



An overview of pivotal trials and real-world evidence for CD20-depleting therapy in multiple sclerosis

Immunotherapy with rituximab, ocrelizumab, and ofatumumab

Arkady Ovchinnikov · Oliver Findling

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Summary Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system leading to demyelination and neurodegeneration of brain tissue. For a long time, research focused on T cells as the primary mechanism of disease. Driven by reports on the clinical results of B cell-depleting therapies, this therapeutic approach has come into focus in the last decade, and new highly effective treatments have been developed and are now complementing the therapeutic landscape. This review provides an overview of the development of B cell-depleting therapies and shows the advantages and disadvantages of current developments. In addition, we discuss basic considerations for CD20-depleted MS patients in the face of the COVID-19 pandemic.

Keywords Neuroimmunology · Autoimmunity · Relapsing-remitting multiple sclerosis · Primary progressive multiple sclerosis · MRI

Abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
ARR	Annualized relapse rate
CNS	Central nervous system
DMT	Disease-modifying therapy
EMA	European Medicines Agency
FDA	US Food and Drug Administration
IFN- β	Interferon beta
IV	Intravenously
MS	Multiple sclerosis

OCR	Ocrelizumab
OFA	Ofatumumab
PML	Progressive multifocal leukoencephalopathy
PPMS	Progressive MS
RRMS	Relapsing-remitting MS
RTX	Rituximab
SC	Subcutaneously
SPMS	Secondary progressive MS

Introduction

Multiple sclerosis (MS) is a life-long disease of autoimmune etiology that affects the central nervous system (CNS). A hallmark of MS is aggregation of inflammatory cells with underlying demyelination and plaque formation. Worldwide, MS has an increasing prevalence and is the most common cause of nontraumatic neurological impairment among young people [1]. The disease is grouped into three subtypes: i) CIS (clinically isolated syndrome): the earliest clinical manifestation of the disease; ii) RRMS (relapsing-remitting multiple sclerosis): primarily clearly defined attacks of new neurological symptoms with complete or incomplete improvement and without or only minimal progression of the disability; iii) SPMS (secondary progressive multiple sclerosis): a secondary transformation of the disease from RRMS with the following accumulation of disability without clinically or temporally defined relapses; and iv) PPMS (primary progressive multiple sclerosis): accumulation of disability without exact clinical relapses from the beginning of the disease.

For decades, the role of T cells in the pathogenesis of MS has been the focus of research. Disease-modifying treatments with T cells as a target have shown notable effectiveness and have slowed disability progression in patients with RRMS. However, as those treatments also target B cells, and there have been

A. Ovchinnikov · Dr.med. O. Findling (✉)
 Department of Neurology, Kantonsspital Aarau,
 Tellstr. 25, 5001 Aarau, Switzerland
oliver.findling@ksa.ch

A. Ovchinnikov
arkady.ovchinnikov@ksa.ch

increasing reports of the success of B cell-depleting therapies in MS patients, this treatment approach has become the focus of interest.

Here we will provide a general overview of the clinical/real-world data and characteristics of the three monoclonal antibodies rituximab (RTX), ocrelizumab (OCR), and ofatumumab (OFA).

T and B cell hypothesis

MS is an autoimmune condition in which the activity of helper T cells, CD4+, CD8+ T cells, B cells, and macrophages leads to damage of the central nervous system tissue, crossing the blood–brain barrier, damage to myelin, and subsequent activation of glia [2]. The immune reaction of T cells leads to the sharp secretion of cytokines and tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma, stimulating an inflammatory response. It leads to gliosis, irreversible damage of myelin sheaths, axonal injury, and dysfunction of the blood–brain barrier. Therefore, MS has been considered to be a T cell-mediated disease.

