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Role of Ocrelizumab in the Treatment of Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is a neurodegenerative disease of the central nervous system, in which B-cells play an important role in its pathogenesis.
However, Ocrelizumab (OCR) is a humanized anti-CD20 monoclonal antibody that can diminish the targeted B-cells through antibody-dependent cell mediated cytotoxicity. It's the only MS drug that has been approved by the US Food and Drug Administration (FDA) for patients with relapsing–remitting MS (RRMS) and primary progressive MS (PPMS).

Phase II clinical trials studies OCR role on MRI and clinical features in patients with RRMS, while Phase III clinical trials have confirmed the results of previous Phase II studies. However, OPERA I and II clinical trials, which were performed on subjects with RRMS, has shown a reduction in the risk of disability progression, the annualized relapse rate, enhancing lesions measured using brain magnetic resonance and the number of enlarging/new T2 lesions.

The ORATORIO trial performed in patients with PPMS, showed that OCR can decrease disability progression, enhance the performance on the timed 25-foot walk, and reduce the number of new/enlarging T2 lesions. This report is aimed to study the role of B-cell in the pathophysiology of MS, OCR mechanism of action and its efficacy in patient with RRMS and PPMS.

Introduction

MS is an autoimmune response against components of the myelin sheath characterized by episodes of disease activity in separated time that produce white matter lesions in separated space[1]. It's the most common demyelinating disorder, include prevalence of approximately 1 per 1000 individuals in Europe and United States[1].

The disease may present at any age, but onset in childhood or after age 50 is rare, females are affected twice as often as males[1]. The most common clinical course is the relapsing-remitting (RR) phenotype, while a minority of patients have an immediate progression of disability, referred to as the primary progressive (PP) phenotype accounts for 10% to 15% of the overall subject's with MS[1].

The mechanisms of tissue injury in MS is unsure, but Both T and B cells are involved in its pathogenesis, and the consequences of their action are demyelination, axonal loss, and gliosis[1]. B-cells secrete pro-inflammatory cytokines, while potent antigen presenting cells (APC) activates the pro-inflammatory T-cells, they may differentiate into plasma cells that produce autoantibodies, including clonally expanded IgG oligoclonal bands (OCBs) directed against myelin sheath[2]. OCBs can be detected in the cerebrospinal fluid (CSF) of about 90% of individuals with MS[2].

The role of B-cells in the pathogenesis of MS is confirmed by several factors as their presence in MS plaques and in the meningeal follicles[2]. Another piece of evidence supporting the role of B-cells in MS, is the identification of some specific genes for B-cell that increase the risk of MS, TNFSF13B gene, encoding for the cytokine *B-cell activating factor (BAFF),* which is important for B-cell activation, differentiation, and survival[2].

However, some clinical trials supports the presence of the B-cells in the pathogenesis of MS by using B-cell depleting monoclonal antibodies[3]. Rituximab (RTX) is the first monoclonal IgG1 mouse –human anti-CD20 antibody, it was initially approved for the

treatment of non-Hodgkin lymphoma and it's the first anti-CD20 antibody used for treatment of MS[3].

Ocrelizumab (OCR, Genentech, Ocrevus) is a second-generation recombinant humanized Selective anti-CD20 monoclonal antibody with an IgG1 tail, its designed to decrease immunogenicity by selective targeting of CD20 which is an antigen (glycosylated phosphoprotein) present on the surface of pre-B cells, mature B cells, and memory B cells but not on lymphoid stem cells and plasma cells[4].

Materials and Methods

After several phase II clinical trials encouraging reported results for the efficacy of the antiCD20 antibody RTX in patients with MS, trials testing OCR as a treatment for MS were launched[2].

