Ocrelizumab: a new milestone in multiple sclerosis therapy

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Abstract: B cells play a central role in the pathogenesis of multiple sclerosis (MS): they are involved in the activation of pro-inflammatory T cells, secretion of pro-inflammatory cytokines and production of autoantibodies directed against myelin. Hence, the use of B cell-depleting monoclonal antibodies as therapy for autoimmune diseases, including MS, has increased in recent years. Previous results with rituximab, the first therapeutic B cell-depleting chimeric monoclonal antibody that showed efficacy in MS clinical trials, encouraged researchers to evaluate the efficacy of a humanized anti-CD20 antibody, ocrelizumab, in MS. A large phase II clinical trial in patients with relapsing-remitting MS (RRMS) designed to explore the effects of two doses of ocrelizumab (600 mg and 2000 mg) compared with placebo showed a pronounced effect on radiological and relapse-related outcomes. These results were confirmed in two phase III trials (OPERA I and II) that compared the efficacies of ocrelizumab with interferon beta-1a in patients with relapsing MS, and showed decreased annualized relapse rates (46% in OPERA I and 47% in OPERA II), as well as fewer numbers of gadolinium-enhanced lesions on magnetic resonance imaging (MRI) scans (94% in OPERA I and 95% in OPERA II). Notably, ocrelizumab is the first drug to lower rates of clinical and MRI-evidenced progression in patients with primary progressive MS (PPMS). The phase III trial (ORATORIO) in patients with PPMS met its primary efficacy endpoint: the percentage of patients with 12-week confirmed disability progression was significantly lower in the active treatment group (32.9%) than in patients receiving placebo (39.3%). In March 2017, this evidence led the US Food and Drug Administration to approve the licence for ocrelizumab (Ocrevus®) as a treatment for MS, as the first treatment approved for PPMS and as the first monoclonal antibody for secondary progressive MS.

Keywords: anti-CD20 antibodies, B-cell therapies, ocrelizumab, progressive multiple sclerosis, relapsing-remitting multiple sclerosis

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Introduction

Although multiple sclerosis (MS) was previously considered a T cell-mediated disorder, the evidence that has accumulated over the past couple of decades has implicated B cells in MS pathophysiology.[1] The increased understanding of the disease process has resulted in the development of B cell-targeting antibodies as potential drugs for both relapsing and progressive forms of MS. Some of these drugs have now been evaluated in phase II and III trials, with more trials currently underway.

One of these drugs, ocrelizumab, was recently found to slow down clinically observed and imaging-based progression of not only relapsing forms of MS but also of the primary progressive form of the disease. As a result, it has been approved by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

In this review, we summarize the role of B-cell involvement in the pathophysiology of MS and the ocrelizumab mechanism of action. Moreover, we review the results of recent randomized controlled trials that have evaluated the effects of ocrelizumab, and review the potential role of the drug in both relapsing and progressive forms of MS.

B-cell involvement in the pathophysiology of MS

B cells act as antigen-presenting cells to activate T cells and produce pro-inflammatory (interleukin-6, interferon-γ and tumour necrosis factor) and anti-inflammatory cytokines (interleukin-10) that regulate the immune process[2,3]; these cells are also the source of mature plasma cells that secrete antibodies. Based on accumulating evidence, B cells participate in the pathogenesis of the disease through this multifunctional mechanism. First, the long-standing recognition of abnormal oligoclonal bands (OCBs) in the cerebrospinal fluid are detected in more than 95% of patients with MS.[4] The presence of OCBs is associated with an increased risk of MS conversion in patients with clinically isolated demyelinating syndrome.[5] Antibodies have also been detected within MS lesions, along with B-cell populations.[6]

With progression of the disease, a compartmentalization of the pathogenic process within the central nervous system is observed. B cell-rich meningeal aggregates associated with subpial cortical lesions are reported to be more common in secondary progressive forms of MS.[7,8] Most therapies for MS target T-cell activation, the trafficking of these cells into the central nervous system and effector functions of lymphocytes, but many of these therapies exert concomitant effects on B cells. However, this pathogenic evidence led to the development and testing of specific anti-B-cell drugs in clinical trials for MS using different strategies and with different results.[9]

Rituximab, a chimeric monoclonal antibody, was the first anti-CD20 drug to show efficacy in MS, although ocrelizumab, a humanized anti-CD20 antibody, was the first drug to show beneficial effects on relapsing MS (RMS) and partial effects on primary progressive MS (PPMS) in phase II trials. Recently, two new anti-CD20 antibodies have been studied: ofatumumab, a human antibody for which there is an ongoing phase III clinical trial in patients with RMS in comparison with teriflunomide [ClinicalTrials.gov identifier: NCT02792218], and ublituximab, a new glycoengineered, chimeric anti-human CD20 that is also being evaluated in a phase III clinical trial in patients with relapsing-remitting multiple sclerosis (RRMS) in comparison with teriflunomide [ClinicalTrials.gov identifier: NCT03277261].