Nevertheless, more and more, the significant role of B cells in the pathogenesis of MS is accepted. Over time, autoimmune activity targeting the myelin sheath results from dysregulation of Th cells and B cells. B cells are classified into two main types: B lymphocytes which are proinflammatory (secreting interleukins, granulocyte-macrophage colony-stimulating factor [GM-CSF], and TNF-alpha protein), and regulatory B lymphocytes as the second main type. The proinflammatory B cells control the activation of T cells towards the inflammatory reaction [3]. The increasing number of B cells during the disease within the CNS tissue in patients with MS suggests that they have an important role in the pathology of the disease. Thus, B cell depletion appears to be a target in MS therapy. The B cell lineage, involved in the chronic inflammatory process, expresses the antigen CD20, a transmembrane 33–35 kDa nonglycosylated protein. CD20 is a general B cell marker expressed in all stages of maturation of B cells, except by the first stages (early pro-B cells) and the last step (plasma cells) [4]. Therefore, the CD20-targeted therapy does not suppress the whole B cell lineage. CD20 also functions in the differentiation into plasma cells and activates antigen response independent from T cells. Recent studies have shown that T cells also highly express the CD20 marker, and they are actively involved in inflammation in MS patients [5]. Interestingly, the number of CD20 T cells in serum is elevated in persons with relapsing-remitting MS (RRMS) and with primary progressive MS (PPMS) compared to healthy controls [6]. The use of antibody therapies to remove B immune cells with CD20 expression makes it possible to interrupt the inflammatory cycle and immune-mediated myelin degeneration and achieve extended periods between relapses.

CD20-depleting immunotherapies

Rituximab

Rituximab (RTX) was the first agent against CD20 to treat MS patients. RTX is a human chimeric monoclonal antibody and was initially licensed to treat non-Hodgkin B cell lymphomas [7] and later to treat rheumatoid arthritis [8]. Since then, RTX has been evaluated in other autoimmune-mediated diseases, including MS. RTX leads to lysis of B cells by three pathways: antibody-dependent cellular cytotoxicity on CD20 B cells as the predominant mechanism of action, activation of complement and formation of membranolytic attack complex, and apoptosis. Although there is no relevant crossing of the blood–brain barrier by RTX, it eliminates B cells in cerebrospinal fluid (CSF) and the CNS perivascular space but has no measurable effect on the oligoclonal bands or the IgG index in CSF. After promising results in a phase I trial, data from a phase II trial (HERMES) were presented in 2008, in which 69 patients received RTX and 35 placebo [9, 10] (Table 1). The patients receiving RTX had a reduction in new and total active lesions at 12, 16, 20, and 24 weeks versus controls ($p \leq 0.001$). Furthermore, those treated with RTX had fewer relapses compared to controls at both 24 and 48 weeks (14.5% vs. 34.3%, $p = 0.02$) and a reduction in the annualized relapse rate (ARR) after week 24 (0.37 vs. 0.84, $p = 0.04$).

Even though there is a lack of formal phase III trials, evidence for the efficacy and safety of RTX is rising, and it has been applied with success as off-label therapy in different countries [18]. RTX has become the main DMT in Sweden for all MS types. The dosing regimen in Sweden is a course of 500 mg twice a year (every 6 months). A different, often used dosage is infusion of 1000 mg RTX IV 2 weeks apart, followed by 1000 mg every 6 months [19]. At least 30–60 min before RTX infusion, premedication with an antihistamine and methylprednisolone (100 mg or an equivalent) is recommended to prevent infusion-related complications [18]. In addition, paracetamol can be administered on the day of the infusion to avoid side effects such as headaches [20].

Patients should be monitored after the infusion for 1 h. However, due to the lack of phase III trials, no formal level I evidence exists for the use of rituximab, limiting its use in many countries. Nevertheless, a promising mechanism of action was pursued and resulted in the development of ocrelizumab.

Ocrelizumab

Ocrelizumab (OCR) is an intravenously used humanized anti-CD20 monoclonal B cell-depleting antibody. It binds to an overlapping epitope to that of rituximab and has higher antibody-dependent cellular cytotoxicity (ADCC) activity compared to RTX. Further-

