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Systematic review on Ocrevus for treatment of multiple sclerosis

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Abstract

Adults with relapsing forms of multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS) are eligible to receive therapy with ocrelizumab (Ocrevus®), an injectable humanized anti-CD20 monoclonal antibody. In pivotal trials (against interferon β-1a) and supportive single-arm studies in certain subpopulations, ocrelizumab's efficacy in lowering relapse rates and disease activity in RMS patients was established. Comparing ocrelizumab to placebo, measures of clinical and MRI progression were less in PPMS patients. Over 7.5 study years of therapy, clinical benefits were sustained. Overall, ocrelizumab was well accepted, and continued treatment hasn't shown any new safety concerns. A large body of real-world (although brief) evidence about ocrelizumab is in line with data from clinical studies.

Clinical tests. The brief, half-yearly injections of ocrelizumab are convenient. As with PPMS patients (for whom there are presently no alternative authorized DMTs), ocrelizumab remains a helpful medication for postponing the course of the disease. It is also a typically well-tolerated, very effective disease-modifying drug (DMT) for RMS.

Keywords: Multiple Sclerosis; Ocrelizumab; Clinical Studies; Relapsing Multiple Sclerosis

1. Introduction

The most prevalent non-traumatic debilitating illness affecting young individuals is multiple sclerosis (MS). MS is becoming more prevalent in both industrialized and developing nations. The fundamental reason for this is yet unknown. MS is a complicated illness; in addition to several well-established environmental variables, such as vitamin D or ultraviolet B light (UVB) exposure, Epstein-Barr virus (EBV) infection, obesity, and smoking, several genes also slightly enhance the risk of developing the condition.[1]. In the past, multiple sclerosis was believed to be an autoimmune illness mediated by T cells that is unique to certain organs. The traditional T-cell autoimmune dogma is challenged by the efficacy of B-cell targeted treatments. According to conventional wisdom, the illness progresses in two stages: delayed neurodegeneration causes non-relapsing progression, or secondary and primary progressive MS, and early inflammation causes relapsing-remitting MS. [2,3]

Reduction of relapses and postponement of disease progression are goals of MS treatment. Disease-modifying treatments (DMTs) are used in long-term care; these treatments usually have therapeutic effects by inhibiting or changing immune response and inflammatory processes. Strong DMTs include monoclonal antibodies (mAbs) that deplete B cells by targeting the CD20 surface antigen; their clinical effectiveness has upended the traditional theory of MS as a T cell-mediated illness and brought to light the crucial roles that B cells play in the pathogenesis of MS. to treat multiple sclerosis, attention has recently been drawn to the development of humanized or human B cell depleting anti-

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CD20 mAbs. Compared to off-label chimeric anti-CD20 mAb medication, they could have higher potency and less immunogenicity. [15,16,17]

An injectable recombinant humanized anti-CD20 mAb called ocrelizumab (Ocrevus®) is authorized for the treatment of relapse types of MS and PPMS in several international nations. Previous reviews of ocrelizumab usage in these indications have been published in CNS Drugs. An updated assessment of the safety and tolerability of ocrelizumab as a treatment for multiple sclerosis is given in the current paper.[5,18]

2. Pharmaceutical therapy of ocrelizumab:

In two major, randomized, double-blind, double-dummy, active-controlled, global phase III studies (OPERA I and OPERA II) with similar procedures, the effectiveness of ocrelizumab in treating patients with relapse MS (RMS) was assessed. Interim data from ongoing phase IIIb or IV trials in patients with treatment-naïve, early-stage RRMS (ENSEMBLE), and RMS previously treated with natalizumab (ENCORE) supplement the OPERA results. These studies include an open-label, single-arm, multicenter, phase IV study in patients with active RMS. In two open-label, single-arm, multicenter phase IIIb trials, the specific efficacy of ocrelizumab has been examined in patients with RRMS who have not responded well to previous DMTs. [6,16]