Here, we review the available data for ocrelizumab as a treatment for MS, including its mechanisms of action, efficacy and safety data.

Mechanism of action

The CD20 molecule is a transmembrane protein with an incompletely understood function. It is expressed on most cells of the human B-cell lineage but not on stem cells, pro-B cells or differentiated plasma cells.[10] A small subset of T cells also express CD20.[11,12]

Ocrelizumab is an anti-CD20 antibody that depletes circulating immature and mature B cells but spares CD20-negative plasma cells. The effector mechanisms of anti-CD20 antibodies are complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.[13] Ocrelizumab completely decreased the CD19+ B-cell count (CD19+ cells represent a measure of B-cell counts in anti-CD20-treated patients) in blood after 2 weeks of treatment in two phase III studies of patients with RRMS.[14] The median time to B-cell replenishment was 72 weeks after the last ocrelizumab infusion in a phase II study of patients with RRMS.[15]

Compared with rituximab, ocrelizumab is associated with increased antibody-dependent, cell-mediated cytotoxic effects and reduced complement-dependent cytotoxic effects *in vitro*.[16] As a humanized molecule, ocrelizumab is expected to be less immunogenic with repeated infusions and thus might have a more favourable benefit–risk profile than rituximab.

Ocrelizumab in RRMS: clinical and radiological efficacy

After several phase II clinical trials[17,18] reported encouraging results for the efficacy of the anti-CD20 antibody rituximab in patients with MS, trials testing ocrelizumab as a treatment for RRMS were launched.

Phase II

Ocrelizumab was first tested in patients with MS in a phase II trial.[16] This placebo-controlled trial was designed to assess the efficacy and safety of two dose regimens of ocrelizumab (600 mg and 2000 mg) in patients with RRMS. The primary objective was to investigate the effect of ocrelizumab

compared with placebo on the total number of gadolinium-enhanced T1 lesions observed on brain magnetic resonance imaging (MRI) scans at weeks 12, 16, 20 and 24. Ocrelizumab was also compared with once weekly interferon beta-1a in an open-label treatment.

A total of 220 patients completed this 24-week study, and highly significant differences in the total number of gadolinium-enhanced T1 lesions were observed in both ocrelizumab groups ($p < 0.0001$) at weeks 12, 16, 20 and 24 when compared with the placebo group. Overall, the relative reductions were 89% in the 600 mg ocrelizumab group and 96% in the 2000 mg group compared with those in the placebo group. As a secondary objective, annualized relapse rates over 24 weeks were reduced by 80% in the 600 mg ocrelizumab group and 73% in the 2000 mg group compared with the placebo group.

Phase III

The efficacy of ocrelizumab against RRMS was confirmed in two phase III clinical trials. OPERA I and II were two identical phase III, multicentre, randomized, double-blind, double dummy trials that randomized (1:1) a total of 1656 patients with RMS to receive 600 mg of ocrelizumab *via* an intravenous infusion every 24 weeks or 44 µg interferon beta-1a *via* subcutaneous injections three times per week throughout a 96-week treatment period.[14] The primary endpoint, annualized relapse rate at 96 weeks, showed a greater reduction with ocrelizumab (OPERA I: 46%; OPERA II: 47%) compared with that in the group treated with interferon beta-1a (both $p < 0.0001$). Both studies also showed a 40% reduction in 12-week and 24-week confirmed disability progression (CDP), a significative reduction in the number of gadolinium-enhanced T1 lesions (OPERA I: 94%; OPERA II: 95%) and a reduction in the number of new/enlarging T2 hyperintense lesions on MRI scans (OPERA I: 77%; OPERA II: 83%). The number of patients with 'no evidence of disease activity' (NEDA3) increased from 29.2% in the group treated with 44 µg of interferon beta-1a to 47.9% in the group treated with ocrelizumab in OPERA I, and from 25.1% to 47.5% in OPERA II. However, these findings were considered to be nonconfirmatory as a result of failure of the hierarchical analysis.