The first trial is a phase II randomized, parallel, double-blind, placebo-controlled trial designed by Kappos L and Calabresi PA, at 2011, took 220 patients from 79 centers in 20 countries, All of the subjects had an aggressive course of disease, with at least three relapses in the 3 years before the baseline and at least one in the past year [2]. The subjects were selected randomly to reserves intravenous OCR 600 mg (lower dose) and 2000 mg (high dose) by four intravenous infusions over 24 weeks or interferon beta-1a at a dose of 30 μg intramuscular injections once a week[2]. All the patients received one 100-mg dose of intravenous methylprednisolone before each infusion, Prophylaxis with analgesic or antipyretic agents and an antihistamine was recommended to avoid infusion related adverse events [2].

Two identical phase III clinical trials which designed by The sponsor, F. Hoffmann–La Roche, OPERA I and OPERA II are multicenter, randomized, double-blind, active-controlled, parallel group trials were performed in patients with RRMS ; the OPERA I trial involved 821 patients from 141 sites in 32 countries, while the OPERA II trial involved 835 patients from 166 sites in 24 countries, Both studies were 96 weeks in duration, age 18–55 years; EDSS score 0–5.5; and at least two relapses in the 2 years before the study, or 1 relapse in the past year [4].

The 2 trials had the same protocol design, in which OCR 600 mg administered to the study group and interferon beta 1a 44 µg subcutaneous injections three times a week to the control group [4]. The infusion protocol was the following; an infusion every 24 weeks, with the first 600 mg dose divided into two infusions, each of 300 mg, administered on days 1 and 15, and the following infusions were single 600 mg administrations similar to that in the Phase II trial [4]. Intravenous 100 mg of methylprednisolone was administered before each infusion, and analgesic or antipyretic with oral antihistamine were recommended [4].

The primary end point of these trials was the annualized relapse rate (ARR) at 96 weeks. However, the study had many secondary end points as: the proportion of patients with disability progression confirmed at 12 weeks, disability improvement confirmed at weeks 12 through 96, gadolinium-enhancing lesions, new or newly enlarged T2 lesions, new hypo-intense T1 lesions and changes in brain volume measured with MRI [4].

The ORATORIO study was a Phase III, randomized, parallel-group, double-blind, placebo-controlled trial [3]. It investigates the efficacy of OCR in 732 patients with PPMS [3]. The inclusion criteria were very strict: age 18–55 years, an EDSS score between 3.0 and 6.5, a short duration of disease (less than 15 years if the EDSS score was more than 5.0, and less than 10 years if the EDSS score was 5.0 or less[3]. The patients received 600 mg of OCR (n = 488) or placebo (n = 244) every 24 weeks for at least 120 weeks[3]. The primary end point of this study was the

percentage of patients with disability progression confirmed at 12 weeks[3]. The study also had some secondary end points; the percentage of patients with disability progression confirmed at 24 weeks, the change in total volume of T2 brain lesions and in brain volume, and the change in performance on the timed 25-foot walk[3].

Results

In phase II trial, the number of gadolinium-enhancing lesions at week 24 was 89% lower in the 600 mg group and 96% lower in the 2000 mg group, compared with those in the placebo group[2]. The patients free of gadolinium-enhancing lesions were 77% in the 600 mg group and 88% in the 2,000 mg group. The ARR over 24 weeks was lower in the OCR treated groups than in the placebo group (80% lower in the 600 mg group and 73% lower in the 2,000 mg group)[2]. Infusion-related adverse events were recorded in 35% of patients treated with 600 mg, 44% with 2000 mg, and 9% with IFN-β1a[2]. There was no difference in serum IgG over time in any group. B-cell counts were reduced by > 99% in both 600 mg and 2,000 mg groups[2].