2.1. In Relapsing Multiple Sclerosis:

2.1.1. Sclerosis Pivotal Trials

In OPERA I and II, individuals with RMS between the ages of 18 and 55 were recruited. The criteria for RMS were based on the 2010 revised McDonald criteria, and eligibility was based on the following: a history of documented clinical relapses (at least two in the previous two years or one in the year before screening), abnormalities consistent with multiple sclerosis (MS) in brain magnetic resonance imaging (MRI), and no neurological worsening for at least 30 days before screening and baseline. Throughout 96 weeks, patients were given either subcutaneous interferon β-1a 44 µg (delivered three times per week) or ocrelizumab 600 mg (every 24 weeks; administered as two 300 mg infusions on days 1 and 15 for the first dosage and a single 600 mg infusions thereafter). The mean duration between MS diagnoses was approximately 4 years in each study at baseline. Seventy-five percent of the patients had not taken any DMT in the two years before being screened. Orelizumab, in OPERA I and II, lowered the annualized recurrence rate (ARR) in comparison to interferon β-1a at week 96 in a substantial way ($p < 0.001$).[1,2,5,6,20]

Compared to interferon β-1a, the ARR was 46% and 47% lower in OPERA I and II, respectively, when using ocrelizumab (Table 1). Within the combined OPERA I and II cohorts, the ARR enhancement using ocrelizumab in comparison to interferon β-1a was noted in pre-established subgroups according to age (< 25 kg/m2 vs ≥ 25 kg/m2), baseline EDSS (< 4 vs ≥ 4) and baseline gadolinium-enhancing T1 lesions (0 vs ≥ 1); rate ratios ranged from 0.36 to 0.74 (p-values < 0.05) in every subgroup, except for patients over 40 years of age (rate ratio 0.76; $p = 0.073$). Compared to interferon β-1a, ocrelizumab improved several other indicators of disease activity or progression. According to predetermined pooled analyses of OPERA I and II data, ocrelizumab significantly ($p \leq 0.02$) increased the proportion of patients whose disability improvement was confirmed at 12 weeks (12-week CDI) and 24 weeks (24-week CDP) and whose disability progression was confirmed at 12 weeks (12-week CDP). Table 1 shows that in both trials, ocrelizumab significantly ($p < 0.001$) decreased the mean number of gadolinium-enhancing T1 lesions, new or enlarged hyperintense T2 lesions (indicating plaque development), and new hypointense T1 lesions about interferon Π-1a. Ocrelizumab was shown to be superior to interferon β-1a in OPERA II ($p = 0.004$), even though treatment groups in OPERA I did not significantly differ in terms of the change in MS Functional Composite (MSFC) score from baseline to week 96. [6,30,29]

The study examined the changes in brain volume between weeks 24 and 96, as well as the physical component summary (PCS) score of the 36-item Short Form Health Survey (SF-36) from baseline to week 96. Additionally, the percentage of patients who had no evidence of disease activity (NEDA), defined as no relapse, no 12- or 24-week CDP, no new or enlarged T2 lesions, and no gadolinium-enhancing T1 lesions, by week 96, revealed that ocrelizumab was more favorable than interferon-β-1a in OPERA I and II.[26,15,35]

2.1.2. During Open-Label Extension

Following two years of double-blind therapy in the OPERA trials, most patients (n = 702 and 623 initially randomized to interferon β-1a and ocrelizumab, respectively) underwent an open-label extension (OLE) when ocrelizumab was given to all patients. Eighty-nine percent of patients who received continuous ocrelizumab (i.e., in both OPERA and OLE) and eighty-eight percent of patients who were initially assigned to interferon-β-1a completed their three years of

treatment in the OLE (total treatment duration: five study years). Over the years, individuals on continued ocrelizumab therapy showed almost total suppression of MRI disease activity.[40,41]

