012$). Mean logMAR at the last visit was 0.97±0.49. This was again significantly lower than baseline acuity ($p= 0.023$).

At the end of 3 months; BCVA increased compared to baseline visual acuity in 41 eyes (55.4%), decreased in 17 eyes (23.0%) and did not change in 16 eyes (21.6%). At the end of average 10.6 months of follow-up period; BCVA increased in 41 eyes (55.4%), decreased in 19 eyes (25.7%) and did not change in 14 (19.0%). As a result, BCVA improved or did not change in 55 eyes (74.3%), decreased in 19 eyes (25.7%).

Difference in mean logMAR before and after Ranibizumab treatment according to the lesion type was as follows: Classic CNV: No statistically significant difference was found ($p=0.363$). Occult CNV: Mean logMAR value was statistically significantly better than baseline ($p=0.009$). Fibrovascular PED: No statistically significant change was found ($p=0.109$) (Figure1).

Mean CFT at baseline was 335.0 µm. This value decreased to 255.1 µm at third month and 275.2 µm at last visit. Maximum change in mean CFT was observed in first three months. This value has increased again at the last visit. Decrease in mean CFT after the treatment as compared to baseline was statistically significant ($p<0.01$). See Figure 2. When patients with visual loss after the treatment were surveyed; it was observed that the fibrotic component was prominent and eventually a fibrotic scar developed in these patients.

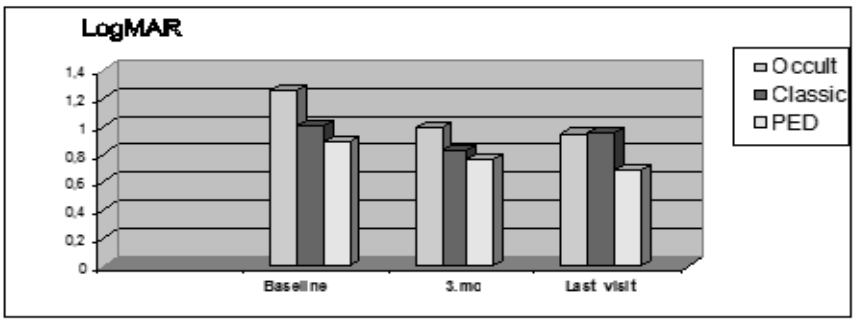

Figure 1: Difference in mean LogMAR before and after Ranibizumab treatment according to the type of CNV**.**PED: Fibrovascular pigment epithelial detachment.

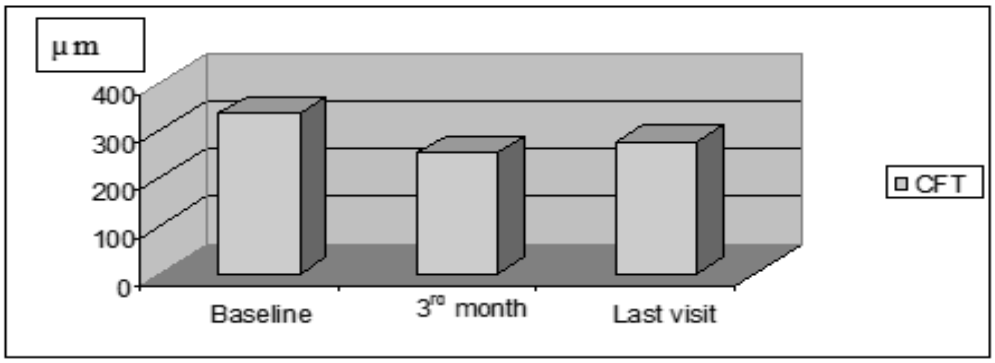

Figure 2: Mean central foveal thickness (CFT) before and after IVR treatment.

