Research Article (Araştırma Makalesi)

Retrospective Evaluation of Attacks, EDSS Scores, and MRI Changes Before the Start of Treatment and One Year After the Start of Treatment in Patients Followed by a Diagnosis of Multiple Sclerosis and Using Ocrelizumab in Our Clinic

Kliniğimizde Multiple Skleroz Tanısı ile Takip Edilen ve Ocrelizumab Kullanan Hastaların Tedavi Başlangıcından Önce ve Bir Yıl Sonraki Atak, EDSS Skoru ve MR Değişikliklerinin Retrospektif Değerlendirilmesi

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Özet

Amaç: Anti-CD20 monoklonal antikorlar tarafından B hücrelerinin tüketilmesinin, relapsing remitting Multiple Skleroz (RRMS) aktivitesini ve primer progresif MS'nin (PPMS) ilerlemesini azalttığı kanıtlanmıştır. Biz araştırmamızda Ocrelizumab kullanımı sonrasında retrospektif olarak klinik tecrübemizi ortaya koymayı, gerçek yaşam verilerine katkı sağlamayı hedefledik.

Gereç ve Yöntemler: McDonald 2017 kriterlerine göre değerlendirilerek MS tanısı almış Ocrelizumab kullanan 18-55 yaş aralığındaki hastalar dahil edildi. Engellilik düzeyinin değerlendirilmesinde dosya kayıtlarımızda mevcut olan nörolojik muayene bulguları ve EDSS bulguları kullanıldı. 24 saatten fazla süren klinik yakınması ile uyumlu MRG lezyonları olan hastaları atak olarak değerlendirildi. Hastaların yaşları, MS tanı süreleri, daha önce kullandıkları immun modülatör tedaviler kaydedildi. Ocrelizumab öncesi T2, FLAIR sekans MR lezyon sayısı, EDSS ve ocrelizumab aldıktan bir yıl sonraki T2, FLAIR sekans MR lezyon sayısı, EDSS kaydedildi. Hastaların bir yıllık takibi sonrasında atak olmaması, MRG'da lezyon sayısında artış olmaması ve EDSS'de ilerleme olmaması NEDA 3 olarak kabul edildi.

Bulgular: Bu çalışmadaki olgularımız 30 MS hastasını içermektedir. Hastaların %26,7'si relapsing remitting MS (RRMS), %26.7 primer progresif MS (PPMS) ve %46.7'si sekonder progresif MS (SPMS) hastasıydı. Olguların %10'u naif hasta idi ve %90'ı daha önce bir veya iki DMT ile tedavi edilmişti. RRMS hasta grubunda %87.5 atak görülmedi. SPMS hasta grubunda ataklı seyreden olgularda ocrelizumab sonrası ataklar gözlenmedi. Çalışmamızda yeni T2 lezyon geliştirmeyen ve lezyonlarda kaybolma görünen hasta oranı RRMS hasta grubunda %62.5, SPMS hasta grubunda %78.5, PPMS hasta grubunda %75 olarak saptanmıştır. Total hasta grubunda EDSS artışı olmayan hasta oranı %93 (28 hasta) olarak saptanmıştır.

Sonuç: Çalışmamızda ocrelizumabın atak oranlarını azaltarak, EDSS puanlarını koruyarak ve lezyon yükünde artışı önleyerek etkili olduğu saptanmıştır. Bulgularımız gerçek yaşam verileri ile uyumluluk göstermektedir.

Anahtar Kelimeler: Multiple skleroz, Ocrelizumab, Gerçek yaşam verileri

Abstract

Objective: Depletion of B cells by anti-CD20 monoclonal antibodies has been proven to reduce relapsing remitting multiple sclerosis (RRMS) activity and progression of primary progressive MS (PPMS). In our study, we aimed to retrospectively present our clinical experience and contribute to real-life data after the use of Ocrelizumab.

Material and Methods: Patients aged 18-55 years using Ocrelizumab and diagnosed with MS by McDonald's 2017 criteria were included. Neurological examination findings and EDSS findings available in our file records were used to evaluate the level of disability. Patients with MRI lesions consistent with their clinical complaint lasting more than 24 hours were evaluated as an attack. Patients' ages, MS diagnosis times, and previous immune modulatory treatments were recorded. The number of T2, FLAIR sequence MRI lesions, EDSS before ocrelizumab, and the number of T2, FLAIR sequence MRI lesions 1 year after receiving ocrelizumab were recorded. After 1 year of follow-up, the absence of attacks, no increase in the number of lesions in MRI, and no progress in EDSS were accepted as NEDA 3.

