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RESEARCH ARTICLE

Real-world Results of Ocrelizumab in the Treatment of Multiple Sclerosis: A Gulf Region Single-center Experience

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Abstract

Objective: This study aimed to describe the real-world effectiveness and tolerability of ocrelizumab treatment at MS Clinic, Tawam Hospital.

Materials and Methods: This retrospective, observational, single-center study analyzed the medical records of patients with multiple sclerosis (MS) receiving the standard dose of ocrelizumab.

Results: After starting ocrelizumab, 3 of the 19 patients included in the study experienced disease progression, 3 showed disability improvement, and the remaining 13 had stable status. None of the 15 patients with relapsing-remitting MS experienced a relapse. The average expanded disability status scale of all patients dropped from 2.32 to 2.22, when switched to ocrelizumab. After the follow-up period, 16 (84.21%) patients did not have any magnetic resonance imaging activity.

Conclusion: As an MS treatment, ocrelizumab is associated with a favorable response in terms of both efficacy and safety in clinical practice settings. The efficacy and safety demonstrated must be further evaluated to provide real-world evidence for the use of ocrelizumab.

Keywords: Multiple sclerosis, ocrelizumab, Gulf region

Introduction

Multiple sclerosis (MS) is a chronic inflammatory, immune-mediated disease affecting the myelin sheath of the nerves within the central nervous system (1). It is defined pathologically by the accumulation of demyelinating lesions in the white and gray matter of the brain and spinal cord. These lesions invade peripheral immune cells and cause leakages in the blood-brain barrier, with mechanisms involved in the direct effects of pro-inflammatory cytokines and chemokines produced by resident and endothelial cells in addition to indirect cytokine-dependent and chemokine-dependent leukocyte-mediated injury (2,3). However, the exact mechanisms are still not completely understood.

MS has a highly variable and unpredictable clinical presentation; however, it is often characterized by initial episodes of reversible neurological deficits, followed by gradual neurological deterioration as the disease progresses (4). The etiology of the disease remains unknown (1). Patients with MS can be classified according to MS phenotypes. Patients with accumulating neurological deficits, with no phases of relapse or remission, are said to have primary progressive MS (PPMS). This phenotype represents approximately 10% of patients with MS (5). Other phenotypes often manifest in patients with MS as a continuum, where patients commonly experience an initial phase of relapsing-remitting MS (RRMS), followed by a gradual conversion to secondary progressive MS in a phase referred to as transitional MS (6,7).

Accordingly, RRMS is the most common form, accounting for approximately 87% of patients with MS (1). The diagnosis of MS is based on clinical symptoms and supported by neuroradiological findings using magnetic resonance imaging

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(MRI) and the McDonald criteria, which comprise a clinically validated tool for early and accurate diagnosis (8).

The prevalence of MS is increasing worldwide, with the latest evidence from the MS International Federation revealing that approximately 2.8 million people are living with MS globally (9). Approximately twice as many women are affected than men, and the disease is commonly diagnosed in adults aged 20-45 years (2). The significant disabling effect on young adults results in the deterioration of health over time, in which approximately 50% of the patients require help when walking within 15 years of disease onset (10). This requires long-term rehabilitation, which places a significant economic burden on healthcare providers (11,12).

In the Middle East and North Africa, epidemiological studies reported that the prevalence of MS ranges from 30 to 38/100,000 people (13). These rates have risen over the first decade of the twenty-first century; however, they remain below the rates reported in North America and Europe (14). Data on the prevalence of MS in the United Arab Emirates (UAE) are limited. According to a 2011 study by Inshasi and Thakre (15), the estimated prevalence of MS in Dubai in 2007 was approximately 54.77/100,000, with an annual incidence rate of 6.8/100,00; however, of the patients identified, only 55.6% were Dubai natives and 44.4% were immigrants. A more recent study by Schiess et al. (16) determined the total crude prevalence of MS in Abu Dhabi to be 18/100,000 in Emiratis and expatriates combined. Age-/sex-standardized prevalence in the Abu Dhabi Emirati population is one of the highest and most reliable in the Arabian peninsula at 64.44/100,000 (16).