The unadjusted rate of newly expanded or new gadolinium-enhancing T1 lesions was 0.031 over year 5 of therapy (vs 0.017 at year 2) and the unadjusted rate of newly formed or newly enlarged T2 lesions was 0.006 at year 5 of treatment (vs 0.063 over year 2). Patients who transitioned from interferon β-1a to ocrelizumab in the OLE experienced rates of 0.038 (against 2.583) and 0.004 (vs 0.491). Patients receiving continuous ocrelizumab treatment showed reduced brain atrophy compared to those switching from interferon β-1a, as indicated by adjusted rates of change in whole brain volume, cortical grey matter volume, and white matter volume from double-blind baseline ($p < 0.01$ for all). However, no differences were observed in MRI lesion counts at year 5 Over the course of 7.5 study years of follow-up (5.5 years in the OLE, which 76% of patients who joined the OLE completed), the therapeutic benefits of ocrelizumab were sustained. When patients were moved from interferon β-1a to ocrelizumab upon entering the OLE (as opposed to 0.12 pre-switch), the adjusted ARR at OLE year 5.5 was 0.03 for those who received ocrelizumab during both the double-blind therapy and the OLE (as opposed to 0.20 pre-switch). Rates of needing walking assistance (i.e., EDSS > 6.0) were 6.6% and 9.5% (compared with 0.8% and 3.1%), whereas rates of 48-week CDP were 17.9% and 21.5% in the corresponding groups (compared with 4.1% and 8.5% after double-blind therapy). Patients who received ocrelizumab continuously during the double-blind period and OLE had a lower risk of 48-week CDP (HR 0.77; 95% CI 0.60–0.98; $p = 0.034$) and a lower risk of needing a walking aid (HR 0.65; 95% CI 0.44–0.97; $p = 0.034$) compared to patients who switched from interferon β-1a to ocrelizumab.[49,50,15,6]

Table 1 Efficacy of ocrelizumab in the management of relapsing multiple sclerosis: result of OPERA I and OPERA II

	ARR at week 96	**12 week CDPa (%of points)**	**24 week CDPa (% of points)**	**12 week CDPb (% of points)**	**Mean no of lesions per MRI scan by weak 96** **GD+ on T1W, NNEH on T1W, NH on T3W**
OPERA 1e Ocrelizumab 1e (n= 410)	0.16	7.6	5.9	20.0	0.02, 0.32, 0.42 0.29, 0.41, 0.98
Interferon beta 1a (n=411)	0.29	12.2	9.5	12.4	0.6(0.03-0.10), 0.23(0.17-0.30), 0.43(0.33-0.56).
RR/HR (95%cl) or difference %	0.54 (0.40-0.72)	0.57 (0.37-0.90)	0.57 (0.34-0.95)	0.61	
OPERA 2c Ocrelizumab (n=417)	0.16	10.6	7.9	21.4	0.02, 0.33, 0.45 0.42, 1.90, 1.26
Interferon beta 1a (n=418)	0.29	15.1	11.5	18.8	0.05(0.03-0.09), 0.17(0.13-0.23), 0.36(0.27-0.47)
RR/HR (95%cl) or difference %	0.53(0.40-0.71	0.63(0.42-0.92)	0.63(0.40-0.98)	14	
POOLED OPERA 1&2 Ocrelizumab(n=827)	NA	9.1	6.9	20.7	NA, NA, NA,
Interferon beta 1a (n=829)	NA	13.6	10.5	15.6	NA, NA, NA,

HR (95% cl) or difference %	NA	0.60 (0.45-0.81)	0.60 (0.43-0.84)	33	NA, NA, NA.

2.2. Primary Progressive Multiple Sclerosis:

Adults between the ages of 18 and 55 who had PPMS (based on the 2005 revised McDonald criteria) and MS symptoms for less than 15 years (in patients with an EDSS score of >5) or less than 10 years (in patients with an EDSS score of ≤ 5) at screening were recruited by ORATORIO. Additionally, patients had to have an elevated IgG index or at least one IgG oligoclonal band detected in the cerebrospinal fluid (or a documented history thereof), as well as functional systems, scale pyramidal functions component score of ≥ 2. Every 24 weeks, patients received a matched placebo or ocrelizumab 600 mg (provided as two 300 mg infusions given two weeks apart), with randomization occurring in a 2:1 ratio and stratified by age and geographic location.[10,6]