After the positive results of the Phase II study, in the two Phase III studies (OPERA I and OPERA II), the primary endpoint, ARR at 96 weeks, showed a greater reduction with OCR (OPERA I: 46%; OPERA II: 47%) (0.16) compared with that in the group treated with interferon beta-1a (0.29)[4]. The hazard of disability progression confirmed at 12-week and 24-week was 40% lower in the OCR group (9.1% vs 13.6%) [4]. MRI analysis showed a 94% (OPERA I) and 95% (OPERA II) reduction in the number of gadolinium-enhancing lesions with OCR than with interferon beta (0.02 versus 0.29 in OPERA I; 0.02 versus 0.42 in OPERA II) [4]. Patients treated with OCR had a lower number of new or newly enlarging T2 lesions than patients treated with interferon beta in both OPERA I (77%, 0.32 versus 1.41) and OPERA II (83%, 0.33 versus 1.90) Compared to the interferon

beta group [4]. The Lesions were 94% (OPERA I) and 96% (OPERA II) lower from week 24 to week 48, while 98% (OPERA I) and 97% (OPERA II) lower from week 48 to week 96 in the OCR group [4]. The number of patients with "no evidence of disease activity" (NEDA) increased from 29.2% in the group treated with 44 μg of interferon beta-1a to 47.9% in the group treated with OCR in OPERA I, and from 25.1% to 47.5% in OPERA II [4].

Infusion-related reactions were reported in 34.3% of OCR treated patients vs 9.7% treated with subcutaneous IFN-β1a and placebo infusions [4]. Infection was reported in 56.9% of the patients in the OCR group and in 54.3% in the interferon beta-1a group. Three deaths occurred, including one death in the OCR group and two in the interferon beta-1a group [4].

In ORATORIO, a phase III trial, the primary end point was reached, the disability progression at 12 weeks was reduced 32.9% with OCR and 39.3% with placebo, and at 24 weeks was 29.6% with OCR and 35.7% with placebo [3]. The drug was also more effective in improving the performance on the timed 25-foot walk was exacerbated to a significantly less extent in patients treated with OCR than in patients treated with placebo (change of 38.9% versus 55.1%, respectively, relative reduction with OCR of 29.3%group) [3]. Regarding the radiological endpoints, the total volume of brain lesions on T2-weighted MRI scans decreased by 3.4% in patients treated with OCR and increased by 7.4% in patients treated with placebo[3]. The percentage of brain volume loss was significantly lower in patients treated with OCR than in patients treated with placebo (0.9% versus 1.09%) [3]. Moreover, the mean number of new or enlarging T2 lesions from baseline to week 120 was 0.31 with OCR and 3.88 with placebo [3].

Discussion

In the OPERA I and OPERA II clinical trials, OCR had lower ARR (the primary end point) than the active comparator, interferon beta-1a, at a 96-week treatment period[4]. In addition, subjects who reserved OCR had greater outcomes as estimated in the secondary end points[4]. OCR is the first drug that has been able to significantly slow disability progression during the 12 and 24 weeks in patients with PPMS[3]. It was also related to a higher rate of improvement in disability during the 12 weeks (a secondary end point) than interferon beta-1a in the pooled analysis[3]. These findings were confirmed by a significantly suppression in the development of new inflammatory areas (as measured by means of brain MRI with the application of gadolinium enhancement) and new/enlarged plaque formation (as assessed by lesions on T2-weighted MRI) [4].

In both trials, the percentages of patient's with no evidence of disease activity were higher with OCR than with interferon beta-1a[4]. The adverse event with OCR group were less than in interferon beta-1a group, and the most common adverse events were Infusion-Related Reactions and nasopharyngitis in the group treated with OCR, influenza-like illness and injection-site erythema in the group treated with interferon beta-1a[4]. However, headache, urinary tract infection and upper respiratory tract infection were found in both groups[4]. But infection cases were reported more in the OCR group than in the interferon beta-1a group, the upper respiratory tract infection was more frequent in the OCR group, whereas urinary tract infection was more reported in the interferon beta-1a group[3]. Through the two trials, the percentage of subjects reporting herpesvirus-associated infection in the OCR group was 5.9% and 3.4% in the interferon beta-1a group[4].

Across these two 96-week trials, in the OCR group four neoplasms occurred (two cases of invasive ductal breast carcinoma, one case of malignant melanoma, and one case of renal-cell carcinoma), and two reported in the interferon beta-1a group (one case of squamous-cell carcinoma in the chest and one case of mantle-cell lymphoma)[4].

