

Mini-review

# The Arrival of B Cell Targeted Monoclonal Antibody Therapies in Multiple Sclerosis

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## Abstract

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. There is a growing body of evidence that many of the cells along the B cell lineage play a pivotal role in the pathogenesis of MS. We are currently in the midst of a therapeutic revolution within the field of MS, and the newer disease modifying therapies have proven to be very effective at controlling disease activity. Among the most efficacious therapies for MS are monoclonal antibodies (mAbs). In this review, we will focus on understanding the role B cells play in the pathogenesis of MS, and we will discuss B cell targeted mAbs, with a specific focus on anti-CD20 mAbs.

**Keywords:** monoclonal antibody, B cell, multiple sclerosis, rituximab, ocrelizumab, ofatumumab

**Abbreviations:** ADCC: Antibody-Dependent Cell-mediated Cytotoxicity; APC: Antigen Presenting Cell; ARR: Annualized Relapse Rate; CDC: Complement-Dependent Cytotoxicity; CDP: Confirmed Disability Progression; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; EDSS: Expanded Disability Status Scale; FDA: Food and Drug Administration; IFN- $\beta$ 1a: Interferon-beta 1a; mAb: Monoclonal Antibody; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; OCB: Oligoclonal Band; PML: Progressive Multifocal Leukoencephalopathy; PPMS: Primary Progressive Multiple Sclerosis; RRMS: Relapsing-Remitting Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; Th: T helper

## Introduction

Multiple Sclerosis (MS) is the prototypical central nervous system (CNS) autoimmune disease because it has no systemic manifestations or other direct organ involvement. MS affects nearly 1500 per 1,000,000 people per year [1]. The diagnosis is based on the McDonald's criteria that stipulate the presence of CNS lesions and clinical attacks separated in time and space [2]. Two separate clinical attacks involving two independent regions of the CNS (i.e., spinal cord, infratentorial, juxtacortical, and periventricular) are needed to confirm the diagnosis. Due to the heterogeneity of the location, size, and clinical effect of these lesions, the variability of clinical presentation is

substantial. The target of the immune attack is the protein produced by the oligodendrocyte, which forms an intricate matrix that envelopes and protects the nerve axon with multiple layers, known as the myelin sheath [3]. The demyelination of the neuron can lead to axonal destruction that contributes to the neurodegenerative features of MS. The factors that lead to the autoimmunity are not fully understood but are known to involve genetic and environmental components. The majority of patients will exhibit a relapsing and remitting pattern, while a small minority shows either a purely progressive pattern or relapsing progressive pattern. For the last several years, T cells were thought to be the main source of pathogenicity in MS, but more recent evidence has emerged to suggest that B cells are equally implicated. The purpose of this article will be to discuss the role of B cells and B cell mediated therapies in the treatment of MS.

## Immunopathology of Multiple Sclerosis

MS is an immune-mediated demyelinating disease that affects the CNS, with predilection for both white and grey matter [4]. Over the last few decades, innovative studies including utilization of the experimental autoimmune encephalomyelitis model have advanced the understanding of the immunopathology of MS while unearthing key therapeutic targets [5]. Still, the etiology of MS remains unclear. Some proposed etiologic factors for MS include environmental influences (e.g., Vitamin D, Epstein-Barr virus, tobacco smoking), genetic vulnerability (e.g., HLA-DRB1\*1501) and immune system factors [4]. Regarding the latter, the dysregulated immune system in patients with MS facilitates two significant abnormal pathological responses. The first response is focal inflammation aiding a breach of the blood brain barrier leading to macroscopic plaques [6]. This macroscopic injury is a hallmark of relapsing forms of MS and correlates with contrast enhancing lesions on magnetic resonance imaging (MRI). The second includes microscopic injury activating a neurodegenerative process, which is thought to be more prominent in progressive forms of MS [7]. Though both the adaptive and innate immune responses are believed to have roles in the pathogenesis of MS, therapies to-date have focused largely on targeting the adaptive immune components, namely T cells. This is based on the accepted view that a portion of the immune mediated damage in MS is secondary to the systemic autoreactive CD4+ T helper cells' effect on myelin components of the CNS, along with accompanying proinflammatory cytokine production and T helper (Th) 1 and Th17 reactions [4,6]. The systemic proinflammatory T cell response ultimately results in demyelination, glial activation and subsequent loss of neurons and axons [4,6]. Conversely, more recent data from novel clinical trials demonstrates clear efficacy of B cell depleting therapies in patients with both relapsing and progressive forms of MS [8,9]. This has promoted a surge of interest toward further understanding the important role of B cells and B cell related therapies in MS, which is the emphasis of this review.