Recent treatment strategies for MS have revolved around disease-modifying therapy (DMT), with a large expansion in therapeutic options in recent years revolutionizing the care of patients with a relapsing disease (1). These medications help control the underlying disease process, aiming to shorten the duration and frequency of acute exacerbations and providing symptomatic relief (2). Ocrelizumab is a humanized anti-CD20 B-cell antibody that depletes immature and mature B-cells, but spares CD20-negative plasma cells (17). This drug slows the clinical and imaging-based progression of both relapsing and primary progressive forms of MS. As a result, ocrelizumab has been approved by both the US Food and Drug Administration in 2017 and the European Medicines Agency in 2018 (18,19). Real-world evidence of patients treated with ocrelizumab has been reported in North American, Latin American, and European patient populations (20-26). To our knowledge, this is the first report of real-world results of ocrelizumab treatment for patients with MS in the Middle East. Thus, this study aimed to describe the real-world effectiveness and tolerability of ocrelizumab treatment in patients with RRMS and PPMS in the Middle East.

Materials and Methods

Patients and Study Design

This retrospective, observational, single-center study analyzed the medical records of patients with MS at MS Clinic, Tawam Hospital. The main inclusion criterion was at least one infusion of ocrelizumab between January 1, 2018, and February 28, 2021. Patients were diagnosed with MS according to the most recent 2017 revision of the McDonald criteria (8). The indication for ocrelizumab therapy was determined based on disease activity and the MS type. A high disease activity, defined as high lesion load, was required, with patients either being treatment naive or shifted from another DMT because of disease activity, side effects, or safety concerns [namely, positive John Cunningham virus (JCV) antibodies on natalizumab]. Once determined, patients underwent screening for hepatitis B, human immunodeficiency virus, varicella antibodies, and tuberculosis, as per recommendations. In addition, any history of malignancy in the patients or their families was reviewed, with referral to screening programs if required, particularly for breast cancer in older female patients. Disease progression was defined as the deterioration of the expanded disability status scale (EDSS) score compared with baseline. The study was approved by the institutional ethics committee of Tawam Hospital (reference no: AA/AJ/682, date: 19.01.2021). All procedures were completed in accordance with the guidelines of the Declaration of Helsinki for research practice. As this study only used historically, routinely observed information from clinical practice, informed consent was not required. All data were documented anonymously and safely stored.

Treatment Protocol

Ocrelizumab (Ocrevus) was administered at a standard dose of 600 mg every 6 months. The first dose was divided into two, with each 300 mg dose separated by 2 weeks. All doses were preceded by premedication of 125 mg of intravenous methylprednisolone and 50 mg of Diphenhydramine HCl 30 min before ocrelizumab. Paracetamol and metoclopramide were administered as needed to ease any symptoms of nausea, headache, or fever. Patient data at months 6, 12, 18, and 24 were collected for the clinical review. Neuroimaging follow-up was conducted annually in asymptomatic cases according to recommendations and as soon as possible in patients who developed symptoms of disease progression.

Clinical and Radiological Outcome Measures

The following baseline patient data were collected: patient demographics, MS subtype, annualized relapse rate (ARR), DMTs before ocrelizumab administration, EDSS score, MRI activity before ocrelizumab initiation, reason for switching to ocrelizumab, emergency room (ER) visits while on prior DMT, adverse events while on prior DMT, and treatment compliance. The variables and outcomes assessed during the follow-up

period included ARR, EDSS, MRI activity, ER visits due to MS, adverse events, and treatment compliance.

Statistical Analysis

Descriptive analysis for quantitative data included the mean and standard deviations for normally distributed variables. When variables deviated from the normal distribution, the median and interquartile ranges were used instead. For qualitative categorical variables, frequency, percentage, and 95% confidence intervals were applied.

Results

Patient Baseline Characteristics

Of the 295 patients with MS included in the center's database, those who were receiving ocrelizumab during the study period were enrolled. After the study period (February 2021), a total of 20 patients were enrolled in the study. Only one patient received the first full dose of ocrelizumab and was lost to follow-up. Four patients of the remaining patients were diagnosed with PPMS and 15 with RRMS. The baseline characteristics of the patients are provided in Table 1.

The most common reason for switching to ocrelizumab was seropositivity, identified through a positive JCV test (n=11), followed by radiological and clinical activity (n=3), clinical activity alone (n=3), radiological activity alone (n=1), change of diagnosis to PPMS (n=1), and change in social status (n=1). Three of the patients were treatment-naive.

Clinical and Radiological Outcomes

While being on ocrelizumab therapy, patients' clinical conditions were monitored over a mean period of 27.4 (range, 18-41) months, during which an average of 4.4 (range, 1-7) doses were administered. After starting ocrelizumab therapy, none of the 15 patients with RRMS experienced a relapse, whereas the average ARR for this group before starting ocrelizumab was 0.63. The average EDSS of all patients dropped from 2.32 to 2.22 when switched to ocrelizumab.

