Review Article

The Role of Ocrelizumab in Multiple Sclerosis Treatment; Literature Review

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Abstract

Multiple sclerosis is a common leading cause of disability worldwide. CD20-expressing B cells play a major role in multiple sclerosis pathogenesis. Hence, anti-CD20 monoclonal antibodies effectively deplete B cells mainly by complement-dependent cytotoxicity, antibody-dependent cell-mediated phagocytosis, and antibody-dependent cellular cytotoxicity. While the precise etiology remains unknown, it is now recognized that environmental factors, such as smoking, vitamin D deficiency, Ebstein-Barr virus (EBV) infection, adolescent obesity, and sedentary lifestyle in addition to certain genes that are involved in disease progression. This literature reviews the current data supporting the efficacy and safety of ocrelizumab in the multiple sclerosis population. Relevant articles to the topic were searched in the PubMed database. The MeSh words were used are multiple sclerosis, anti-CD20 monoclonal antibodies, and ocrelizumab. Anti-CD20 monoclonal antibodies, particularly ocrelizumab, have gained attention in this targeted population. Based on the currently available data, ocrelizumab seems effective in B cells depletion and provides favorable outcomes in multiple sclerosis patients. Nevertheless, although most reported adverse events are infusion-related, several reported serious infections were reported in response to ocrelizumab infusion.

Keywords: Multiple sclerosis, Ocrelizumab, AntiCD20, Demyelinating disease

Introduction

Multiple sclerosis (MS), which is a chronic autoimmune inflammatory demyelinating disease, affects the CNS [1, 2]. It is a broad disabling and debilitating neurological condition commonly diagnosed in the young adult population. MS affected individuals are commonly affected those between twenty and forty years of age, and it is considered the most prevalent autoimmune inflammatory demyelinating disease worldwide. Common clinical features are bladder dysfunction, pain, sexual impairment, tiredness, visual changes, muscular spasm, spasticity, cognitive dysfunction, and mood changes [1].

Additionally, MS lesions can result in severe motor abnormalities, including several motor spasticity, weakness, tremor, and ataxia. Upper motor neuron (UMN) signs, such as spasticity, resulted from losing inhibitory inputs from the corticospinal tract to γ-motor neurons and interneuron networks. Weakness and fine motor control impairment resulted in interruption of input to α-motor neurons. Although the primary pathologic findings in MS are UMN in nature, a chronic disease often causes muscle weakness, wasting, and atrophy, representing lower motor neuron disease [3].

While the precise etiology remains unknown, it is now recognized that environmental factors, such as smoking, vitamin D deficiency, Ebstein-Barr virus (EBV) infection, adolescent obesity, and sedentary lifestyle in addition to certain genes that are involved in disease progression [1, 2]. Immunological, genetic, and histological trials of MS patients support the theory that autoimmunity plays a significant role in disease pathophysiology. In addition, it is also well recognized that MS also results in neurodegenerative sequelae [2].

The course of MS is highly variable and classified into four subclasses. Most MS patients experienced recurring clinical

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symptoms followed by total or partial recovery, which was identified as the classical relapsing-remitting form of multiple sclerosis (RRMS), affecting 85% of the US population [1-3]. After ten to fifteen years, the disease course switched to progressive in up to 50% if the patient left untreated, for which the clinical manifestations slowly resulted in a progressive deterioration over many years, defined as secondary progressive multiple sclerosis. Around 10-15% of MS patients experienced a relentless disease progression from the onset, identified as a primary progressive multiple sclerosis (PPMS) [2, 3]. The fourth subclass is a clinically isolated syndrome (CIS), referred to as the primary acute demyelination attack in the CNS, which carries a high risk of developing MS, particularly if associated with MRI brain lesions similar to the MS lesions [1].

Discrete attacks of neurological dysfunction that occur over hours to days are called flares, relapses, or exacerbations. MS is diagnosed following two distinct attacks of neurological deficits within at least 30 days apart in several CNS locations [3]. In the latest decades, better comprehension of the mechanism underlying RRMS causes the evolution of various disease-modifying agents, in which suppressing or altering the immune system helps decrease the intensity and incidence of new relapses [2]. The most effective MS therapy is the one targeting B cells, including monoclonal antibodies that deplete B cells by the mechanisms of antibody-dependent cellular cytotoxicity (ADCC), antibody-triggered apoptosis, and complement-dependent cytotoxicity (CDC). Moreover, other therapeutic methods include blocking Bruton's tyrosine kinase and targeting B cells cytokines or their receptors. All other MS therapeutic strategies have resulted in suppression or immunomodulatory on B cells function [4].