Table 1 Overview of the RTX-, OCR-, OFA-therapies in different studies

Authors	Patients participated in trails	Trails	Clinical outcomes	Changes in MRI	Adverse effects (AE)
Summary of the treatment with rituximab in different studies:					
Hauser et al., 2008 [10]	104 RRMS patients	Phase II, 48 weeks, double-blind, randomized, placebo-controlled trial	Reduction of patients with relapse (24 and 48 weeks) and reduced ARR (24 weeks)	Reduced number active lesions under treatment	Infusion-related adverse effects in patients receiving RTX (78.3%). comparable infection rate between treatment arms
De Flon et al., 2016 [11]	75 patients with RRMS	Uncontrolled, open-label phase II study	No clinical approved data	Reduced number of active cerebral lesions	8% of the patients presented with severe AEs
Summary of the treatment with ocrelizumab in different studies:					
Kappos et al., 2011 [12]	220/RRMS	48 week, parallel, double-blind phase II, placebo-controlled trial	Reduction of ARR and in clinical disease activity	Decreased Number active lesions	More infusion-related adverse events in OCR
Hauser et al., 2017 [13]	Two trials: 821 and 835 RRMS	96 weeks, double-blind randomized, parallel-group, active-controlled trials, phase III	Decreased ARR	Reduction in T2 lesions and active lesions in OCR-treated patients	Moderate infusion-related events by OCR and IFN- β 1a. IgG low levels
Montalban et al., 2017 [14]	732/PPMS	120 weeks, double-blind, placebo-controlled randomized, phase III, with parallel-group trial	With OCR decrease in disability at weeks 12 and 24	In OCR-treated patients T2 lesion in brain reduced by 34%	Predominantly upper respiratory infections were reported
Summary of the treatment with ofatumumab in different studies:					
Sorensen et al., 2014 [15]	38 RRMS patients	Phase II, 48 weeks, placebo-controlled, randomized, double-blind trial	Lower incidence of relapses vs. placebo (19% vs. 25%)	Reduction of expanding and new MRI lesions and number of GAD-enhancing T1 lesions	Moderate adverse events
Bar-Or et al., 2014 [16]	231 RRMS patients	Phase II, 48 weeks, randomized, placebo-controlled, double-blind trial	No data	Dose dependence in the reduction of active lesions	Infection rate increased
Hauser et al., 2019 [17]	900 RRMS patients	(ASCLEPIOS I & II) 30 months, placebo-controlled, double-blind, randomized trials	In comparison to teriflunomide sufficient disease improvement	Reduction of radiological disease activity (number of T1, T2 and GAD lesions)	Estimated the same number of AEs compared to teriflunomide
ARR Annualized relapse rate, OCR Ocrelizumab, RTX Rituximab, OFA Ofatumumab, RRMS relapsing-remitting MS, PPMS progressive MS, SPMS secondary progressive MS, IFN- β 1a Interferon- β 1a					

more, there are data about the impact on CD20⁺ T cells found in MS patients. This suggests an alternative involved mechanism, which could be an alternative way of treating MS [21].

The double-blind OPERA I and II randomized trials assessed the efficacy and safety of OCR versus IFN-beta-1a in RRMS patients. These phase III studies over 96 weeks observed 821 and 835 patients with RRMS between 18 and 55 years. The patients were treated with 44 μ g of subcutaneous (sc) IFN-beta-1a three times a week or 600 mg of intravenous (iv) OCR every 24 weeks. The Expanded Disability Status Score (EDSS) in the studies ranged from 0 to 5.5, and the participants had had at least two clinical relapses in the 24 months or at least one in the past 12 months before study entry. In these studies, patients treated with OCR had a significant ($p \leq 0.001$) decrease in the annualized relapse rate (ARR) after 96 weeks compared to those receiving IFN-beta-1a (0.16 vs. 0.29). The proportion of participants with disability progression was less at 12 weeks (9.1 vs. 13.6% $p \leq 0.001$) as well as at 24 weeks (6.9 vs. 10.5% $p = 0.003$), and a 94% reduction of active lesions was seen in OCR-treated patients compared to IFN-beta-1 [13] (Table 1).

As with RTX, the infection risk associated with OCR therapy remains an important concern due to the profound depletion of circulating B cells. In the OPERA I and II trials, infections occurred in about 60% of patients receiving OCR compared to about 54% in patients receiving IFN-beta-1a [13]. However, the risk of infection in longer CD20 depletion remains open. No progressive multifocal leukoencephalopathy (PML) was reported in the OCR trials [14] (Table 1). After the market launch of OCR, PML cases were reported but are still under investigation to determine whether they are related to prior treatments [22]. In the RRMS trials, four malignancies (0.5%) were reported in patients treated with OCR compared with two cases (0.2%) in the IFN-beta-1a arm [13] (Table 1). However, during the COVID-19 pandemic, patients on CD20-depleting therapies, particularly OCR, were at risk for a severe course of SARS-CoV-2 [23]. Recent data further demonstrated that these patients had a reduced humoral immune response after standard SARS-CoV-2 vaccination and a third vaccination [24]. To obtain an optimal vaccination response, current guidelines recommend that the COVID-19 vaccine be applied 4 weeks before the new administration of CD20-depleting agents [25].

