Intravitreal Ranibizumab Injection in Chronic Central Serous Chorioretinopathy: The Correlation of Outer Segment Integrity and Visual Acuity

Kronik Santral Seröz Koryoretinopatide Ranibizumab Enjeksiyonu: Dış Segment Bütünlüğü ve Görme Keskinliği İlişkisi

Sibel DEMİREL[1], Esra SAVKU[2], Figen BATIOĞLU[3], Emin ÖZMERT[3]

ABSTRACT

Purpose: To evaluate the therapeutic efficacy of intravitreal ranibizumab injection in patients with chronic central serous chorioretinopathy (CSC) and the effect of outer segment integrity on visual acuity after treatment.

Material and Methods: The records of patients with chronic CSC who were treated with intravitreal ranibizumab were reviewed. The baseline and follow-up examinations included best corrected visual acuity (BCVA) and spectral domain optical coherence tomography (OCT). The main outcome measures were the changes in BCVA and central macular thickness (CMT) between the baseline and follow-up examinations.

Results: Twenty-eight eyes of 25 patients were retrospectively analyzed. The mean follow-up period was 11.5 months. The mean pre-injection BCVA was 0.31 logMAR (range 0-1.8) and improved to 0.19, 0.26 and 0.22 logMAR at the 3rd month, 6th month, and at the final visit (p=0.014), respectively. The mean CMT was 315 µm (range 185-607) at baseline and regressed to 218, 208 and 199 µm in the 3rd month, 6th month, and on the final visit, respectively. There was a significant difference between baseline and all follow-up measurements (p<0.001). However, a direct correlation was not detected between anatomic improvement and visual recovery. The defects of ISOS (p=0.001) and ELM (p=0.008) were significantly related to poor visual outcome.

Conclusion: Although, intravitreal ranibizumab injection was used as an alternative treatment method for treating patients with chronic CSC, nearly half of the patients were refractory to treatment and most of the others needed re-injections. It doesn't seem to be an ideal treatment for chronic CSCR.

Key Words: Central serous chorioretinopathy, eksternal limiting membrane, optical coherence tomography, outer photoreceptor layer, ranibizumab.

ÖZ

Amaç: Kronik santral seröz koryoretinopatili (SSR) olgularda intravitreal ranibizumab enjeksiyonunun tedavi etkinliğinin saptanması ve dış segment bütünlüğünün tedavi sonrası görme keskinliğine etkisini araştırmak.

Gereç ve Yöntem: Kronik SSR nedeni ile ranibizumab tedavisi almış hastaların kayıtları retrospektif olarak incelendi. Başlangıç ve takip muayenelerindeki görme keskinliği (GK) ve spektral domain optik koherens tomografi (OCT) bulguları kaydedildi. Çalışmanın birincil amacı başlangıç ve takip muayenelerinde GK ve santral makula kalınlıklarındaki (SMK) değişimi saptamaktı.

Bulgular: Dahil edilme kritelerini karşılayan 25 hastanın 28 gözü çalışmaya alındı. Ortalama takip süresi 11,5 aydı. Ortalama GK enjeksiyon öncesi 0.31 logMAR (0-1,8) ve sırasıyla tedavi sonrası 3., 6. ve ve final vizitte 0.19, 0.26 ve 0.22 logMAR olarak saptandı. Tedavi öncesi ve final görme keskinlikleri arasında istatistiksel olarak anlamlı artış vardı (p=0.014). Ortalama SMK başlangıçta 315 µm (185-607) idi ve tedavi sonrası sırasıyla 3., 6., ve final vizitte 218, 208 and 199 µm'e geriledi. SMK değişimi açısından başlangıç ile tüm visitler arasında istatistiksel olarak anlamlı azalma mevcuttu (p<0,001). Fakat anatomik düzelme ile görme keskinliği arasında direkt bir korelasyon saptanmadı. Fotoreseptör tabakası dış ve iç segmentlerinin birleşim yerinin (p=0.001) ve dış sınırlayıcı membranın (p=0.008) hasarlı olması kötü görme keskinliği ile belirgin şekilde ilişkiliydi.

