

A Comparison of B Cell-Targeting Treatments for Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is the most common chronic inflammatory neurodegenerative disease in young adults and a leading cause of nontraumatic neurological disability. The cause of MS is not fully understood, but both genetic and environmental factors are believed to play a role. B cells are an important part of the immune response and have been shown to play a significant role in MS. This paper reviews studies on various B cell-targeting treatments for MS to determine which are the most effective at specific stages of the disease. In the end, all of the treatments that were investigated were found to be effective for treating relapsing-remitting MS, and results varied for primary progressive and secondary progressive MS.

Introduction

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS), where the immune system attacks the myelin sheath coating the axons of neurons. It is the most common cause of nontraumatic neurological disability in young adults [1]. An estimated 900,000 people in the US and 2.8 million worldwide have MS, with its prevalence increasing, and women are twice as likely as men to have MS [2,3]. Common symptoms include numbness or weakness in the limbs or torso, tingling, lack of coordination, blurry vision, vertigo, and hearing loss. There are three main clinical subtypes of MS. Relapsing-remitting multiple sclerosis (RRMS) is most common at the onset of MS, where episodes of disease activity, or relapses are followed by periods of partial or complete remission. Usually, relapses become less frequent and RRMS develops into secondary progressive multiple sclerosis (SPMS). In SPMS, disease worsening is gradual and generally uninterrupted with occasional relapses. In some cases, progressive worsening occurs from the onset of the disease, and this is known as primary progressive multiple sclerosis (PPMS) [1].

While the exact cause of MS remains unknown, several environmental factors have been associated with MS. These include vitamin D levels, Epstein-Barr virus infection, and tobacco smoking [3]. Some genetic factors involved in the immune system, such as the HLA-DR1*15:01 allele, have been associated with MS as well. The autoimmune response in MS was previously thought to be primarily mediated by T cells, but more recent research has shown that B cells also have a central role in the disease [1,3]. Due to this, an increasing focus has been placed on

B cells as a target for treatments of MS. This review will cover the role of B cells in MS and compare several key treatments targeting B cell activity in the disease.

B Cells in Multiple Sclerosis

B cells are a type of white blood cell involved in the adaptive immune response. They originate and mature in the bone marrow, then enter the bloodstream as mature naive B cells and gather in lymphoid tissues. Once exposed to an antigen, naive B cells are activated, and they proliferate and differentiate into either plasmablasts or memory cells. Plasmablasts are short-lived cells that may terminally differentiate into plasma cells, and both plasma cells and plasmablasts produce antibodies. Memory cells can remember antigens allowing for a faster and more effective response upon second exposure to the same antigen by producing highly specific antibodies [4,5].

Antibodies can lead to cell death through various methods. One is antibody-dependent cellular cytotoxicity (ADCC), where after an antibody has bound to the antigen on the target cell or pathogen, a receptor on the surface of an effector cell, such as a natural killer cell, a macrophage, or an effector T cell, will bind to the antibody, and the effector cell will destroy the target. Another is complement-dependent cytotoxicity (CDC), where the binding of the antibody to the target cell or pathogen recruits complement factors to the surface of the pathogen, eventually leading to the formation of an attack complex on the surface of the target that causes cell death [4].

B cells contribute to the autoimmune response in MS in several ways. First, plasmablasts and plasma cells secrete autoantibodies against myelin and various CNS cells, including neurons, oligodendrocytes, and astrocytes [6,7]. Abnormalities in the production of cytokines, a category of signaling molecules involved in immune responses, by B cells have also been observed in MS. Specifically, B cells produce excessive amounts of the immune-activating cytokines lymphotoxin- α , tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and granulocyte macrophage-colony stimulating factor (GM-CSF). Conversely, B cells become deficient in production of the anti-inflammatory cytokine IL-10 [5,6]. Notably, MS patients have reduced numbers of IL-10-producing B cells during disease relapse compared to remission [5]. Patients in relapse also possess a reduced ratio of naive to memory B cells, suggesting that memory B cells may play a significant role in MS [5]. Targeting molecules involved in the development of these cells is a promising strategy to selectively reduce certain B cell types [5].

Treatments

Rituximab

Rituximab is a mouse-human chimeric monoclonal antibody approved for the treatment of B-cell non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, and granulomatosis with polyangiitis [5]. Rituximab targets CD20, a protein found on the surface of certain B cell types including pre-B cells, mature B cells, memory cells, and some plasmablasts, but not B cell progenitors and plasma cells. The mechanisms of B cell depletion include both CDC and ADCC [5,8].