## B cells in Multiple Sclerosis

B cells are one of the key components of the adaptive immune system and regulate CNS inflammation in various ways. Some essential roles of B cells include antigen presentation, proinflammatory and anti-inflammatory cytokine production, antibody production/secretion and immune system memory upon re-exposure to formerly encountered antigens [5]. B cells have been found in the CNS tissue and cerebrospinal fluid (CSF) of patients with MS yet remain a relatively rare finding in these areas in healthy control subjects. Some of the early evidence that B cells are involved in the pathogenesis of MS originates from the detection of the characteristic oligoclonal immunoglobulins or oligoclonal bands (OCB) in CSF [6]. More than 90% of patients with MS have CSF OCBs present [10]. Additionally, meningeal lymphoid follicles with germinal centers have been detected in patients with progressive MS and have been linked to more severe cortical demyelination and neurological disability [11]. Even more impressive is the increasing clinical trial data indicating successful outcome measures in patients with MS treated with B cell

targeted monoclonal antibody (mAb) therapies. For example, clinical trials OPERA I and OPERA II displayed successful reductions in annualized relapse rates, a decrease in disability progression, and a reduction in the number of lesions on MRI with B cell depleting therapy compared to interferon beta-1a (IFN- $\beta$ 1a) [8]. Furthermore, the ORATORIO trial revealed a lower relative risk of disability progression after treatment with a B cell depleting therapy when compared to placebo [9]. The specifics regarding B cell targeted mAb therapies will be discussed in further detail in the subsequent sections.

## **B cell (CD20) Targeted Monoclonal Antibody Therapies**

The CD20 antigen is expressed on most cells of the B cell lineage, from pre-B cell to mature B cells, but not on stem cells, pro-B cells or plasma cells [12]. Three anti-CD20 mAbs (rituximab, ocrelizumab, and ofatumumab) have been studied in phase II and III clinical trials in relapsing MS, and a fourth anti-CD20 mAb, ublituximab, is currently in clinical development. Additionally, ocrelizumab has shown efficacy in primary progressive MS (PPMS). Given that CD20 targeting via anti-CD20 mAbs results in depletion of circulating B cells with sparing of stem cells and plasma cells, it would be expected that there is preservation of humoral immune responses via plasma-cell mediated antibody production.

### **Rituximab**

Rituximab is a chimeric mAb against B cells expressing CD20 (not plasmablasts or plasma cells) leading to apoptosis, via complement-dependent cytotoxicity (CDC) and to a lesser extent antibody-dependent cell-mediated cytotoxicity (ADCC), of B cells and their peripheral depletion [13]. The efficacy of rituximab in relapsing MS was tested in the phase II trial HERMES, a randomized, double-blind study involving 104 patients, 69 of whom received rituximab compared to 35 patients who received placebo. Rituximab-treated patients had a significant reduction (91%) in the total number of T1 gadolinium-enhancing lesions on brain MRI ( $p < 0.001$ ) and a lower annualized relapse rate (ARR) at 24 weeks (58%) ( $p = 0.04$ ) [14]. Phase III trials with rituximab have not been carried out in relapsing-remitting MS (RRMS) to look at disease modification; however, a retrospective, uncontrolled observational study in a Swedish cohort of 822 patients - including 557 with RRMS, 198 with secondary progressive MS (SPMS), and 67 with PPMS - has been completed. In the RRMS patients, stability of disease over 21 months as measured by Expanded Disability Status Scale (EDSS) was noted, although it was not statistically significant ( $p = 0.42$ ), and the ARRs were 0.044 (RRMS), 0.038 (SPMS), and 0.015 (PPMS) [15]. In PPMS, a phase II/III randomized, double-blind, parallel-group, placebo-controlled study (OLYMPUS) showed that rituximab reduced T2 lesion volume on brain MRI, and trends were observed in subgroup analyses on delay of clinical disease progression in younger patients ( $< 51$  years of age). Unfortunately, the primary endpoint of the study, the reduction of time to confirmed disability progression (CDP) over 96 weeks, was not met [16].