Tartışma: İntravitreal ranibizumab enjeksiyonu görme keskinliği ve anatomik olarak sağladığı fayda nedeni ile kronik SSR'li olguların tedavisinde alternatif tedavi yöntemi olarak denenmektedir. Fakat, olguların yaklaşık yarısında tedaviye yanıt alınamaması ve diğerlerinde de tekrarlayan enjeksiyonlaragerek duyulmuş olması nedeni ile ideal tedavi seçeneği gibi gözükmemektedir.

Anahtar Kelimeler: Santral seröz koryoretinopati, dış sınırlayıcı membran, optik koherens tomografi, dış nükleer tabaka; ranibizumab.

1- M.D. Asistant Professor, Ankara University Faculty of Medicine, Department of Ophthalmology Ankara/TURKEY
DEMIREL S., drsibeldemireltr@yahoo.com.tr
2- M.D. Islahiye State Hospital, Department of Ophthalmology, Gaziantep/TURKEY
SAVKU E., esavku@yahoo.com
3- M.D. Professor, Ankara University Faculty of Medicine, Department of Ophthalmology Ankara/TURKEY
BATIOGLU F., fbatioglu@gmail.com
OZMERT E., eozmert56@gmail.com

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Yazışma Adresi / Correspondence Adress: M.D., Asistant Professor, Sibel DEMIREL
Ankara University Faculty of Medicine, Department of Ophthalmology Ankara/TURKEY

Phone: +90 312 595 62 60
E-mail: drsibeldemireltr@yahoo.com.tr

INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neurosensory retina which is related to idiopathic leakage at the level of retinal pigment epithelium (RPE).[1] Although the pathophysiology of CSC remains controversial, it is believed that initial choroidal vascular compromise subsequently leads to secondary dysfunction of the overlying RPE.[2,3] Type A personality, systemic hypertension and obstructive sleep apnea are thought to play various roles in the pathogenesis which elevates cortisol and epinephrine levels and affects the autoregulation of the choroidal circulation.[4]

Central serous chorioretinopathy may be divided into two distinct clinical presentations. Although most cases are self limiting with spontaneous resolution, some patients have recurrent or chronic serous retinal detachments which result in progressive RPE atrophy and permanent visual loss. Treatment should be considered if there is angiographic evidence of ongoing foveal leakage in chronic CSC. Treatment options include medical therapy with acetazolamide, carbonic anhydrase inhibitors or non steroid anti-inflammatory drugs, as well as other techniques such as laser photocoagulation and photodynamic therapy (PDT).[5]

Photodynamic therapy has been shown to be effective in chronic CSC. It has been suggested that PDT provides reduction in choroidal hyperpermeability and vascular leakage via choriocapillary trombosis and occlusion in the short term. Therefore, it is believed to achieve fluid resorption and visual recovery. However, recurrence may be seen due to choroidal vascular remodelling in the long term.[6,7] Also, PDT is limited by potential adverse effects such as choroidal ischemia, RPE atrophy and iatrogenic choroidal neovascularization (CNV).[8-11]

Recently, anti-vascular endothelial growth factor (VEGF) therapy has attracted attention because of its use in the treatment of chronic CSC. It is well known that VEGF is a potent inducer of vascular permeability so anti-VEGF agents are assumed to reduce choroidal hyperpermeability in chronic CSC. Intravitreal application of anti-VEGF agents has been reported to have beneficial effects in many retinal diseases.[12-14] Ranibizumab is preferable to bevacizumab since it has a shorter half life and less systemic side effects. However, there are few reports concerning the use of intravitreal ranibizumab injection in the treatment of chronic CSC.[15,16]

The presence of chronic fluid under the retina appears to disrupt the photoreceptor outer segments and although the symptoms and fluid improve, the presence of distruption of outer segment can effect the final visual acuity. In the present study, we aimed to evaluate the therapeutic efficacy of intravitreal ranibizumab injection in treating chronic CSC. We also evaluated the anatomic features of the inner segment/outer segment (IS/OS) junction and external limiting membrane (ELM) both before and after treatment by spectral domain optical coherence tomography (OCT).