One randomized controlled trial compared rituximab to placebo in 104 RRMS patients. Patients received 1000 mg of intravenous rituximab or placebo on days 1 and 15 and were monitored for 48 weeks [9]. The study found that rituximab significantly decreased the number of gadolinium-enhancing lesions on an MRI, which show a disruption in the blood-brain barrier and active inflammation, with a mean of 0.5 lesions compared to a mean of 5.5 lesions in patients receiving the placebo [9]. The study also found that rituximab reduced the proportion of patients with relapses compared to placebo at 24 weeks (14.5% vs. 34.2%) and 48 weeks (20.3% vs. 40.0%) [9]. In regards to safety, more patients in the rituximab group experienced infusion-associated adverse events (AEs) following the first infusion than the placebo group (78.3% vs. 40.0%). After the second infusion, both groups had similar numbers of infusion-associated AEs, and both groups had similar amounts of infections and serious AEs [9].

Another randomized controlled trial compared rituximab to placebo in 439 PPMS patients. Patients received 1000 mg of intravenous rituximab or placebo every 24 weeks up to week 96 [10]. The study found no significant difference in time to confirmed disease progression (CDP), measured by a specific increase in the expanded disability status scale (EDSS) depending on the baseline EDSS that is sustained for 12 weeks, between the two groups. However, the study also found that in patients aged under 51 with gadolinium-enhancing lesions at baseline, the placebo group was three times as likely to have CDP [10]. The study also found that the rituximab group had significantly less increase in T2 lesion volume compared to placebo (301.95 mm³ vs. 809.50 mm³) [10]. This study also found that infusion-associated AEs were more common in the rituximab group than placebo at the initial infusions, but they decreased to a similar number to the placebo with successive infusions. Both groups had similar levels of total AEs [10].

The results of these two studies show that rituximab is effective at decreasing inflammation and lesions within the brain and reducing relapses in RRMS [9,10]; however, it does not appear to significantly affect the rate of gradual disease worsening in PPMS [10]. For safety, rituximab did have slightly more infusion-associated AEs than placebo injections for initial infusions, but after that there was no significant difference in infusion-associated AEs [9,10]

Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody that targets the protein CD20, and it binds to a region overlapping with that of rituximab [11]. Also similarly to rituximab, ocrelizumab depletes B cells through CDC and ADCC, though it uses ADCC to a greater extent [11]. It is currently approved to treat RRMS and PPMS [5,11].

In two identical randomized controlled trials, ocrelizumab was compared to interferon beta (IFN β)-1a, a disease-modifying therapy that has been shown to moderately reduce relapse rate and slow disability accumulation in RRMS [1]. In the trials, 821 and 835 patients with RRMS were randomly assigned to receive either 600 mg of intravenous ocrelizumab every 24 weeks or 44 μ g of subcutaneous IFN β -1a three times weekly for 96 weeks [12]. The IFN β -1a groups also received placebo infusions. Both studies found that the ocrelizumab group had a lower annualized relapse rate (0.16 vs 0.29 in both trials) and mean number of gadolinium-enhancing lesions (0.02 vs. 0.29 and 0.02 vs. 0.42) than the IFN β group [12]. Analysis of the combined results showed that the ocrelizumab groups had a lower percentage of patients with CDP compared to IFN β at weeks 12 (9.1% vs 13.6%) and 24 (6.9% vs 12.5%). More patients in the ocrelizumab group experienced infusion-associated AEs (34.3% vs. 9.7%), and most of those occurred at the first infusion. The number of total AEs, serious AEs, and infections were similar in both groups [12].

Another randomized controlled trial compared ocrelizumab to placebo in 732 PPMS patients. Patients received 600 mg of intravenous ocrelizumab or placebo every 24 weeks for 120 weeks [13]. The study found that a lower percentage of the ocrelizumab had CDP at weeks 12 (32.9% vs. 39.3%) and 24 (29.6% vs. 35.7%). It also found that T2 lesion volume decreased by 3.4% in the ocrelizumab group, while it increased by 7.4% in the placebo group [13]. The percentage of patients with at least one AE was higher in the ocrelizumab group (95.1% vs. 90.0%), and the percentage of patients with serious AEs was similar in both groups. A greater percentage of the ocrelizumab group experienced infusion-associated AEs (39.9% vs. 25.5%), but the frequency decreased with subsequent infusions [13].