The double-blind medication was administered for a minimum of 120 weeks, or five doses, or until approximately 253 12-week CDP episodes occurred. The percentage of patients with a 12-week CDP was the main outcome. In each therapy group at baseline, the mean duration since PPMS diagnosis was around three years. Before joining the trial, most patients (88%) had not taken a DMT in the two years. Compared to a placebo, ocrelizumab significantly decreased the percentage of patients with a 12-week CDP and was effective in postponing the clinical development of PPMS patients. Compared to a placebo, ocrelizumab lowered relative risk by 24% (HR 0.76; 95% CI 0.59–0.98; p = 0.03). Prespecified subgroup analyses of the 12-week CDP revealed somewhat more pronounced treatment benefits in patients with baseline T1 gadolinium-enhancing lesions (HR 0.65) than in those without (HR 0.84) and in younger patients (i.e. ≤ 45 years; HR 0.64) than in older patients (i.e. > 45 years; HR 0.88), despite ORATORIO not being powered to demonstrate between-group differences among subgroups. [6,57]

According to further exploratory subgroup analysis, regardless of treatment arm, around 36% of female patients developed 12-week CDP, but in male patients receiving ocrelizumab and placebo, the percentages were approximately 30% and 43%, respectively. Using ocrelizumab instead of a placebo also improved several indicators of clinical or MRI progression. Ocrelizumab significantly decreased the performance change in the timed 25-foot walk (T25FW) from baseline to week 120, as well as the percentage of patients with 24-week CDP (a relative risk reduction of 25%). Crelizumab significantly improved the mean changes in brain volume from week 24 to week 120 and in the total volume of T2 hyper-intense lesions from baseline to week 120 in terms of MRI results. The quality of life linked to physical health did not significantly differ between ocrelizumab and placebo patients between baseline and week 120. The benefits of ocrelizumab were further supported by the outcomes of pre-planned exploratory analyses. The results of the 12-week and 24-week composite CDP analyses, which were defined as the first confirmed occurrence of an increase in EDSS score and a 20% increase in T25FW time, indicated that ocrelizumab was superior to placebo (HRs 0.74 and 0.71; both p ≤ 0.001). Similarly, the adjusted mean number of new or enlarging T2 hyperintense lesions from baseline to week 120 (0.31 vs 3.88; p < 0.001) also showed favoritism. Lowering the probability of 12- or 24-week 9HPT progression in comparison to the placebo, ocrelizumab was protective against the advancement of upper extremity disability (HRs 0.56 and 0.55; both p < 0.001). [6,10]

Table 2 Efficiency of ocrelizumab in the management of primary progressive multiple sclerosis: results of ORATORIO

	12-week CDP[2] (% of pts)	**24-week CDP[2] (% of pts)**	**T25FW performance (%Ab from BL to week 120)**	**T25FW lesion volume (% Ab from BL to week 120)**	**Brain volume (%Ab from week 24 to 120)**	**SF-36 PCS sco (%Ab from BL to week 120**
Ocrelizumab[e] (n=488)	32.9	29.6	38.9	-3.37	-0.90	-0.7
Placebo[e] (n=244)	39.3	35..7	55.1	7.43	-1.09	-1.1

HR or relative difference (95% Cl)	0.76 (0.59 to 0.98)	0.75 (0.58 to 0.98)	29.3 (-1.6 to 51.5)	0.90(0.88 to 0.92)	17.5 (3.2 to 29.3)	0.38(-1.05 to 1.80)