MATERİALS AND METHODS

The records of 25 consecutive patients with chronic CSC who were treated with 0.5 mg/0.05 ml intravitreal ranibizumab injection were retrospectively reviewed. Inclusion criteria included the following;

1. Visual impairment history with a duration of at least six months,
2. CSC with subretinal fluid (SRF) involving the fovea documented by OCT,
3. Presence of single or multiple active leakage sites on baseline fluorescein angiography (FA),
4. Absence of prior laser photocoagulation or PDT.

All patients underwent complete ophthalmic examination including Snellen visual acuity, intraocular pressure measurements, dilated fundus examination, and spectral domain OCT (Cirrus high-definition OCT; Carl Zeiss, Dublin, California, USA) before and after injections at monthly intervals. Fluorescein angiography (HRA-2; Heidelberg Engineering, Germany) was performed before the first injection.

The study was conducted in compliance with the Declaration of Helsinki. The patients signed an informed consent before proceeding with all the examinations and treatments. Under sterile conditions, 0.5 mg (0.05 ml) of ranibizumab was injected into the vitreus in the inferior temporal quadrant with a 30 gauge needle. Patients were followed up at first day, first month and at monthly intervals afterwards. The morphologic results of the treatment were evaluated by OCT imaging. The need for retreatment was decided according to the presence of SRF at the 1-month follow-up examination. The records of the patients at the 3rd month, 6th month, and at the final visit were analyzed. The OCT foveal findings were also classified as a continuous or disrupted IS/OS and eksternal limiting membrane layer. The integrity of the outer segment layer was evaluated in central 1000 micron of the fovea. Any damage that was seen more than 50% of the lenght of layers in central 1000 micron was defined as distrupted.

The patients were divided into three groups defined as complete resolution, incomplete resolution and persistance according to their responses to treatment. Complete response was defined as the complete resolution of SRF. Any increment or decrement ≤ 100 µm in SRF was defined as persistance and a decrement >100 µm in SRF was defined as incomplete response.

All measurements were compared to the baseline. The main outcome measures were changes in best corrected visual acuity (BCVA) and central macular thickness between (CMT) the baseline and follow-up examinations. The second outcome measure was to investigate any correlation between intergrity of IS/OS junction, ELM and visual acuity after treatment.

For statistical analysis, Snellen visual acuity measurements were converted to the logarithm of minimum angle of resolution (logMAR). Statistical analysis was performed using SPSS software for Windows version 15.0 (SPSS, Inc., Chicago, IL). Comparisons of categorical variables between the two groups were performed using the chi-square test or the Fisher exact test, and continuous variables were compared using a 2-tailed t test or Mann-Whitney test. A p value of <0.05 was considered as statistically significant.

RESULTS

Twenty-eight eyes of the 25 patients were analyzed. There were 17 (68%) males and 8 (32%) females. The mean age (±SD) of the patients at presentation was 49.7±8.6. The mean duration of chronic CSC was 9.3 months (range 6-22). The mean follow-up period after the first injection was 13.5 months (range 6-24). None of the patients had received prior treatment. The average number of injections was 3.92 (range 3-6). No systemic or ocular side effects occured.

The mean pre-injection BCVA was 0.31 (0-1.8) logMAR and improved to 0.19, 0.26 and 0.22 logMAR in the 3rd month, 6th month, and at the final control, respectively. There was a statistically significant difference between the preinjection BCVA and final BCVA (p=0.014). Subretinal fluid was observed in all eyes at the baseline. Complete response was achieved in 8 (28.6 %), 14 (50%) and 14 (50%) eyes in the 3rd month, 6th month and at the final control, respectively (Figure 1). Incomplete response (Figure 2) or persistence (Figure 3) was seen in the rest of the eyes. The distribution of patients according to treatment responses are shown in table 1.

The mean CMT was 315 µm (range 185-607) at the baseline and regressed to 218, 208 and 199 µm in the 3rd month, 6th month and final control respectively. Concerning the mean CMT, there was a statistically significant difference between baseline and all follow-up measurements (p<0.001). However, a direct correlation was not detected between anatomic improvement and visual recovery (p>0.05).