DISCUSSION

Although several treatment modalities have been evolved, there is no standard regime for the treatment of wet AMD has been established at the moment. Treatment alternatives such as photodynamic therapy (PDT) approved by FDA, intravitreal pegaptanib, ranibizumab and bevacizumab provide only visual stabilization. PDT is used to destroy CNV directly, while anti-VEGF agents are used to break angiogenic cycle. With an aim of reducing the frequency of injections, a double masked, controlled, multicenter study entitled PIER has been conducted. In this trial, all the cases received monthly injections during first three months, then injection frequency was reduced to three monthly. An improvement in VA was observed after first three 0.5mg IVR injections, however, BCVA returned to the baseline value at the end of 12 months (13). Hallmark showed a marked effect of monthly injections with ranibizumab compare to placebo in his randomized clinical trials, and when the trials were extended to 24 months, he demonstrated that there was a sustained treatment effect(1).

In our study, one line improvement was achieved in mean BCVA after 10.6 months of follow-up. BCVA was stabilized or improved in 74.3% of the eyes with IVR treatment. This rate was slightly lower than reported in MARINA study (95.0% success at 12 months). In that study, mean 7.2 letter gain was achieved with monthly IVR regimen at 12 months(14). Wykrotaet al(15) reported 12.4 letter improvement in BCVA with three 0.5 mg IVR injections given monthly followed by pro re nata (PRN) regimen. They have also found a vison loss of less than 15 ETDRS letters in 93.2% of patients. In single center phase III study of PRONTO, three monthly 0.5 mg IVR injections followed by PRN regimen guided by OCT was implemented. With this treatment, mean BCVA improvement of 11.1 letters and CFT decrease of 212 microns was achieved at the end of two years. 15 letters or more vision gain was obtained in 43% of patients, and mean injection number was found as 9.9. Visual results attained in PRONTO study which are comparable to MARINA and ANCHOR studies show that customized treatment protocol guided by OCT is a reasonable choice in treatment of AMD (16,17).

In subgroup analysis of our patients, less than 3 line of visual loss was found 90% in classic CNV, 93.9% in occult CNV and 84.7% in fibrovascular PED. A statistically significant improvement in mean BCVA was found in occult CNV patients, whereas not in fibrovascular PED or classic CNV. Mean 60.0 micron decrease was achieved in CFT at the end of 10.6 months follow-up with mean 3.12 IVR injections.

In the first year of MARINA and ANCHOR studies, myocard infarction and cerebrovascular event (stroke) rates were found slightly higher than control group with 0.5mg IVR treatment. Therefore, it has been emphasized that the risk of cerebrovascular event may increase with 0.5mg IVR treatment especially in patients who had experienced cerebrovascular event earlier (16,17). In our study, a subconjunctival hemorrhage developed in 15% of eyes and no other complications have been observed. No systemic complication occurred leading to quit injections. No endophthalmitis was observed in our patients. It may be a result of the sterile injection technique employed in our main operation theatre.

Results of MARINA and ANCHOR studies showed that monthly injections of IVR provided patients with visual improvement in the beginning and this level was preserved during follow-up. In this biphasic course, visual improvement usually takes place in the first three months. Whereas in PIER study a different course of visual acuity was observed, initial visual improvement during first three months slowly returned to the baseline. This result implies that three monthly injections are not as effective as monthly injections. However, a group of patients showed a visual course similar to that of MARINA and ANCHOR studies. This difference

in visual response has been thought to be a result of that the severity of AMD was different in each individual(13,14,18).

There are some limitations of the current study: Visual acuity measurements were performed by using the Snellen chart and converted to logMAR values later on. If the measurements had been measured by using ETDRS chart and verified in number of letters, it would be possible to compare our results with the literature. Moreover, there is a lack of standardization in follow-up. Despite our mean follow-up was 10.6 months, the range has been varied from 4 to 24 months.

Although controlled clinical trials have shown the effective dosage of IVR, the exact treatment regimen has not been established yet. Many authors believe that the treatment should be tailored according to the patient's individual features and response to the treatment. Our results showed that IVR is a safe and effective method in the treatment of wet type AMD. It provides patients with visual stabilization and some improvement in at least half of the patients without any significant side effects. More studies are necessary to assess the long term efficiacy and complications of intravitreal ranibizumab treatment.

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