Results and Discussion

The Role B Cells in the MS Pathogenesis

B cells represent a significant role in the MS pathogenesis through producing autoantibody, presentation of antigen, producing pathogenic cytokine, and meningeal ectopic lymphoid tissues formation [5]. Systemic B and T cell activation of immune cells and their diapedesis through the blood-brain barrier (BBB) describe the relapsing-remitting disease aspect. It is initially suggested that B cells involvement in MS through the presence of CSF-specific oligoclonal bands (OCBs) in most patients with MS, and autopsy studies found antibodies that are bound to myelin remnants within phagocytic cells in the CNS tissues [6, 7]. Indeed, OCBs are detected in more than 90% of MS cases along with elevated intrathecal IgG levels, and in patients with CIS, the presence of OCBs is predictive of conversion to MS [7, 8].

Additionally, B cells, plasmablasts, and plasma cells are increasingly found in the CSF of MS patients, correlating to intrathecal immunoglobulin synthesis and CNS inflammation [7].

Although OCBs show the activation of a limited number of B cell subsets in the CNC with the production of local antibodies. B cells were neglected in MS research for decades due to their seemingly trivial role in experimental autoimmune encephalomyelitis (EAE) [8].

Immunoglobulin and complement deposition in actively demyelinating lesions have been notified in the brain of MS cases; however, comparable findings have also been described in other neurological diseases without any pathological significance. Nevertheless, plasma cells in progressive MS brain and a higher perivascular infiltration of CD20 B cells in RRMS brain compared with normal brain or another inflammatory brain has lately been identified, implying a continuous B cells differentiation in plasma cells. Also, B cells act as antigen-presenting cells (APCs) activating T cells, but in patients with MS, in comparison with healthy donors, naive B cells and memory induce a more significant differentiation and activation of CD + T cells to respond to neuro-antigens, like myelin oligodendrocyte glycoprotein (MOG) and myelin binding protein (MBP) [7].

Introduction to AntiCD20 and Its Role in the Pathogenesis of MS

CD20 is a transmembrane ion channel protein found on the surface of pre, immature, mature, and memory B cells, and to some extent, on early plasmablasts [4, 9]. The MS4A1 gene encodes it *on chromosome 11* with a 33-36 kD molecular weight. CD20 presented as tetramers associated with lipid rafts and suggested to be associated with the calcium release from the intracellular store during B-cell activation on the cell surface. CD20 molecules, which are expressed on the lineage of the B cells from the pre-B cell to the early plasmablast stage, are targeted by Anti-CD20 antibodies. CD20 is also expressed to a lesser extent on a subset of T cells. Anti-CD20 is classified into type 1 and type 2 antibodies based on the mechanisms by which B-cell depleted. Type 1 anti-CD20 antibodies cross-link CD20, leading to the buildup of CD20 aggregates molecules in lipid rafts and allowing for effective activation of complement-dependent cytotoxicity. In comparison, type 2 anti-CD20 antibodies are unable to cross-link CD20 molecules in rafts and do not activate complement. However, they stimulate programmed cell death more effectively than type 1 antibodies [10].

Notably, by binding to the Fc domain of the antibody, complement-dependent cytotoxicity (CDC), and antibody-dependent cell-mediated phagocytosis (ADCP), all anti-CD20 antibodies provoke antibody-dependent cellular cytotoxicity (ADCC) regulated [9-11]. Current anti-CD20 monoclonal antibodies provoke B-cell depletion mainly by ADCC, ADCP, and CDC [11]. Importantly, some T cells express CD20 as well, directly correlating to the disease intensity, and may accordingly influence the therapeutic impact of anti-CD20 therapy [9]. The infusion of anti-CD20 monoclonal antibodies induces CD20 B cells depletion within hours, mainly hepatic, for which it returned to the base

typically after 8 weeks and can be remained for several weeks to months based on the posology and the specific characteristics of anti-CD20 monoclonal antibody [11].