Results: Our cases in this study include 30 MS patients. Patients were 26.7% relapsing remitting MS (RRMS), 26.7% primary progressive MS (PPMS), and 46.7% secondary progressive MS (SPMS). There was no attack in 87.5% of the RRMS patient group. In the SPMS patient group, no attacks were observed after ocrelizumab in the cases with attacks. In our study, the rate of patients who did not develop new T2 lesions and whose lesions disappeared was 62.5% in the RRMS patient group, 78.5% in the SPMS patient group, and 75% in the PPMS patient group. In the total patient group, the rate of patients without EDSS increase was 93% (28 patients).

Conclusion: In our study, it was determined that ocrelizumab was effective by reducing the attack rates, preserving the EDSS scores and preventing the increase in the lesion burden. Our findings are consistent with real-life data.

Keywords: Multiple sclerosis, Ocrelizumab, Real World data

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INTRODUCTION

Multiple sclerosis (MS) is caused by immune-mediated inflammation, demyelination, and axonal damage of the central nervous system; It is a chronic disease characterized by motor, sensory, cognitive, and cerebellar symptoms or visual function loss according to the affected area. Disease-modifying therapies are a component of the long-term management of patients with MS. The goal of disease modification is to reduce early clinical and subclinical disease activity, which is thought to contribute to long-term disability. Current treatments for MS, for which there is no effective cure, are aimed at slowing disease progression, reducing disability as much as possible, or stopping it. In the last decade, the role of B cells in the pathogenesis of MS has come to the fore. Depletion of B cells by anti-CD20 monoclonal antibodies has been proven to reduce relapsing-remitting MS (RRMS) activity and progression of primary progressive MS (PPMS). In our study, we aimed to retrospectively present our clinical experience and contribute to real-life data after the use of Ocrelizumab (OCR) (1).

MATERIAL AND METHODS

Our study included patients aged 18-55 years who were using Ocrelizumab and were diagnosed with MS after being evaluated according to the McDonald 2017 criteria, followed in the Neurology Department of Kahramanmaraş Sütçü imam University 30 patient files were evaluated retrospectively. The study was started after the approval of the ethics committee of non-interventional clinical research of Kahramanmaraş Sütçü imam University Faculty of Medicine, dated 21.12.2020 and numbered 02. Neurological examination findings and Expanded Disability Status Scale (EDSS) findings available in our file records were used to evaluate the level of disability. Patients with MRI lesions consistent with their clinical complaint lasting more than 24 hours were evaluated as an attack. Patients' ages, MS diagnosis times, and previous immune modulatory treatments were recorded.

The number of T2, FLAIR sequence MRI lesions, EDSS before ocrelizumab, and the number of T2, FLAIR sequence MRI lesions 1 year after receiving ocrelizumab were recorded. After 1 year of follow-up, the absence of attacks, no increase in the number of lesions in MRI, and no progress in EDSS were accepted as no evidence of disease activity (NEDA 3). For PPMS patients, NEDA was accepted as no increase in the number of lesions on MRI and no progression in EDSS, since it did not progress with attacks.

While evaluating the findings obtained in the study, the IBM SPSS 22.0 program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, and rate) were used when evaluating study data. In the comparison of quantitative data, the independent t-test was used for within-group comparison, which is one of the parametric tests in the case of normal distribution. If it did not show normal distribution, the Wilcoxon signed-rank test was used for in-group comparisons, which is one of the non-parametric tests. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$.

RESULTS

Our study included 8 (26.7%) patients with RRMS, 14 (46%) patients with secondary progressive MS (SPMS), and 8 (26.7%) patients with PPMS. Twenty-three (76.7%) of the patients were female and 7 (23.3%) were male. The mean age of the patients was 38.03 (min 20-max 61). When we look at the number of attacks as a result of one-year follow-up, it was determined that 20 MS patients did not have an attack, 5 MS patients had an attack once, and 3 MS patients had an attack twice. When the attack rates were evaluated according to MS types, no attacks were observed in 7 cases (87.5%) in the RRMS patient group. In the SPMS patient group, no attacks were observed after ocrelizumab in the cases with attacks. The number of patients with no change in lesion burden on MRI was 20 (66%), the number of patients with regression was 3 (10%), and the number of patients with an increase was 7 (23%). The rate of patients without an increase in lesion burden was 76% (23 patients). The rate of patients who did not develop new T2 lesions and whose lesions disappeared was 62.5% in the RRMS patient group, 78.5% in the SPMS patient group, and 75% in the PPMS patient group.

