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Anti-CD20 MONOCLONAL ANTIBODIES IN THE TREATMENT OF MULTIPLE SCLEROSIS: MECHANISMS OF ACTION, CLINICAL EFFICACY, SAFETY, AND CONTEMPORARY THERAPEUTIC PERSPECTIVES

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ABSTRACT

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system in which B lymphocytes play a central role in disease pathogenesis. The development of anti-CD20 monoclonal antibodies has transformed the therapeutic landscape of MS by providing highly effective disease-modifying therapies with sustained reductions in relapse activity, magnetic resonance imaging disease activity, and disability progression. This review summarizes the current evidence regarding the biological rationale for B-cell depletion and discusses the mechanisms of action, efficacy, safety, and clinical applications of rituximab, ocrelizumab, ofatumumab, and ublituximab. Particular attention is given to adverse events, including infusion- and injection-related reactions, infections, hypogammaglobulinemia, vaccine responsiveness, and long-term monitoring strategies. Current treatment recommendations and the evolving role of anti-CD20 therapies within contemporary MS management are also reviewed. Overall, anti-CD20 monoclonal antibodies represent a cornerstone of modern MS therapy, offering substantial clinical benefit when combined with individualized patient selection, appropriate monitoring, and preventive measures.

KEYWORDS

Multiple Sclerosis, Anti-CD20, B Cells, Ocrelizumab, Ofatumumab, Rituximab, Ublituximab, Monoclonal Antibodies, Disease-modifying Therapy, Safety

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory and neurodegenerative disease of the central nervous system affecting approximately 2.8 million people worldwide. The disease most commonly begins with a relapsing-remitting course, although many patients eventually develop progressive neurological disability. Over the past two decades, advances in disease-modifying therapies (DMTs) have substantially improved relapse control, delayed disability progression, and altered the long-term prognosis of MS. [1,2]

Although MS was historically regarded as a predominantly T-cell-mediated disease, accumulating experimental and clinical evidence has established B lymphocytes as central contributors to disease pathogenesis. Beyond antibody production, B cells participate in antigen presentation, cytokine secretion, and activation of autoreactive T cells. Ectopic B-cell follicles and plasma cell infiltrates identified within the meninges and demyelinating lesions further support their role in sustaining chronic CNS inflammation. [2–4]

The clinical success of therapies targeting the CD20 antigen has provided compelling evidence for the pathogenic importance of B cells. CD20 is expressed on pre-B and mature B lymphocytes but is absent on stem cells and terminally differentiated plasma cells. Anti-CD20 monoclonal antibodies deplete circulating B cells through complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and apoptosis while largely preserving long-term humoral immunity. [2–4]

Currently available anti-CD20 therapies include rituximab, ocrelizumab, ofatumumab, and ublituximab. These agents have consistently demonstrated high efficacy in reducing clinical relapses, MRI disease activity, and disability progression. Ocrelizumab represented a major therapeutic milestone as the first treatment to demonstrate efficacy in primary progressive multiple sclerosis, while newer fully human antibodies have further expanded therapeutic options. [2,4]

Despite their excellent efficacy, anti-CD20 therapies require careful safety monitoring. Prolonged B-cell depletion may predispose patients to infections, hypogammaglobulinemia, and reduced vaccine responsiveness, highlighting the importance of individualized risk assessment, laboratory surveillance, and optimized vaccination strategies before and during treatment. [1,2,4,19–23]

The aim of this review is to summarize current evidence regarding the mechanisms of action, clinical efficacy, safety profile, and contemporary role of anti-CD20 monoclonal antibodies in the management of multiple sclerosis.

The Role of B Lymphocytes in the Pathogenesis of Multiple Sclerosis

B lymphocytes are now recognized as central mediators of multiple sclerosis (MS) pathogenesis. Although MS was traditionally regarded as a T-cell-driven autoimmune disease, extensive experimental, pathological, and clinical evidence has demonstrated that B cells contribute to disease activity through multiple complementary mechanisms extending far beyond antibody production.