The adverse effects of rituximab have been mostly infusion-related, most often occurring within the first 24 hours post-infusion and most commonly including chills, rigors, hypotension, headache, nausea, fatigue, rash or pruritus, with mild to moderate severity. Upper respiratory and urinary tract infections have occurred, and serious infections have been rare; however, neither severe opportunistic infections nor any progressive multifocal leukoencephalopathy (PML) cases have been reported to-date in MS patients treated with rituximab. It is worth noting that PML has been observed in other autoimmune conditions, notably rheumatoid arthritis and systemic lupus erythematosus, but these cases were confounded by patients receiving additional immunosuppressive therapy concurrent with or just prior to rituximab therapy [17].

## Ocrelizumab

Ocrelizumab is a recombinant humanized IgG1 antibody that binds to the CD20 antigen with a higher affinity compared to rituximab and on a different, but overlapping, epitope [18]. Given that is a humanized mAb, it is expected to have a reduced immunogenicity potential. Also, compared to rituximab, ocrelizumab has a reduced CDC and an increased ADCC [13,19].

Ocrelizumab was studied in relapsing MS in a phase II randomized, parallel, double-blind, placebo-controlled trial where patients received either placebo, low-dose (600mg) or high-dose (2000mg) ocrelizumab, or once-weekly intramuscular IFN- $\beta$ 1a 30 $\mu$ g. The primary outcome measure of the study was the effect of ocrelizumab on the total number of T1 gadolinium-enhancing lesions on brain MRI. At week 24, ocrelizumab-treated patients had a significant reduction in T1 gadolinium-enhancing lesions for both the 600mg arm (89% relative reduction;  $p < 0.001$ ) and the 2000mg arm (96% relative reduction;  $p < 0.001$ ) compared to placebo.

Two phase III double-blind studies were then completed with ocrelizumab (OPERA I and II) involving 1656 patients randomized in a 1:1 fashion to receive either ocrelizumab 600mg intravenously every 24 weeks or IFN- $\beta$ 1a 44 $\mu$ g subcutaneously three times per week. The results showed that ocrelizumab-treated patients had a significant reduction in ARR compared to IFN- $\beta$ 1a (47%,  $p < 0.0001$ ) and a reduced risk of CDP of 40% at 12 ( $p < 0.0006$ ) and 24 weeks ( $p < 0.0025$ ) [20]. ORATORIO was a randomized, double-blind, placebo-controlled phase III PPMS study in which 732 patients received either ocrelizumab 600mg or placebo intravenously every 24 weeks for a minimum of 120 weeks. Patients were randomized in a 2:1 fashion, and the primary endpoint was time to CDP, which was defined as  $\geq 12$ -week sustained increase in EDSS score. The results showed a significant reduction in time to CDP in ocrelizumab-treated patients at 12 ( $p < 0.0321$ ) and 24 weeks ( $p < 0.0365$ ) [9].

In the aforementioned phase III studies with ocrelizumab, the most common adverse events were infusion-related reactions, which were mostly mild to moderate in severity [14,20]. There was an increased risk of infections with ocrelizumab, with respiratory infections, mostly mild to moderate in nature, being the most common. PML has not yet been reported with ocrelizumab use, but given that another anti-CD20 therapy, rituximab, does have reported cases in other autoimmune conditions, long-term safety monitoring in both the ongoing extension studies and post-marketing safety surveillance is needed.

Based on the data from the aforementioned phase III RRMS and PPMS studies, the Food and Drug Administration (FDA) approved ocrelizumab for both relapsing and primary progressive forms of MS on March 28, 2017, making it the first MS therapy to be approved for both forms of the disease.

## Ofatumumab

Ofatumumab is a fully humanized IgG1 mAb that targets CD20 B cell lineage cells. Its specific difference compared to rituximab and ocrelizumab, other than being fully humanized, is that it targets a different epitope than these two therapies [18]. Given that it is a fully humanized antibody, it is likely to have an improved safety profile due to its low immunogenic risk. It was first studied and FDA-approved in 2009 as a treatment for chronic lymphocytic leukemia [21]. Two separate phase II trials have been completed evaluating its effect in patients with relapsing MS. The first was a randomized, double-blind, placebo-controlled study with 38 patients. These patients were randomized to receive either placebo or one of three different doses of ofatumumab (100mg, 300mg, or 700mg) given as two infusions separated by 2 weeks [22]. At week 24, patients received an alternate treatment. The MRI efficacy endpoints showed significant reduction in the total number of T1 gadolinium-enhancing lesions from weeks 8 to 24 ( $> 99\%$ ). Additionally, there were significant reductions in number of new T1 gadolinium-enhancing lesions ( $p < 0.001$ ), total number of T1 gadolinium-enhancing lesions ( $p < 0.001$ ), and new or enlarging T2 lesions ( $p < 0.001$ ). Human