The results of these studies show that like rituximab, ocrelizumab is also effective at reducing relapses in RRMS [12]. However, unlike rituximab, ocrelizumab is also effective at slowing the gradual disease progression of PPMS [12,13]. Additionally, ocrelizumab did have more infusion-associated AEs than placebo infusions, which decreased after the first infusion [12,13].

Ofatumumab

Ofatumumab is a fully human monoclonal antibody, and, like both rituximab and ocrelizumab, it targets the CD20 protein found on certain types of B cells, though it binds to a distinct region of the protein [11]. Ofatumumab also depletes B cells through similar methods to

the other two, though it causes more CDC than ADCC [11]. Ofatumumab is currently approved to treat RRMS and SPMS [5,11].

One randomized controlled trial of RRMS patients compared ofatumumab to a placebo. In the study, 232 patients were randomized to receive 3, 30, or 60 mg of subcutaneous ofatumumab every 12 weeks, 60 mg of subcutaneous ofatumumab every 4 weeks, or a placebo for 24 weeks [14]. The study found that all of the ofatumumab had a dose-dependent reduction in the number of new gadolinium-enhancing lesions compared to placebo (placebo: 0.84, 3 mg: 0.25, 30 mg 0.09, 60 mg every 12 weeks: 0.08, 60 mg every 4 weeks: 0.07). Additionally, over the 24 weeks, a greater percentage of patients relapsed in the placebo group (25%) than across the ofatumumab groups (9%-22%) [14]. The incidence of total AEs was higher for the ofatumumab group than the placebo (74% vs. 64%). All groups had similar numbers of infections, but the rate of injection-related AEs was much higher in the ofatumumab groups than the placebo (41%-66% vs. 15%), though after the first dose, the rates were similar to the placebo [14].

In another study, two identical randomized controlled trials compared ofatumumab to teriflunomide, a pyrimidine synthesis inhibitor that reduces activation of both T and B cells [1,15], in 927 and 955 patients with RRMS or SPMS. Patients received either 20 mg of subcutaneous ofatumumab every 4 weeks or 14 mg of oral teriflunomide once daily for 30 months. Teriflunomide groups received placebo injections and ofatumumab groups received oral placebos [15]. In both trials, the ofatumumab group had a lower annualized relapse rate than the teriflunomide group (0.11 vs. 0.22 and 0.10 vs. 0.25), as well as a lower mean number of gadolinium-enhancing lesions (0.01 vs. 0.45 and 0.03 vs. 0.51). The combined results of the two trials showed that the ofatumumab group had a lower percentage of patients with CDP at 3 months (10.9% vs. 15.0%) and 6 months (8.1% vs. 12.0%) [15]. The numbers of total AEs and infections were similar in both groups, though injection-related AEs were higher in the ofatumumab group (20.2% vs. 15.0%), though most occurred at the first injection [15].

The results of these studies show that similarly to rituximab and ocrelizumab, ofatumumab is effective at reducing relapses and inflammatory lesions in RRMS [14,15]. Also like ocrelizumab, ofatumumab was shown to be effective at slowing progressive disease worsening, just in SPMS rather than PPMS [15]. For safety, ofatumumab had increased injection-related AEs which decreased with successive injections [14,15].

Bruton Tyrosine Kinase Inhibitors

Bruton Tyrosine Kinase (BTK) is a signaling molecule that is produced in B cells and some other blood cell lineages [16]. In B cells, BTK is a critical part of various signaling pathways that control B cell maturation and activation following exposure to an antigen,

production of cytokines, and stimulation of T cells [5,16]. BTK inhibitors are used to treat certain B cell malignancies and are being tested for treatment of various autoimmune disorders including MS [5,16].

One randomized controlled trial compared evobrutinib, a BTK inhibitor, to dimethyl fumarate (DMF), a disease-modifying therapy that reduces inflammation and protects neurons [1], and a placebo in 267 patients with RRMS. Patients received either 25 mg daily, 75 mg daily, or 75 mg twice daily of oral evobrutinib, 240 mg oral DMF twice daily, or a placebo for 24 weeks [17]. The study found that the mean number of gadolinium-enhancing lesions was lower than the placebo (3.85 lesions) and DMF (4.78 lesions) groups in the evobrutinib 75 mg daily (1.69 lesions) and 75 mg twice daily (1.15 lesions) groups. The study also found that the annualized relapse rate was lower in the 75 mg daily (0.13) and twice daily (0.08) evobrutinib groups compared to the placebo (0.37) and DMF (0.20) groups, though it was higher in the 25 mg daily evobrutinib group (0.57) [17]. For safety, the study found that the 75 mg twice daily group had the highest rate of serious AEs (7%), and the evobrutinib 75 mg daily and twice daily groups had higher rates of total AEs (66% and 63%) than the placebo (56%) and evobrutinib 25 mg (54%) groups [17].