According to recent reports and if clinically justifiable, extending the infusion interval between anti-CD20 infusions may be another option to increase the chances of successful vaccination against SARS-CoV-2 [26, 27].

The United States Food and Drug Administration (FDA) approved OCR in March 2017, followed by the European Medicines Agency (EMA) in 2018 to treat RRMS and PPMS. The used dosing regimen is generally 300 mg at the beginning, followed by a second infusion after 2 weeks, and after that, every 6 months, 600 mg intravenously. Like in RTX, premedication with an antihistamine and methylprednisolone (100 mg) is recommended to prevent infusion-related complications, and patients should be monitored afterward for 60 min following OCR infusion. Like in RTX, paracetamol can be administered on the infusion day to avoid side effects such as headaches [20].

In addition to the promising data in the treatment of RRMS patients, OCR is the first treatment option available for patients with primary progressive multiple sclerosis (PPMS). The phase III trial enrolled 732 patients with PPMS in a 2:1 ratio treated intravenously with ocrelizumab (600 mg) or placebo every 24 weeks for 120 weeks. The results showed that OCR therapy was associated with a lower percentage of clinical and MRI disease progression compared to placebo [14] (Table 1). The safety profile was comparable to the RRMS trials.

Due to the success of anti-CD20 therapies and a better understanding of the role of B cells, different approaches to manipulating B cells are being developed to improve their effectiveness and minimize undesired effects. Ofatumumab (OFA) is a successful further development of this therapeutic approach, which has recently been approved.

Ofatumumab

Ofatumumab (OFA) is a human recombinant IgG1 CD20 next-generation monoclonal antibody [15] (Table 1). Like other CD20 drugs, it aims to decrease CD20 immune cells, acting on CD20 epitopes of the cells without eliminating B cell levels [28]. In animal studies, it has been demonstrated that the precise mode of action of OFA administered subcutaneously enables the drug to act precisely in the lymph nodes in which the B cell life cycle takes place [15] (Table 1), so that B cell depletion, which is important for MS treatment, takes place there. At the same time, the B lymphocytes in the peripheral blood and spleen, which help preserve protective immunity, are relatively spared [16] (Table 1).

To treat RRMS, OFA was investigated in two phase III trials [17] (Table 1). After 3 and 6 months, a relative reduction of the ARR was reported in the OFA arm (50.5% and 58.5%, respectively) compared to teriflunomide. In addition, the risk for confirmed dis-

ability was significantly reduced (34.4% and 32.5%, respectively). The most frequent side effects were mild to moderate injection-related events on the same or the following day of application and were mainly related to the first OFA injection and decreased in frequency with further doses. The incidence of adverse events was similar in both treatment arms, and there was no evidence of increased malignancy [17] (Table 1). An ongoing open-label study is evaluating the long-term effectiveness, safety, and tolerability in patients with RRMS (ClinicalTrials.gov identifier: NCT03650114).

In the face of the COVID-19 pandemic, the question arises of how ofatumumab affects the efficacy of vaccination against SARS-CoV-2. Recently published preliminary data suggest that in MS patients treated with OFA, the third vaccination with mRNA vaccines induces a stronger humoral immune response than two vaccinations alone [29]. The ongoing KYROS study is an open-label, nonrandomized, prospective study of 40–60 RRMS patients treated with OFA, investigating specific T cells and humoral immune response after vaccination against SARS-CoV-2 (ClinicalTrials.gov Identifier: NCT04869358). Another study observed the severity of SARS-CoV-2 infection in OFA-treated patients with RRMS and revealed that the course of the infection was mostly mild to moderate [30].