antihuman antibody formation did not occur in any patients, nor did any patients experience an opportunistic infection during the study. The other phase II clinical trial for relapsing MS, the MIRROR study, had a randomized, double-blind, placebo-controlled, parallel-group structure with patients receiving subcutaneous ofatumumab administered either every 4 weeks (60mg) or every 12 weeks (4mg, 30mg, or 60mg), or placebo [23]. There was a significant reduction of >90% of new T1 gadolinium-enhancing lesions from weeks 4 to 12 in ofatumumab-treated patients ( $\geq 30\text{mg}$ ) compared to placebo ( $p < 0.001$ ). Similar to the previous phase II study, ofatumumab-treated patients did not experience any opportunistic infections, but 52% of patients treated with ofatumumab did report injection-related reactions (compared to 15% of placebo-treated patients).

Given the promising results of these phase II studies, there are two randomized, double-blind, double-dummy phase III clinical trials currently enrolling to evaluate the safety and efficacy of ofatumumab compared to teriflunomide in relapsing MS (ASCLEPIOS I and II) [24].

### Ublituximab

An additional anti-CD20 mAb, ublituximab, is undergoing a phase II randomized, double-blind, multicenter study for relapsing MS [25]. Ublituximab is a novel, B cell targeted mAb that binds to the CD20 antigen on a unique epitope different from that of other anti-CD20 mAbs including rituximab and ofatumumab. Preclinical data with ublituximab has shown that natural killer cells were better able to cause ADCC B cell destruction in comparison to rituximab in patients with Waldenstrom macroglobulinemia [26]. This enhancement in ADCC is due to ublituximab being glycoengineered to exhibit a low-fucose fragment crystallization region [27].

### Other B cell (non-CD20) Targeted Monoclonal Antibody Therapies

With respect to B cell development, the CD19 antigen, in contrast to the CD20 antigen, is also expressed on pro-B cells, plasmablasts and plasma cells [28]. Therefore, mAbs that target CD19 have the potential to have improved efficacy over CD20 targeted mAbs, as they will target both circulating B cells and pathogenic autoantibody-producing cells [29]. MEDI-551, an anti-CD19 mAb, has shown in animal models to deplete a broad array of B cells as well as lower most disease-driving autoantibodies but with relative preservation of total serum immunoglobulin levels [30]. MEDI-551 was recently studied to assess the tolerability and safety in relapsing MS via a phase I randomized, blinded, placebo-controlled, dose-escalation study [31]. The study has been completed; however, the data have not been published. Therefore, the efficacy of anti-CD19 mAbs for relapsing MS remains unclear at this time.

### Conclusion

The long-standing axiom in the pathogenesis of MS is that T cells play a central role. However, given the excellent efficacy of B cell targeted therapies in clinical studies, is it becoming quite clear just how significantly B cells contribute to the pathogenesis of MS. B cells have a multi-faceted role within the human body. They serve as antibody secreting cells, antigen presenting cells, and potent producers of pro-inflammatory cytokines. The early disease course of MS is dominated by acute bouts of CNS inflammation, and based on these immunological properties, B cells seem to have a direct contribution to acute relapses. Additionally, a subset of B cells seems to help produce anti-inflammatory cytokines, among other immunological effects, that promote the down-regulation of CNS inflammation, thus contributing to the resolution of acute relapses. Therefore, B cell targeted therapies have the double-edged potential to aid in the removal of pathogenic immune responses involved in MS but also hinder the beneficial regulatory aspects that B cells provide. How to balance this negative and positive impact of B cell depletion will be the aim of future studies in MS.

The approval of an anti-CD20 mAb, ocrelizumab, has been a welcome addition to the treatment armamentarium for relapsing forms of MS and has offered promise to PPMS patients who have desperately awaited an approved therapy for this often aggressive form of the disease. Given the success of the current FDA-approved mAb therapies in MS, including a B cell targeted mAb, a number of new mAb therapies are currently being investigated in clinical trials. The future looks very promising for improving the treatment of MS.

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