Table 1. Baseline patient characteristics

	Total patients (n=19)
Male sex (%)	10 (52.63)
Mean age, years (range)	33.89 (21-54)
RRMS (%)	15 (78.94)
Family history of MS (%)	1 (5.26)
Previous DMTs, mean None (%) One (%) Two (%) Three (%) Four (%)	2.11 3 (15.79) 3 (15.79) 6 (31.58) 3 (15.79) 4 (21.05)
Baseline EDSS, mean (range)	2.32 (0-7)
ARR for previous years, mean (range)	0.63 (0-2)
Heavy MRI activity (%)	19 (100)

ARR: Annual relapse rate, DMT: Disease-modifying therapy, EDSS: Expanded disability status scale, MRI: Magnetic resonance imaging, MS: Multiple sclerosis, RRMS: Relapsing-remitting multiple sclerosis

Among the combined 19 patients, 3 (15.79%) experienced disease progression, of which 2 were diagnosed with RRMS and 1 with PPMS. Three patients showed disability improvement while on ocrelizumab therapy (2 RRMS and 1 PPMS), and the remaining 13 patients had a stable status.

After the follow-up period, 16 (84.21%) patients did not have any MRI activity; 2 (10.53%) patients showed MRI activity; however, one of these patients received their first dose of ocrelizumab only two weeks prior. This patient had another MRI follow-up after 1 year of treatment, which showed no new or enlarged T2 lesions. Follow-up imaging after starting the drug had not been performed for one patient.

Safety and Compliance

Two patients (10.53%) reported adverse events. One patient experienced a mild infusion reaction. Another patient reported skin discoloration, muscle pain, and fatigue for 1 month following the administration of the first ocrelizumab dose. Most patients did not report adverse events (n=17, 89.47%) or visit the ER because of their MS (n=16, 84.21%) while on ocrelizumab treatment. Patients were deemed compliant if no scheduled clinical follow-ups and treatments were missed. Seventeen (89.47%) of the 19 patients complied with their ocrelizumab treatment.

Discussion

To the best of our knowledge, this is the first single-center, retrospective, observational study to provide real-world evidence of ocrelizumab treatment in the UAE before and after the coronavirus disease-2019 pandemic. The results of this study show that ocrelizumab therapy was associated with an expected reduction in the ARR in patients with RRMS and no evidence of MRI activity in patients with MS with a high baseline lesion load. Ocrelizumab was generally well tolerated, and the compliance rates were high.

The results of this study support those of the initial OPERA I and II phase 3 clinical trials on RRMS and the ORATORIO phase 3 trial on PPMS. These trials found lower rates of disease activity and progression under ocrelizumab therapy than those under interferon beta-1a and placebo for 96-120 weeks (27,28). The proportion of infusion-related reactions in these trials (34.3%) was higher than the rate in the present study (n=1, 5.24%), suggesting that further research on infusion management in clinical practice is warranted. Further positive results can be seen in other real-world studies on ocrelizumab treatment. Daniels

et al. (22) showed clinically relevant improvement in disability status following ocrelizumab treatment in patients with PPMS. Similarly, a recent study by Fernandez-Diaz et al. (20) presented a suppressed disease activity in patients with MS treated with ocrelizumab, while exhibiting a favorable safety profile. The growing evidence base of positive clinical outcomes supports the inclusion of ocrelizumab in MS treatment.

Study Limitations

This study is subject to the limitations of the observational, retrospective study design, such as the absence of a control group and interpretation errors when analyzing medical records. The relatively small sample size of the study meant that the sample had insufficient power to perform subgroup analyses.

Conclusions

Although the study was not powered to assess the efficacy and safety of ocrelizumab, it provides insights into the effectiveness and tolerability of this DMT in a clinical practice setting. Moreover, the clinical course presented in this study is the longest in a real-world setting for ocrelizumab, with a mean period of 27.4 months. To validate our results, further research using real-world evidence from a larger sample size is necessary. Additional studies with a longer follow-up could clarify the long-term safety of ocrelizumab infusion in a real-world patient population.

Ethics

Ethics Committee Approval: The study was approved by the institutional ethics committee of Tawam Hospital (reference no: AA/AJ/682, date: 19.01.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.H., H.E., N.S., M.S., Concept: A.H., N.S., Design: H.E., M.S., Data Collection or Processing: A.H., H.E., N.S., M.S., Analysis or Interpretation: A.H., M.S., Literature Search: A.H., H.E., N.S., M.S., Writing: A.H., M.S.

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