B cells participate in antigen presentation by expressing major histocompatibility complex class II (MHC II) molecules and costimulatory proteins, thereby promoting activation and expansion of autoreactive CD4⁺ T cells. In parallel, they produce pro-inflammatory cytokines, including interleukin-6, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor- α , while a reduction in regulatory B-cell subsets impairs the production of anti-inflammatory cytokines such as IL-10. This imbalance favors persistent neuroinflammation.

Histopathological studies have demonstrated B-cell infiltration within active demyelinating lesions, the perivascular space, and meningeal ectopic lymphoid follicles. These structures are particularly associated with cortical demyelination and accelerated disability progression in progressive MS. The persistence of intrathecal oligoclonal immunoglobulin bands further supports chronic B-cell activation within the CNS.

The remarkable efficacy of anti-CD20 monoclonal antibodies has provided compelling clinical confirmation of the pathogenic importance of B cells. Rapid suppression of inflammatory disease activity following B-cell depletion occurs despite persistence of plasma cells and pre-existing antibody concentrations, indicating that antigen presentation and cytokine-mediated immune regulation are more important therapeutic targets than antibody production alone. [2,4–7]

Ocrelizumab

Ocrelizumab is a humanized IgG1 monoclonal antibody directed against the CD20 antigen expressed on pre-B and mature B lymphocytes. By selectively depleting circulating CD20-positive B cells while sparing hematopoietic stem cells and terminally differentiated plasma cells, ocrelizumab effectively suppresses the inflammatory processes driving multiple sclerosis (MS). [4,8]

The efficacy of ocrelizumab in relapsing MS was established in the pivotal OPERA I and OPERA II phase III trials, in which treatment significantly reduced the annualized relapse rate, MRI disease activity, and confirmed disability progression compared with interferon beta-1a. [8]

The ORATORIO trial demonstrated that ocrelizumab significantly delayed confirmed disability progression in patients with primary progressive multiple sclerosis (PPMS), becoming the first disease-modifying therapy to show convincing efficacy in this disease phenotype. [8,10]

Ocrelizumab is administered as an intravenous infusion every six months after an initial split-dose regimen. Premedication with corticosteroids and antihistamines is recommended to reduce infusion-related reactions. [4,8]

Long-term extension studies have confirmed sustained efficacy together with an acceptable safety profile. The most common adverse events include infusion-related reactions and upper respiratory tract infections. Monitoring serum immunoglobulin concentrations and ensuring appropriate vaccination before treatment initiation are recommended, particularly during long-term therapy. [9–12,19,21–23]

Ofatumumab

Ofatumumab is a fully human anti-CD20 IgG1 monoclonal antibody that binds to a membrane-proximal epitope of the CD20 antigen. Compared with earlier anti-CD20 agents, its molecular structure enables potent complement-dependent cytotoxicity while maintaining a favorable tolerability profile. [13,14]

Unlike ocrelizumab, ofatumumab is administered as a monthly subcutaneous injection, allowing patients to self-administer the treatment at home after appropriate training. This mode of administration improves convenience and may reduce the burden associated with hospital-based infusions. [13,14]

The efficacy of ofatumumab was demonstrated in the pivotal phase III ASCLEPIOS I and ASCLEPIOS II trials. Compared with oral teriflunomide, ofatumumab significantly reduced the annualized relapse rate, the number of new or enlarging T2 lesions, gadolinium-enhancing lesions, and the risk of confirmed disability worsening. In addition, treatment resulted in lower serum neurofilament light chain concentrations, suggesting a reduction in ongoing neuroaxonal injury. [13,14]

Long-term extension studies have confirmed sustained disease control with continuous therapy and no new safety concerns. The most common adverse events include injection-related reactions, upper respiratory

tract infections, urinary tract infections, and headache. Serious infections remain uncommon, although monitoring for hypogammaglobulinemia and hepatitis B virus reactivation is recommended in selected patients. [13,14,19]