Another randomized controlled trial compared a different BTK inhibitor, tolebrutinib, to a placebo in 130 patients with RRMS. Patients were randomized to receive either 5, 15, 30, or 60 mg oral tolebrutinib or a placebo once daily for 12 weeks [18]. The study found that the number of new gadolinium-enhancing lesions decreased with increasing doses of tolebrutinib (placebo: 1.03, 5 mg: 1.39, 15 mg: 0.77, 30 mg: 0.76, 60 mg: 0.13). The study also found a significant reduction in the number of T2 lesions for the 60 mg group versus placebo (0.23 vs. 2.12) [18]. For safety, all treatment groups had similar numbers of total AEs (5 mg: 58%, 15 mg: 53%, 30 mg: 55%, 60 mg: 50%), but the study did not measure AEs in the placebo group [18].

The results of these two studies show that BTK inhibitors are effective at reducing inflammatory lesions in patients with RRMS, but no data was available on their efficacy for SPMS or PPMS. For safety, evobrutinib may increase AEs in higher doses. As for tolebrutinib, no conclusions can be made about its relative safety due to the absence of a control.

Conclusions

MS is a debilitating immune-mediated neurodegenerative disease that drastically impacts the lives of millions. Recent research has increasingly shown the large role that B cells play in MS, making them an attractive target for new treatments. This paper explored the role of B cells in MS, as well as the efficacy and safety of five different B cell-targeting treatments for MS.

All five treatments were found to be effective at reducing both relapses and inflammatory lesions in RRMS. For slowing progression in SPMS and PPMS, ofatumumab was found to be effective in SPMS, and ocrelizumab was found to be effective in PPMS, making it superior to rituximab, which had no effect on progressive worsening in PPMS. No data was available for rituximab, ocrelizumab, and BTK inhibitors in SPMS, and no data was available for ofatumumab and BTK inhibitors in PPMS. In regards to safety, all three anti-CD20 monoclonal antibodies had higher infusion or injection related AEs at the first dose, decreasing with successive doses. Evobrutinib led to an increase in total AEs, and tolebrutinib had no dose-dependent increase in AEs, with about half of the patients experiencing an AE, but there was no control group for comparison. None of these findings are drastic enough to prevent use of these drugs altogether, though each patient may react differently. As for which treatment is the best, all five were effective for treating RRMS, and ocrelizumab appears to be the best for treating PPMS, though the only other treatment with data for PPMS was rituximab.

Drawing comparisons between the treatments' efficacies in RRMS was difficult due to some significant limitations. First, many of the studies used different metrics to measure similar outcomes. For example, to measure the treatments' effect on relapses, some studies measured annualized relapse rate, while others measured the number of patients who relapsed in varying time periods. This meant that while it could be determined if the treatments were effective, it was not always possible to compare their relative efficacies.

Another significant limitation was that for all of the treatments, there is limited data about their efficacy for treating the progressive forms of MS. This may be due to the fact that PPMS is very rare, affecting less than 10% of MS patients. Additionally, studies on SPMS alone are difficult to find, as it is often combined with RRMS because SPMS patients may still experience some relapses. Testing these treatments on all the subtypes of MS could be an area of interest for future research, as it could help to treat SPMS and PPMS.

Another potential area of future research is to repurpose existing B cell-targeting treatments for MS. Both rituximab and BTK inhibitors were originally used to treat other diseases, so testing existing treatments on MS could help to discover more effective treatments. For this future research, an important aspect to focus on would be standardizing the methods used to measure MS activity and disease worsening. This would allow for better comparisons between treatments so that the best ones can be determined.

While there are many treatments available for MS, there is still more work to be done to optimize their efficacy and safety. The five treatments discussed in this paper show the promise of targeting B cells for the treatment of MS. More research into these treatments and others and how they differentially impact the subtypes of MS will be critical for improving therapeutic interventions for MS in the future.

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