3. Result

We conducted a systematic review of the retrospective observational studies that reported 235 RMS patients from tertiary care center hospitals from April 2016 to January 2022. From those studies we reported that the majority of patients (157/235 (66.8)) had an average age of 40.6 years (95% confidence interval 95%CI) (38.8–41.9); n = 235. 235 people had a median EDSS of 2.0 (interquartile range (IQR) ±1.5) before receiving OCR therapy. With 235 patients, the average duration of the illness was 9.3 years (95%CI 8.4–10.2). Of the 235 patients with RMS, 75 (31.9%) were naïve, meaning they had never received immunotherapy before. Most RMS patients (95/235) switched from very aggressive therapy, whereas the majority of patients (65/235) switched from mild/moderate therapy. In our cohort, seven people were on rituximab. The switch to ocrelizumab in these patients was caused by adverse effects. Twelve months before starting OCR treatment, 66/160 of pretreated patients and 49/75 of naïve individuals, respectively, had relapses. The EDSS median for both groups was 2.0 (pretreated mean (±IQR) 2.0 (±1.6), n = 160; naïve median (±IQR) 2.0 (±1.5), n = 75). Of the 65 naïve individuals whose MRI data were available, 41/65 had radiological activity. 56/148 of the 148 pretreated individuals whose MRIs were available had MRI activity. For the 12 months following the commencement of OCR, 190 patients had data on relapses, EDSS progression, and MRI activity available. One year after OCR was started, individuals with RMS showed fewer signs of disease activity. Pre-OCR: 60/190 (31.6%) vs. post-OCR: 5/190 (2.6%), p-value <0.001), represents the number of patients experiencing recurrence. And after OCR was started, the ARR dramatically decreased by 92.5%. Before OCR, the ARR was 0.4 (0.3–0.4), n = 190; after OCR, it was 0.03 (0.003–0.05), n = 190, p-value <0.001. On average, relapses under ocrelizumab happened 1.1 years (95 %CI 0.20–3.08, n = 11) following the initiation of treatment. Also, the activity of the MRI illness was significantly reduced. [50,5,15,57]

Most patients had a median EDSS that was steady (stable EDSS: 165/190 (86.8%); EDSS improvement: 9/19 (4.7%); EDSS decline: 16/190 (8.4%). In our study, 152/190 (80.0 %) RMS patients met the requirements for NEDA-3 12 months after OCR began, while 38/190 (20.0 %) showed evidence of disease activity (EDA), primarily presenting with MRI activity alone (19/38 radiological activity without relapse or EDSS progression; 11/38 only progression; 2/38 radiological activity with progression; 4/38 only relapse; 1/38 relapse with progression and 1/38 with all 3 activity criteria). Taking into account the new term "Progression Independent of Relapse Activity" (PIRA), 13/38 of the patients with disease activity met the requirements for PIRA after 12 months.[57]

The 12-month NEDA-3 status did not correlate with either the pre-treatment status (p = 0.172) or the duration of the disease (p = 0.115). Even after a full year, full data sets on the clinical and paraclinical courses of 104 out of 190 individuals were still available. The illness course remained stable in this population with a 24-month follow-up, showing low ARR (mean (95 %CI) 0.04 (0.001–0.08), n = 104), and modest radiological activity (4/104, 3.8%). At 24 months, 88/104 (84.6%) of the RMS patients met the criteria for NEDA-3, with 9/104 patients' primary cause of EDA being EDSS development. The entire group showed a little but noteworthy rise in EDSS (before OCR 2.0 (±2.0), n = 104, compared to after OCR 2.5 (±1.5), n = 104, p = 0.003). Nine out of the 104 patients had EDSS progression, while 89 of the patients had a stable EDSS and only 6 of the patients had EDSS improvement. Nineteen out of sixteen patients who still had disease activity after a year satisfied the PIRA requirement. Neither the pretreatment status (p = 0.353) nor the illness duration (p = 0.119) was related to NEDA-3 status at 24 months.[56,57]

Table 3 Comparison of baseline characteristics of Diem et al. and the OPERA I. trial

Baseline characteristics	**Diem *et .al* (n=235)**	**OPERA OCR arm (n=410)**	**OPERA interferon arm (n=411)**
Age(years), mean, SD	40.4 (12.1)	37.9(9.3)	37.9(9.3)
Female n(%) Duration of the disease, Y, mean, SD,	157(67) 9.3±9.0	270(66) 3.8±4.8	272(66) 3.7±4.6
EDSS before OCR, Median, SD,	2.3+1.6	2.9±1.2	2.8±1.3