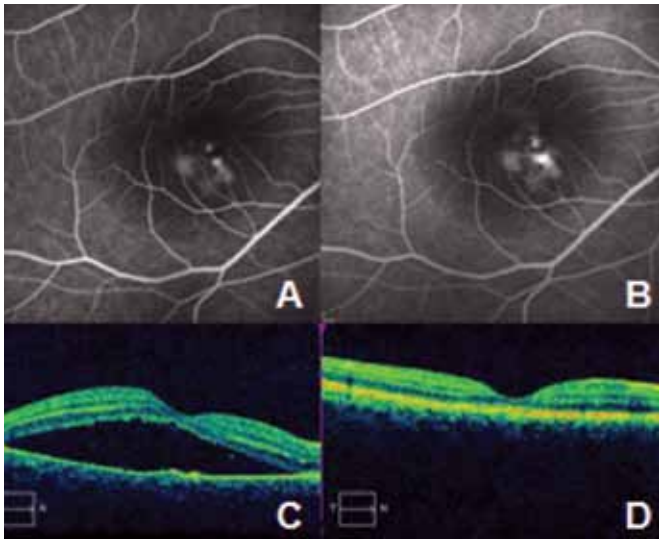

Figure 1a-d: *Baseline early (a) and late (b) phase fluorescein angiography (FA) images show one active leakage site in a 47-year old man. Pre-treatment optical coherence tomography (OCT) image shows subfoveal fluid (c). Post-treatment OCT image reveals complete resolution of subretinal fluid after 4 intravitreal ranibizumab injections (d).*

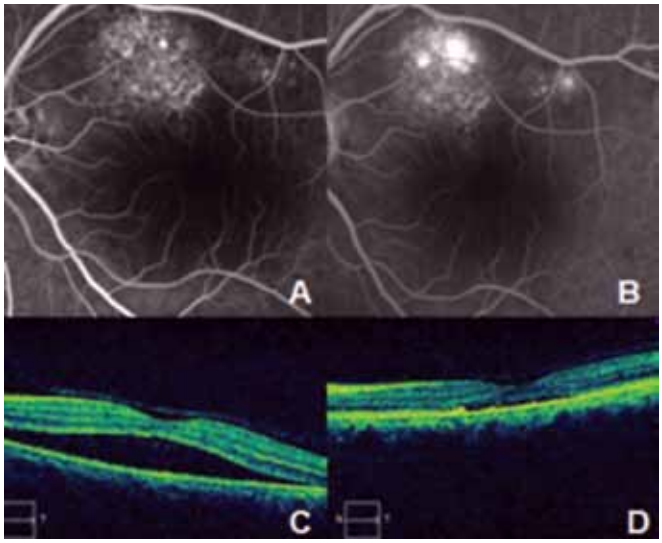

Figure 2a-d: *Baseline early (a) and late (b) phase fluorescein angiography (FA) images show multipl mottled hyperfluorescence areas in a 54-year old man. Pre-treatment optical coherence tomography (OCT) image shows subfoveal fluid (c). Post-treatment OCT image reveals incomplete resolution of subretinal fluid after 3 intravitreal ranibizumab injection (d).*

Table 1: *Distribution of patients according to their responses to treatment.*

Follow-up	Total no of Eyes	Complete response	Incomplete Response	Persistence	Recurrence
3rd month	28	8 (28.6%)	13 (46.4%)	7 (25%)	
6th month	28	14 (50%)	7 (25%)	7 (25%)	0
Final visit	28	14 (50%)	8 (35%)	6 (21.4%)	1 (3.6%)
6. ay	32;85	61±12.2	243.2;307.7	281.8±14.9	165;322