OFA is the first mAb administered by subcutaneous injection by patients at 4-week intervals without visiting the medical center/hospital, whereas RTX or OCR are administered intravenously.

Future perspectives of anti-CD-20 treatment

A novel anti-CD20-targeted agent is ublituximab (UTX). It is a third-generation glycol-engineered chimeric anti-CD20 mAb that targets an epitope other than OFA or OCR. A phase II multicenter study including 48 patients with RRMS demonstrated UTX to provide a complete (>99%) CD20 depletion within the first 28 days after initial application [31]. The ARR at week 48 in the investigated population was 0.07, and 93% of patients perceived no new relapses during the study. After 48 weeks, the radiological and clinical evaluation revealed that 74% of the patients met the NEDA-3 criteria. The most common side effects were grade 1 or 2 infusion-related reactions in 11% of the patients. No severe adverse effects were noted [31]. After a median follow-up time of 125 weeks in an open-label extension trial, this safety profile was not changed [31]. Currently, UTX is being tested against teriflunomide in two phase III studies (ULTIMATE I and II) in RRMS-patients (ClinicalTrials.gov Identifier: NCT03277261, ClinicalTrials.gov Identifier: NCT03277248).

Current guidelines for the treatment of SARS-CoV-2 in CD20-depleted patients

Treatment with CD20-depleting agents is associated with a blunted humoral immune response after vaccination against SARS-CoV-2 and a severe course of COVID-19 disease [32–34]. Passive immunization with SARS-CoV-2-neutralizing monoclonal antibodies may be effective in the early phase of COVID-19 infection, as these neutralizing monoclonal antibodies can partially neutralize the virus before it causes severe COVID-19 disease. Therefore, current guidelines recommend treatment with the antibody combination casivirivimab/imdevimab (Ronapreve®), approved for treatment in the EU since November 2021. Sotrovimab (Xevudy®) is another monoclonal antibody recently approved in the EU to treat immunocompromised patients with SARS-CoV-2 infection [30]. Both agents should be administered as soon as possible after exposure to SARS-CoV-2.

Conclusion

The opinion that the pathogenesis of MS is mainly T cell-mediated, which prevailed for many decades, has been supplemented in recent years by new findings regarding the importance of B cells. For example, human tissue pathology studies have shown infiltration of B cells, especially tertiary lymphoid-like structures in the meninges, and B cell studies in the peripheral blood and cerebrospinal fluid in MS patients have revealed anomalous production of inflammatory cytokines by B cells as well as excessive levels of B cell-related chemokines. As knowledge about the importance of B cells in the pathogenesis of MS grew, the first off-label treatment trials with RTX were conducted [35]. The data were so promising that B cell-depleting therapy with RTX became standard in some countries, although having no formal phase III trials [19]. The further development of this therapeutic approach led to phase III trials with OCR with a convincing efficacy and side effect profile, which was confirmed in real-life experience in patients with both RRMS and PPMS [14, 36]. However, in some regions of the world, RTX remains the mainstay of MS treatment, not least because of its lower price compared to other MS therapeutics [19, 37].

The most recent approved development, OFA, has further enriched the therapeutic spectrum. The subcutaneous use of OFA is an advantage and a simplification of therapy for some patients. In contrast, others who cannot administer a subcutaneous drug themselves or who appreciate personal care during an infusion can continue with intravenous CD20-depleting therapy.

In summary, recognizing the pathogenetic significance of B cells in MS and the therapeutic options developed as a result can be seen as a success story. However, where there is light, there is also shadow

in the course of the COVID 19 pandemic. Recently published data show that MS patients treated with B cell-depleting therapies have a higher risk of severe SARS-CoV-2 [23]. Furthermore, there is evidence that at least the mRNA vaccines against SARS-CoV-2 may not have the same efficacy in these patients, even after a third immunization, as in patients treated with other non-B cell-affecting therapies [24, 33]. It is currently unclear whether these data will influence the future use of B cell-depleting therapies. Furthermore, further research is needed to assess the total benefit–risk relationship of anti-CD20 agents. New scientific approaches towards understanding the pathways by which depletion of B cells is so efficient in MS will further help to understand the pathogenesis of multiple sclerosis.

Conflict of interest A. Ovchinnikov and O. Findling declare that they have no competing interests.

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