Naïve, n(%), Previously treated patients, n (%)	75(32) 160(68)	301(74) 107(26)	292(71) 117(29)

Table 4 Comparison disease activity before and 12 months after Ocrelizumab start in RMS patients**.**

	Before starting OCR therapy	**12 months after OCR therapy start**	**P value**
Median EDSS,(±IQR), n	2.0, (±2.0), 190	2.0, (±2.0), 190	0.043
Patients with relapse, n (%)	60/190 (31.6)	5/190(2.6)	<0.001
Mean ARR, (95C1%), n	0.4(0.3-0.4), 190	0.03(0.003-0.05), 190	<0.001
Radiological activity, n (%)	88/190, (46.3)	22/190, (11.6)	<0.001

Table 5 Comparison disease activity before and 24 months after Ocrelizumab start in RMS patients.

	Before starting OCR therapy	**24 months after OCR therapy start**	**P value**
Median EDSS, (±IQR), n	2.0, (±2.0), 104	2.5, (±1.5), 104	0.003
Patients with relapse, n(%)	42/104, (40.4)	4/104, (3.8)	<0.001
Mean ARR, (96C1%), n	0.2, (0.2-0.4), 104	0.04, (0.001-0.008), 104	<0.001
Radiological activity, n(%)	38/104,(36.5)	5/104, (4.8)	<0.001

4. Discussion

In 2018, Ocrelizumab became available to those with RMS. However, there are currently insufficient real-world data on Ocrelizumab post-marketing applications. Our study presents actual data from two Swiss MS facilities. The following are the main conclusions:

RCT findings and previously published real-world data indicated that it was beneficial for RMS patients. Even though Ocrelizumab was usually well tolerated, infections, a drop in IgG, and the association between the two that our group observed highlight the need for pharmacovigilance and treatment strategies for MS patients utilizing Ocrelizumab. Real-world data often have different demographics than randomized controlled trials. Indeed, our RMS sample has a higher percentage of patients with pre-treatment and a longer duration of illness than the OPERA population.

In this, the RMS cohort was similar to most Real-World Data studies (RWDS) in terms of age (mean our study: 40.6 vs. Range (mean age in years) RWDS 36.3–43.9) and disease duration (mean our study: 9.3 vs. Range (mean disease duration in years).[28,33,57]. Furthermore shown is the EDSS (mean 2.3 vs. range (mean EDSS) RWDS 2.5–2.9). On the other hand, our study's pre-treatment RRMS patient percentage (mean 68.1% vs. range RWDS 7.8–20%) was higher than that of most RWDS. Our systematic review analysis confirmed the pivotal trial and other RWDS's findings that Ocrelizumab is useful in treating RMS patients. The main finding of the OPERA trials was a minimal rate of disability advancement at 12 and 24 weeks of follow-up. Like earlier RWDS, a comparable proportion of patients met NEDA-3 criteria. In the OPERA trial, the most utilized previous drugs for the approximately 75% of RMS patients who were not receiving therapy were interferon and glutamate acetate. However, most RMS patients are reported by cohort and comparable observational studies had already had therapy, most of which used highly active DMTs. A quarter or so of patients changed because of illness activity.[50,54]

Abbreviations

- OCR: Ocrelizumab;
- DMT: Disease Modifying Therapies;

- MS: Multiple Sclerosis;
- RMS: Remitting Multiple Sclerosis;
- RRMS: Relapsing Remitting Multiple Sclerosis;

5. Conclusion

Many Ocrelizumab users report improved overall quality of life, decreased relapse rates, and slower disease progression. Mobility, cognitive function, and fatigue levels have all seen notable improvements, according to a few research studies, Ocrelizumab might have side effects, just like any other medicine. Typical adverse effects include upper respiratory tract infections, responses at the injection site, and infusion reactions (such as fever, chills, and skin rash). Significant adverse effects, like infections or liver issues, are also possible for certain persons.

Ocrelizumab may be less helpful for certain patients or may not help them at all, while some patients report significant improvements with the medication. How well Ocrelizumab works for each individual can vary depending on factors like the severity, duration, and biology of the condition.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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