The favorable efficacy, safety profile, and convenient route of administration have established ofatumumab as one of the leading high-efficacy disease-modifying therapies for relapsing forms of multiple sclerosis. The possibility of home administration makes it particularly attractive for patients seeking highly effective treatment with minimal disruption to daily life. [13,14]

Ublituximab

Ublituximab is a novel glycoengineered chimeric IgG1 monoclonal antibody targeting the CD20 antigen on mature B lymphocytes. Glycoengineering enhances its affinity for FcγRIIIa receptors on effector cells, resulting in increased antibody-dependent cellular cytotoxicity (ADCC) while maintaining effective B-cell depletion. [15,16]

The clinical efficacy of ublituximab was demonstrated in the phase III ULTIMATE I and ULTIMATE II trials, which compared ublituximab with oral teriflunomide in patients with relapsing multiple sclerosis. Ublituximab significantly reduced the annualized relapse rate and MRI disease activity, with fewer gadolinium-enhancing and new or enlarging T2 lesions than the comparator. [15,16]

An important practical advantage of ublituximab is its relatively short intravenous infusion time after the initial doses, improving patient convenience and infusion-center efficiency. Treatment is administered every 24 weeks following the induction regimen. [15,16]

The safety profile of ublituximab is generally comparable to that of other anti-CD20 monoclonal antibodies. Infusion-related reactions are the most common adverse events, particularly during the first administration. Upper respiratory tract infections and other mild infections occur relatively frequently, whereas serious infections remain uncommon in clinical trials. Routine screening for hepatitis B virus and appropriate vaccination before treatment initiation are recommended. [15,16,22,23]

The approval of ublituximab has expanded the therapeutic options for patients with relapsing forms of multiple sclerosis. Its high efficacy, rapid infusion protocol, and favorable safety profile make it an attractive addition to the anti-CD20 treatment class. [15,16]

Rituximab

Rituximab is a chimeric IgG1 monoclonal antibody targeting the CD20 antigen expressed on pre-B and mature B lymphocytes. Although it was originally developed for the treatment of B-cell lymphomas and later approved for several autoimmune diseases, rituximab has been widely used off-label in multiple sclerosis owing to its potent B-cell-depleting activity and favorable clinical outcomes. [17,18]

Evidence supporting rituximab in relapsing multiple sclerosis originates from the phase II HERMES trial, which demonstrated marked reductions in gadolinium-enhancing MRI lesions and annualized relapse rates compared with placebo. Subsequent observational studies and real-world registries confirmed sustained disease control and high treatment persistence in routine clinical practice. [17,18]

Rituximab has also been extensively used in Scandinavian countries, where long-term observational cohorts have suggested efficacy comparable to other high-efficacy anti-CD20 therapies despite the lack of formal regulatory approval for multiple sclerosis. These data have substantially influenced clinical practice and treatment guidelines in several regions. [17,18]

The drug is administered as an intravenous infusion, usually every six months following an induction regimen. Premedication with corticosteroids, antihistamines, and antipyretics is recommended to reduce infusion-related reactions. Monitoring of B-cell counts, serum immunoglobulin concentrations, and hepatitis B virus status is advised during prolonged treatment. [17–19]

The safety profile of rituximab is generally consistent with that of other anti-CD20 monoclonal antibodies. Infusion-related reactions are most common during the initial administration, whereas serious infections remain relatively infrequent. Progressive multifocal leukoencephalopathy has been reported only rarely in patients with multiple sclerosis but remains an important consideration during long-term immunosuppressive therapy. [17–21]

Safety of Anti-CD20 Therapy in Multiple Sclerosis

Monoclonal antibodies targeting CD20 are among the most effective disease-modifying therapies for multiple sclerosis (MS). Rituximab, ocrelizumab, ofatumumab, and ublituximab achieve their therapeutic effect primarily through sustained depletion of CD20-positive B lymphocytes involved in antigen presentation, cytokine production, and the maintenance of autoimmune inflammation. However, prolonged B-cell depletion may also compromise humoral immune function and is associated mainly with administration-related reactions, infections, hypogammaglobulinemia, and attenuated vaccine responses. Accordingly, long-term treatment requires appropriate pretreatment assessment, laboratory surveillance, and individualized risk-minimization strategies. [2,4,19–23]