Ocrelizumab in PPMS: clinical and radiological efficacy

In ORATORIO,[19] a phase III trial, 732 patients with PPMS were randomized to receive 600 mg of ocrelizumab ($n = 488$) or placebo ($n = 244$) every 24 weeks for at least 120 weeks. The primary endpoint, the percentage of patients with 12-week CDP, was significantly lower following treatment with ocrelizumab than that following treatment with placebo (32.9% *versus* 39.3%; hazard ratio 0.76; 95% confidence interval [CI] 0.59–0.98; relative risk reduction, 24%; $p = 0.03$). Similarly, the proportion of patients in the active treatment group with 24-week CDP was significantly reduced (29.6% *versus* 35.7%; hazard ratio 0.75; 95% CI 0.58–0.98; relative risk reduction, 25%; $p = 0.04$). For other clinical endpoints, by week 120, performance on the timed 25-foot walk was exacerbated to a significantly less extent in patients treated with ocrelizumab than in patients treated with placebo (38.9% *versus* 55.1%; relative reduction, 29.3%; $p = 0.04$), and no significant difference in change in the Short Form (SF-36) Health Survey Physical Component Summary score was observed between the groups (-0.7 with ocrelizumab and -1.1 with placebo; $p = 0.60$).

Regarding the radiological endpoints, the total volume of brain lesions on T2-weighted MRI scans decreased by 3.4% in patients treated with ocrelizumab and increased by 7.4% in patients treated with placebo ($p < 0.001$). Furthermore, the percentage of brain volume loss was significantly lower in patients treated with ocrelizumab than in patients treated with placebo (0.9% *versus* 1.09%; $p = 0.02$). The adjusted mean number of new or enlarging hyperintense lesions on T2-weighted images from baseline to week 120 (exploratory endpoint) was lower in patients treated with ocrelizumab than in patients treated with placebo (0.31 *versus* 3.88; $p < 0.001$).

Although the OLYMPUS trial, a previous phase II–III trial with rituximab (monoclonal anti-CD20 antibody) in patients with PPMS,[20] did not meet its primary efficacy endpoint, a subgroup analysis showed a delayed progression of disability in younger patients (< 51 years of age) with evidence of radiological activity at the baseline. In the ORATORIO trial, ocrelizumab was effective across the trial population, independent of baseline MRI activity. However, the

trial did not have sufficient power to show differences between these subgroups.

Ongoing clinical trials

The extension phases of the pivotal phase III trials OPERA I–II and ORATORIO remain in progress, with the aim of evaluating ocrelizumab in patients with RMS and PPMS. Additional ongoing phase III studies are evaluating ocrelizumab in patients with early stage RRMS [ClinicalTrials.gov identifier: NCT03085810] and patients with RMS who have a suboptimal response to an adequate course of disease-modifying treatment [ClinicalTrials.gov identifier: NCT02861014]. Other ongoing studies include a phase III biomarker study designed to better understand the mechanism of action of ocrelizumab and B-cell biology in patients with RMS or PPMS [ClinicalTrials.gov identifier: NCT02688985]. Two more clinical trials will evaluate the safety and efficacy of switching from rituximab [ClinicalTrials.gov identifier: NCT02980042] or natalizumab [ClinicalTrials.gov identifier: NCT03157830] to ocrelizumab.

Safety

A pooled safety analysis with patients, including those in the OPERA I and II (825 patients) and ORATORIO (486 patients) trials, showed the most commonly reported adverse events in the ocrelizumab-treatment groups which are described below.

Infections

The incidence of upper respiratory tract infections (mainly nasopharyngitis) was more prevalent in the ocrelizumab-treatment groups (40% [*versus* 33% in interferon beta-1a] in OPERA I and II; 49% [*versus* 43% in placebo group] in ORATORIO). The percentage of patients reporting any infection was 59.9% (*versus* 54.3% in interferon beta-1a) in OPERA I, 60.2% (*versus* 52.5% in interferon beta-1a) in OPERA II, and 71.4% in ORATORIO (*versus* 69.9% in placebo group). Notably, ocrelizumab was not associated with an increased risk of serious infections, which occurred in 1.3% of patients receiving the drug (*versus* 2.9% of patients receiving interferon beta-1a) in OPERA I and II, and 6.2% of patients receiving the drug (*versus* 5.9% receiving placebo) in ORATORIO.