Between the clinical cutoff dates of the two trials (OPERA I trial on April 2, 2015 and OPERA II trial on May 12, 2015) and June 30, 2016, five new cases of neoplasm (two cases of basal-cell skin carcinoma, two cases of breast cancer, and one case of malignant melanoma) were reported during the open-label extension study, where all the patients received OCR[4]. The overall incidence rate of neoplasms in all studies involving patients with MS was 0.40 per 100 patient-years of treatment with OCR, as compared with 0.20 per 100 patient-years of treatment with interferon beta-1a or placebo[4]. No cases of progressive multifocal leukoencephalopathy (PML) have been reported so far with OCR during all clinical studies[3].

Infusion-related reactions were more common and sever in OCR-treated patients than in those treated with interferon beta-1a, and included one case of life-threatening bronchospasm (grade 4) [3]. The mechanism for an infusion-related reaction is a type 2 hypersensitivity reaction, in which cytokines are released from the effector cell after the low-affinity Fc receptors ligation by OCR-opsonized B cells[3]. The frequency and severity of infusion-related reactions reduced with the administration of subsequent doses; however, these reactions can occur at any infusion[3].

Across the clinical trials, six deaths were reported in patient treated with OCR, one of these subjects exposed to a high dose of OCR (2,000 mg) and was enrolled in the Phase II clinical trial[2]. The death In this case was caused by an acute onset of thrombotic microangiopathy, this happened at week 14, and the drug correlation was not excluded[2]. Another patient who was included in the OPERA II trial died from suicide[4]. The rest of patients who died during the ORATORIO study died from pneumonia, pancreatic carcinoma, pulmonary embolism, and aspiration pneumonia[3].

The pathophysiology of MS is predominantly T-cell–mediated disease[1]. However, the findings in our two trials (OPERA I and II) are consistent with evidence that B-cells play an important role in the pathogenesis of MS[4]. In the vast majority of patient the plasma cell is the most significant producer of Auto-antibody, and the levels of antibodies in CSF and blood are generally not decreased after anti-CD20 therapies

(plasma cells and Lymphoid stem cells lack CD20), while B-cells are depleted and diminished by three main mechanisms are: complement dependent cytotoxicity, antibody-dependent cellular cytotoxicity and apoptosis [3].

OCR action is mostly mediated by antibody-dependent cellular cytotoxicity, while RTX by complement-dependent cytotoxicity[3]. Also OCR acts on subtype of circulating T-cells that express CD20 on their surface (representing for ~6% of total T cells) [3]. A depletion of approximately 99% of B cells happened during the first 14 days after infusion of OCR and continued until week 24[4]. Depletion of B-cell could be observed by the assessment of CD19 cells[3]. In a minority of cases, the B-cell depletion persist 2.5 years after the last infusion, so Anti-CD20 therapies can permanently change the pool of reconstituted B cells to produce predominantly naive B-cells and decreased memory B cells and plasma-blasts [4]. However, several medical agencies have already approved OCR, and it's currently under review in a lots of countries around the world. On 28 March 2017 OCR received its first global approval for the treatment of adult patients with RRMS or PPMS in the USA[3]. The European Medicines Agency (EMA) has recently also approved OCR for the treatment of RRMS with active disease and early PPMS[3].

Conclusion

This report concludes that all clinical trials comparing OCR versus placebo or interferon beta have shown the superiority of this monoclonal antibody in many clinical and neuroimaging aspects.

OCR is the first drug that has been shown to be able to significantly slow disability progression at 12 and 24 weeks in patients with PPMS. It is also effective in controlling clinical and radiological activity in patients with RRMS forms, and it is approved and indicated for both phenotypes of the disease.

Treatment involves administration of the drug by intravenous infusion every 6 months. The most frequent adverse events were the infusion-related reactions and infections.

Future work

As for all new drugs, only continuous and long-term assessment of the safety profile of OCR is required in order to fully characterize the risk of uncommon adverse events, including PML and opportunistic infections.

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