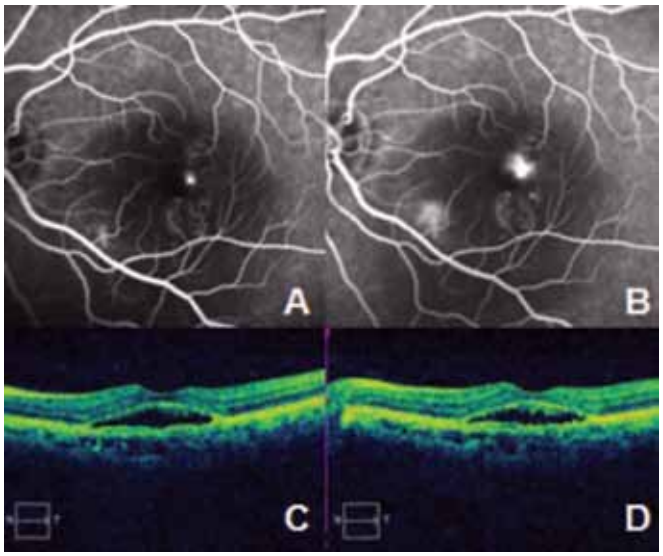

Figure 3a-d: *Images of a 61 year-old woman. Baseline early (a) and late (b) phase fluorescein angiography (FA) images show two active leakage sites. Pre-treatment optical coherence tomography (OCT) image shows subfoveal fluid (c). Post-treatment OCT image reveals persistance of subretinal fluid after 4 intravitreal ranibizumab injections (d).*

Pigment epithelium detachment (PED) was detected in 5 eyes (18.2%) at the baseline and persisted in all the eyes at follow-up examinations.

The continuity of photoreceptor inner and outer segment junction (IS/OS) and external limiting membrane (ELM) were disrupted in 10 (35.7%) and 5 (17.8%) of the eyes respectively. Defects of IS/OS (p=0.001) and ELM (p=0.008) were significantly related to poor visual outcome (Table 2).

DISCUSSION

Chronic CSC is defined basically as persistent SRF for at least 6 months but recent clinical trials have used 3 months with persistent fluid.[10,11] The patients have longstanding SRF that can not be reabsorbed efficiently due to choroidal disease and extensive dysfunction of RPE. The presence of chronic fluid leads to photoreceptor degeneration and may cause permanent visual loss.

Current studies about the pathogenesis of CSC emphasize the importance of the choroid. The choroid is believed to be hyperpermeable possibly as a result of stasis, ischemia or inflammation; the evidence for choroidal hyperpermeability comes from the staining of the inner choroid seen on mid-phase indocyanine green angiography (ICG).[17] The aims of treatment of CSC are to provide resolution of SRF, improve or preserve visual acuity and prevent recurrences. Since the pathogenesis of CSC remains controversial, there is not a definitive universally accepted treatment.

Laser photocoagulation may decrease the amount of SRF in chronic CSC. Typically, laser burns are applied to the focal leakage areas identified on FA. If the area of leakage is subfoveal or juxtafoveal, photocoagulation may induce secondary CNV. Additionally, focal laser may lead to permanent scotoma which enlarges over time with RPE scar expansion.[18] Photodynamic therapy has been shown to be effective in chronic CSC. It has been suggested that PDT provides reduction in choroidal hyperpermeability and vascular leakage via choriocapillary trombosis and occlusion in the short term.[6,7] Unlike laser photocoagulation, PDT can be performed for subfoveal leakage. However, performing PDT often requires ICG angiogram guidance and it is limited by potential adverse effects such as choroidal ischemia, RPE atrophy and iatrogenic CNV.[8-10] On the other hand, the risks of PDT were reported to decrease when half-fluence PDT was used.[10,11]

Recently, anti VEGF therapy has attracted attention for its use in the treatment of chronic CSC. Since VEGF is a potent inducer of vascular permeability, anti VEGF agents are assumed to reduce choroidal hyperpermeability in CSC. Also, choroidal ischemia in CSC may induce an increase in the level of VEGF. Lim et al reported that aqueous levels of VEGF were slightly higher in patients with chronic CSC than healthy people.[19]

Table 2: *Changes in BCVA according to ISOS / ELM defects.*

Mean BCVA (logMAR)	ISOS (+) 18 eyes	ISOS (-) 10 eyes	P value	ELM (+) 23 eyes	ELM (-) 5 eyes	P value
Baseline	0.21	0.70	0.001	0.22	0.70	0.059
3rd month	0.15	0.40	0.004	0.15	0.50	0.008
6th month	0.15	0.40	0.003	0.22	0.50	0.007
Final control	0.05	0.40	0.001	0.12	0.50	0.008

BCVA; Best Corrected Visual Acuity, ELM; External Limiting Membrane, ISOS; Inner and Outer Segments of photoreceptor layer, logMAR; logarithm of the Minimal Angle of Resolution. Kruskal-Wallis test (with Bonferroni correction) was used to evaluate any correlation between ISOS/ELM defects and BCVA. A p value of <0.0125 was considered as statistically significant.