Ocrelizumab; Introduction, Mechanism of Action, And Adverse Events

Ocrelizumab is a refined anti-CD20 monoclonal antibody, the first agent recommended for treating relapsing multiple sclerosis and PPMS, based on the Phase III OPERA I/II and ORATORIO results [12, 13]. Although the mechanisms of ocrelizumab on MS are not entirely understood, its effect is thought to be related to selectively binding to and depleting CD20-expressing B cells [14]. It mediates its effectiveness on CD20-expressing cells by greater ADCC and low CDC activity. Therefore, it was unclear if ocrelizumab might also deplete CD20 T cells that express CD20 to a lower extent than B cells. However, ocrelizumab was found to deplete CD20-expressing T cells along with CD 19 and CD20 B cells 14 days following the administration of one 300mg dose of ocrelizumab [15]. The latter finding concludes that CD20 T cells might present a significant role in the pathophysiology of MS and subsequently be suppressed by ocrelizumab [15].

Infusion-related reactions are the most popular unfavorable outcome reported with ocrelizumab, more common with the first dose, and decreased with consequent dosing [12]. Nonetheless, ocrelizumab has reported an increased risk of serious infection in other studies [16]. Ocrelizumab is currently given as initial two doses of 300mg intravenous infusions two weeks apart, each lasting for at least 2.5 hours. The following doses are given every six months as a single 600 mg infusion lasting at least 3.5 hours [12, 13]. Moreover, the average time for B cells depletion is 72 weeks. B cell counts of 90% of patients increased to either lower normal level or baseline within 2.5 years [9]. In phase I of a study involving 26 patients with MS, the B cells were reconstituted to a mean of 34.5% of baseline 46 weeks following the treatment of rituximab, with a predominance of naive cells [9]. Ordinarily, before each infusion of ocrelizumab, the infusion schedule includes pre-medication 30-60 minutes to minimize systemic reactions and one-hour observation post-infusion [12, 13].

Evidence-Based Medicine

Ocrelizumab was first studied in MS patients in a phase II trial, where two doses (600mg and 2000mg) were evaluated in RRMS in a phase II randomized, multicenter, double-blind placebo-controlled trial involving 79 centers in 20 countries. RRMS patients who received intravenous ocrelizumab 600mg and 2000mg on days 1 and 15 were compared to intramuscular weekly IFNβ-1a 30μg or placebo. 220 patients who finished a 24-week trial found a highly significant difference in the entire number of gadolinium-enhanced T1 lesions in the ocrelizumab groups at weeks 12, 16, 20, and 24 in comparison with the placebo group. The relative reductions were 89% in the 600mg ocrelizumab group and 96% in the 2000 mg ocrelizumab group in comparison to the placebo group. Annualized relapse rate (ARR) was significantly decreased compared with the placebo but did not reach statistical significance compared to IFNβ-1a [17, 18].

In the ORATORIO trial, phase III, 732 patients with PPMS were randomized to ocrelizumab 600mg or placebo every 24 weeks for at least 120 weeks. The percentage of patients with 12-week CDP (primary endpoint) was significantly lesser following ocrelizumab treatment than in the placebo group. Likewise, the percentage of patients in the active treatment group with 24-week confirmed disability progression (CDP) was significantly reduced. Moreover, the total volume of brain lesions on T2-weighted MRI scans (radiological endpoint) decreased by 3.4% in the ocrelizumab group and increased by 7.4% in the placebo group [19].

In a retrospective study including consecutive patients with MS who received ocrelizumab, no evidence of disease activity (NEDA) status was achieved at year 1 in 91.2% of the relapsing MS population. Also, disability progression was observed in 37.5% of the PPMS population in a median follow-up period of 19 months. This trial was conducted on 228 MS patients, where 144 RRMS, 25 SPMS, and 59 PPMS. Common adverse events were infusion-related and self-limiting [20]. Notably, a systematic review conducted by McCool *et al*. approved the superiority of ocrelizumab in 12-week CDP and ARR compared to placebo. In addition, this analysis showed that ocrelizumab is superior to all other currently approved disease-modifying therapies in MS with a similar safety profile [21].

Conclusion

B cells represent a significant role in the pathophysiology of multiple sclerosis. Anti-CD20 monoclonal antibodies, particularly ocrelizumab, have shown great efficacy in the treatment of multiple sclerosis with a favorable safety profile. It effectively suppresses the CD20-expressing B cells, resulting in improved annualized relapsing rate, brain MRI lesions, and other multiple sclerosis parameters. Although most adverse events are infusion-related, some concerns were raised regarding the increased risk of serious infection. Nevertheless, further randomized clinical trials are warranted to establish the effectiveness and safety of ocrelizumab in those populations.

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