When the cases were evaluated according to the EDSS score during the 1-year follow-up period, no progress was observed in EDSS in all of the cases in the RRMS patient group. In the SPMS group, there were 3 (10%) patients whose EDSS Score values decreased, 1 (3%) increased and 10 (33%) patients who did not show any change. In the PPMS group, EDSS remained stable in 6 (20%) patients, and EDSS progressed in 2 (6%) patients ($p> .05$). In the total patient group, the number of patients whose EDSS remained the same was 24 (80%), the number of patients with a decrease in EDSS was 4 (13%), and the number of patients with an increase in EDSS was 2 (6%). The rate of patients without an increase in EDSS was found to be 28 patients (93%).

When the cases were radiologically divided into two groups with EDSS 3 and below and EDSS above 3 and analyzed, it was seen that there were 4 (13%) cases with EDSS 3 and below. It was observed that there was no progression in EDSS after treatment in all cases. There were a total of 26 cases above EDSS 3. In this group, there were 4 (13%) patients who showed a decrease in EDSS, 3 (10%) an increase, and 19 (63%) patients who did not show any change. The rate of patients who provided NEDA-3 in 1 year was 43.3% (13 patients). Looking at the disease-modifying therapies (DMT) use cases before, it was determined that 27 (90%) MS patients received different treatments. When the smoking status of MS patients is examined, 23 people who have never smoked or quit in the last 1 year, 4 people who have smoked less than 1 pack in the last 1 year, and 3 people who still smoke too much **(Table 1)**.

When the lymphocyte profile was examined in the first year, 18 (60%) of the cases showed Grade 1 (800-1000) lymphopenia in the lymphocyte count. Normal values were obtained in 12 patients. Grade 3 and 4 lymphopenia was not observed.

DISCUSSION

Immunomodulatory and immunosuppressive therapies are widely used in MS patients due to their effectiveness in relapse and the development of new brain lesions. Ocrelizumab is a humanized monoclonal antibody that selectively targets CD20, an antigen expressed on the surface of pre-, mature, and memory B cells, which plays a critical role in the pathogenesis of MS. In the pivotal Phase III clinical trials in patients with relapsing MS (OPERA I and OPERA II), treatment with

Table 1. Descriptive information of the patients

		N	%
Gender	Female	**23**	**76.7**
	Male	**7**	**23.3**
Average age Min-max	38.03 ± 9.59		
Disease duration/year	0 – 9	**10**	**33.3**
	10 – 19	**19**	**63.3**
	19 >	**1**	**3.4**
Number of Attacks	0	**20**	**66.6**
	1	**5**	**16.6**
	2	**3**	**10.0**
	3	**1**	**3.4**
	5	**1**	**3.4**
Patients who have taken DMT before	Beta IFN 1-b	**4**	**14.9**
	Beta IFN 1-a(44 mcg)	**5**	**18.5**
	Fingolimod	**8**	**29.6**
	Teriflunamide	**1**	**3.7**
	Dimethyl fumarate	**3**	**11.1**
	Beta IFN 1-a(30mcg)	**1**	**3.7**
	Others	**5**	**18.5**
Naive Patient	Naive Patient	**3**	**100.0**
MS Type	RRMS	**8**	**26.7**
	SPMS	**14**	**46.7**
	PPMS	**8**	**26.7**
Smoking	Never smoked or quit in the last 1 year	**23**	**76.7**
	Has been smoking less than 1 pack of cigarettes in the last 1 year	**4**	**13.3**
	She Still Smokes Too Much	**3**	**10.0**

MS: Multiple sclerosis; DMT: disease-modifying therapies

OCR was associated with significantly lower rates of disease activity and progression than treatment with interferon (IFN) β-1a (2).

The aim of disease-modified treatments is no attack, no radiological activity, and no progression to ensure NEDA status. Real-life data are helpful in many situations, such as addressing issues that have not been evaluated in clinical trials, such as the comorbidities and efficacy of a drug and determining predictors of treatment response. It allows better personalization of treatment and aids in therapeutic decision-making. For this reason, many countries contribute to randomized clinical trials and literature with real-life data.