Intravitreal application of anti VEGF agents has been reported to have beneficial effects in many retinal diseases.[12-14] Ranibizumab is a humanized anti-VEGF antibody which neutralizes all forms of biologically active VEGF.[20] Even though bevacizumab and ranibizumab share many properties, several differences exist between them which include molecule size, development in different cell lines, affinity for VEGF and formulation for intraocular use. Considering the molecular weight of each agent (ranibizumab is a 48-kDa Fab fragment, whereas bevacizumab is a complete 149-kDa antibody), ranibizumab may be more successful in the treatment of CSC because of its smaller molecular weight and the possibility of deeper penetration into the choroid.[21]

In this study, we administered intravitreal ranibizumab to all the 28 eyes and 14 out of the 28 eyes (50%) achieved complete resolution of SRF which took place in the reported spectrum. The variability in the success rates of the different studies may be explained by various factors such as different study designs, treatment regimens, sample sizes and follow-up periods of the studies. Several reports indicate that intravitreal bevacizumab injection results in improved vision and reduced SRF in patients with chronic CSC. According to the study of Lim et al, 33 out of 40 eyes (82.5%) with persistent CSC had complete resolution of SRF and visual recovery within 3 months following intravitreal bevacizumab injection.[22] Other studies including those with smaller number of patients having chronic or recurrent CSC reported complete resorption of SRF of between 50% and 100% and visual improvement.[23-26]

There are two reports conducted by Bae et al concerning the administration of intravitreal ranibizumab injection to chronic CSC patients. In these studies, they compared the efficacy of half-fluence PDT to intravitreal ranibizumab (0.5 mg) on eyes with chronic CSC. In the first study, only 2 out of 8 eyes (25%) had complete resorption of SRF in the ranibizumab group after 3 months of treatment versus 6 out of 8 PDT-treated eyes (75%).[15] The second study, which was characterised by larger number of patients and longer follow up, showed that 5 out of 16 eyes (31.3%) in the ranibizumab group achieved complete resolution of SRF while 16 out of 18 eyes (88.9%) became fluid-free in the low-fluence PDT group at the 3rd month follow-up examination.[16] In accordance with the previous studies reported by Bae et al, SRF completely resolved in only 8 out of the 28 eyes (28.6%) in the 3rd month in our study.

In the latter study, Bae et al also reported the long term results of ranibizumab treatment. They followed up patients with complete resolution after 3 consecutive monthly injections of ranibizumab and the proportion of eyes with resolved fluid decreased from 31.3% to 12.5% at the end of a year.[16] Our treatment regimen is based on retreatment as needed and our final success (50%) rate is better when compared to Bae's study. It seems that either ranibizumab has temporary effects on SRF, or the used therapeutic dose is suboptimal for chronic CSC. A longer duration of treatment with higher doses or shorter intervals may be necessary to get better results.

A significant visual recovery was obtained at the end of our follow-up. However, improvement in visual acuity did not correlate with anatomic restoration at any time. We think that this result depends on the defects of IS/OS and ELM because our results showed that any disruption of these layers was significantly related to poor visual outcome. Piccolino et al.,[27] also reported that patients with well preserved outer photoreceptor layer can have better visual acuity after subfoveal fluid resolution. Similarly, Kim et al.,[28] investigated the possibility of a direct correlation between final visual acuity of 20/40 or more and continuity of IS/OS. Although several prognostic factors could be responsible for the post-treatment visual acuity, we reported that the presence of an intact inner segment/outer segment junction (IS/OS junction) on the baseline spectral-domain OCT images is an important predictor of better visual recovery and better visual acuity after treatment.

Currently, the available treatment options for treating chronic CSC are still far from being perfect. Our study is limited by its retrospective nature, small size and lack of a control group. However, nearly half of the patients were refractory to treatment and most of the others needed re-injections. Larger controlled trials are necessary to evaluate the best treatment option for the treatment of CSC including micropulse laser theraphy and PDT.

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