In the OPERA I–II trials, the proportion of patients reporting herpesvirus-associated infections was 5.9% in the ocrelizumab group and 3.4% in the interferon beta-1a group. In the ORATORIO trial, herpesvirus infections (4.7% with ocrelizumab and 3.3% with placebo) and oral herpes were more common among patients who had received ocrelizumab than among those who had received placebo (2.3% *versus* 0.4%); all cases were mild to moderate. No opportunistic infections were reported in any study over the controlled treatment period.

One of the most concerning and devastating complications of some of the disease-modifying treatments used for MS is progressive multifocal leukoencephalopathy (PML). In patients with MS, PML is an infection mainly related to the use of natalizumab, although cases associated with other drugs have been described. Regarding monoclonal anti-CD20 antibodies, the association between PML and rituximab in the context of rheumatological or lymphoproliferative disorders is well known,[21] although no cases of PML have been observed in the MS population treated with this drug. In these other scenarios, the concomitant use of other immunosuppressive drugs, in the case of rheumatological diseases or the state of immunosuppression secondary to lymphoproliferative diseases, has been suggested as a factor related to the appearance of PML under rituximab. No cases of PML were reported in patients treated with ocrelizumab across all clinical studies of the drug; however, 2 months after the approval of ocrelizumab in March 2017 by the FDA, the first case of PML was reported in a patient who had received the first dose of ocrelizumab in April 2017 and developed PML 1 month later. The patient was JC virus-antibody positive and had been treated with natalizumab for 3 years, receiving the last natalizumab infusion in February 2017. Although alarming, this case was thought to be due most likely to the natalizumab-associated carry-over risk of PML.[22]

Infusion-related reactions

Infusion-related reactions were more prevalent in ocrelizumab-treated patients (34% [*versus* 10% with interferon beta-1a treatment or placebo] in OPERA I and II; 40% [*versus* 26% with placebo] in ORATORIO). Most infusion-related reactions in ocrelizumab-treated patients were mild or moderate in severity, were reported during the

first infusion of the drug, and were managed with infusion rate adjustments and symptomatic treatment. Two ocrelizumab-treated patients discontinued treatment in the ORATORIO trial due to infusion-related reactions. Regarding preventive strategies, all patients in the OPERA and ORATORIO trials were premedicated with intravenous methylprednisolone; prophylaxis with analgesics/antipyretics and antihistamines was recommended.

Neoplasm

Clinicians have expressed some concern about the increase incidence of neoplasms in patients treated with ocrelizumab. Although a higher incidence of neoplasms was not reported in ocrelizumab-treated patients in the phase II clinical trial[16] and in the extended phase,[23] a greater incidence of malignancies was observed in patients treated with ocrelizumab compared with those patients who received placebo in the phase III trials. In the OPERA I and II trials, four patients (0.7%) treated with ocrelizumab developed neoplasms compared with two patients (0.2%) treated with interferon beta-1a. Of these two patients, two suffered from breast cancer. This increase in malignancies in patients treated with ocrelizumab has also been reported in the ORATORIO trial, with an incidence of neoplasms in 11 patients (2.3%) (4 with breast cancer) receiving ocrelizumab compared with 2 patients (0.8%) in the placebo group. These data have raised some concern about the possibility of an increase in the rate of breast cancer in patients receiving treatment with ocrelizumab. Although incidence rates of malignancies and breast cancer observed in patients with MS who were treated with ocrelizumab remain within the range of epidemiological background data, this imbalance of breast cancer cases in the ocrelizumab group will be better characterized with longer follow-up monitoring.

Current status

Although the therapeutic armamentarium of MS has fortunately expanded in recent years, studies aiming to develop and identify more effective, convenient and safer treatments are still needed. In addition, the mechanism of progression of the disability is still a challenge. Data from ocrelizumab clinical trials reveal the significant efficacy of this drug in treating RMS and, more strikingly, the favourable results for PPMS. The potential placement of this drug in the MS therapeutic algorithm could be as a first-line treatment in patients with highly active disease, or in patients with suboptimal responses to other drugs. Regarding the progressive forms, the potential benefits probably could be clearer in patients with early disease and some degree of inflammatory activity, although this is purely speculative.

Ocrelizumab has already been approved by several medical agencies and currently is under review in countries worldwide. Ocrelizumab received its first global approval on the 28 March 2017 for the treatment of adult patients with RMS or PPMS in the USA.[24] The EMA has recently also approved ocrelizumab for the treatment of RMS with active disease and early PPMS.[25]

Anti-CD20 antibody treatment constitutes a distinct, convenient and highly efficacious strategy for treating MS. The long-term safety profile must be elucidated to understand the impact of these molecules on MS evolution.

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Conflict of interest statement

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