In our study, the mean age was consistent with the general MS population. When we look at the female/male ratio, we see that this ratio is compatible with other studies and the general MS population. In our study, the distribution of cases according to MS types was found to be 26.7% of patients with RRMS, 46% with SPMS, and 26.7% with PPMS. The patient population in the progressive form was more than the normal MS population ratio.

In a Latin American cohort that included a total of 81 patients, there was 38% relapse activity during the 12 months before starting Ocrelizumab. There was an average attack rate of 1.3 ± 0.6 during this time. Clinical relapses were not observed in 75% of relapsing-remitting MS patients. There was no contrast enhancement in the lesions in 91% of the patients (3). In our study, 26.7% of the cases consisted of the RRMS patient population. There was no attack in 87.5% of the RRMS patient group.

In a study by Ellwardt et al., 13% of patients experienced a relapse (annual relapse rate 0.17). 5% of all patients with MS experienced a 12-week confirmed disability progression (4). In our study, the annual relapse rate decreased from 1.75 to 0.125 in the RRMS group. 13% of our patients were patients with EDSS 3 and lower than this value. There was no progression in EDSS in 93% of our cases. The disability progression rate in the PPMS group was 32.9% in the ORATORIO study, and 37.5% in a study by Fernandez-Diaz et al. In our cohort, this rate was 25%. It is worth noting that our follow-up period is shorter. About three-quarters of the RMS patients included in the OPERA trial were previously untreated, and the most common prior therapies were interferon and glatiramer acetate (5).

In our study, 10% of the patients were naive patients who had not used a DMT before, and the remaining 90% of the patients had a DMT used before. Among these DMTs, treatments such as fingolimod and dimethyl fumarate were also available. In a study of 90 patients by Moss et al., none of the patients had clinical or MRI evidence of disease activity during the first 3 months (6). In the study conducted by Canibono et al., which included 60 MS patients (57 RRMS, 3 SPMS), presented as real-life data, the radiological activity was found to be 7% after ocrelizumab in 1 year (7). Fernandez-Diaz et al. found 6.9% MRI activity 12 months after Ocrelizumab in their study involving 228 MS patients (4).

In our study, the rate of patients who did not develop new T2 lesions and whose lesions disappeared was 62.5% in the RRMS patient group, 78.5% in the SPMS patient group, and 75% in the PPMS patient group. Our findings were obtained at a high rate in line with the literature. In addition, similar effects were observed on periventricular, juxtacortical, infratentorial, and spinal lesions.

In a study by Weinstock et al., in patients with RRMS and a history of suboptimal response to prior DMT, NEDA was detected in 48.1% of patients after 96 weeks of follow-up after initiation of ocrelizumab therapy reductions in disease activity were detected in both clinical and MRI measurements (8). In a study by Koç et al., 240 MS patients (58.75%) were included in RRMS, (21.25%) in SPMS, and (20%) in PPMS). The most common reason for switching to ocrelizumab was clinical and/or radiological activity. First-year NEDA status was achieved in 88.54% of the RRMS population, and disability progression in the same MS subtype was found in 12.77% (9). In our study, the percentage of NEDA 3 was 43.3%. The most important reason for switching to ocrelizumab was EDSS progression to the progressive phase.

In the study of Bollin et al., after starting Ocrelizumab, the most common abnormal laboratory values were decreased leukocyte, neutrophil, lymphocyte, and T cell counts, and low immunoglobulin-A and immunoglobulin-M levels. They reported that more data are needed to confirm trends and potential correlations in laboratory values (10). Lopez et al. found grade 2 lymphopenia in 5 patients and grade 1 lymphopenia in 6 patients in the RRMS 18-month follow-up study, which included 52 patients (11). In our study, when the lymphocyte profile was examined in the first year, Grade 1 (800-1000) lymphopenia was observed in the lymphocyte count in 18 (60%) of the cases. Normal values were obtained in 40% of the cases. Grade 3 and 4 lymphopenia was not observed.

As a result; In our study, it was determined that ocrelizumab was effective in reducing the attack rates, preserving the EDSS scores, and preventing the increase in the lesion burden. Our findings are consistent with real-life data.

Ethical approval: The study is approved by Sütçü İmam University Clinical Research Local Ethics Committee (date: 21.12.2020; decision number: 02). The 1964 Helsinki Declaration principles were followed. An informed consent form was taken from the participant.

Authors' contribution: The authors declare that they have contributed equally to the study.

Conflict of Interest: In this study, there is no conflict of interest among the authors on any subject.

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