Administration-Related Reactions

Administration-related reactions are the most frequently reported adverse events associated with anti-CD20 monoclonal antibodies. Rituximab, ocrelizumab, and ublituximab are administered intravenously and may cause infusion-related reactions, whereas subcutaneous ofatumumab is associated predominantly with injection-related systemic or local reactions. Typical manifestations include fever, chills, flushing, pruritus, rash, headache, nausea, fatigue, throat irritation, and transient changes in blood pressure. Most events are mild or moderate, occur during or shortly after the first administration, and become less frequent with subsequent doses. Temporary interruption or reduction of the infusion rate is usually sufficient; permanent discontinuation is rarely required. Premedication with a corticosteroid, an antihistamine, and, where appropriate, an antipyretic is recommended before intravenous administration, together with clinical observation during and after infusion [2-4,13–18,22]

Infections

Sustained B-cell depletion may increase susceptibility to infection, particularly with increasing treatment duration, advancing age, greater disability, relevant comorbidity, previous immunosuppressive exposure, and declining immunoglobulin concentrations. The infections reported most often are upper respiratory tract infections, nasopharyngitis, urinary tract infections, and generally mild viral infections. In a systematic review and meta-analysis of 19,139 patients with MS treated with anti-CD20 agents, respiratory infections were the most frequent infectious complication, while serious infections remained substantially less common [23]. Before treatment initiation, patients should be screened for hepatitis B virus (HBV) infection, including HBsAg and anti-HBc testing. Those with evidence of current or previous HBV infection require specialist assessment and may need antiviral prophylaxis. Progressive multifocal leukoencephalopathy appears to be very rare during anti-CD20 therapy in MS; nevertheless, new or unexplained neurological deterioration should prompt immediate diagnostic evaluation [2,4,19,20,22].

Hypogammaglobulinemia

Hypogammaglobulinemia is an important cumulative complication of long-term anti-CD20 therapy. Persistent depletion of circulating B cells reduces the renewal of antibody-producing cell populations and may lead to progressive decreases in immunoglobulin concentrations, particularly IgM and, in a subset of patients, IgG. A meta-analysis of 19,139 treated patients estimated an overall prevalence of hypogammaglobulinemia of approximately 11%, with the highest pooled prevalence among rituximab-treated cohorts [23]. Lower IgG concentrations, longer exposure, older age, and greater cumulative treatment burden have been associated with a higher risk of clinically relevant infections [7,23,24]. Serum IgG, IgM, and IgA should therefore be measured before treatment and periodically thereafter. In patients with marked hypogammaglobulinemia and recurrent or severe infections, management may include delaying or extending the interval between doses, switching therapy, specialist immunological assessment, or immunoglobulin replacement in selected cases [7,19–21,24].

Vaccination and Immune Response

Vaccination is a central component of preventive care in patients considered for anti-CD20 therapy. Because B-cell depletion attenuates humoral vaccine responses, the vaccination history should be reviewed and, whenever feasible, indicated immunizations should be completed before treatment begins. Live attenuated vaccines should generally be administered at least 4 weeks before therapy and avoided during active B-cell depletion; a longer interval may be appropriate for selected vaccines and agents according to product information and specialist guidance. Inactivated vaccines can be given during treatment, although antibody

responses may be reduced, particularly when vaccination is performed soon after an anti-CD20 dose. Vaccination against influenza, pneumococcal disease, HBV, and COVID-19 should be considered according to age, comorbidity, exposure risk, and national recommendations. Despite attenuated humoral responses, vaccination may still generate cellular immunity and clinically meaningful protection; it should therefore not be withheld solely because a patient is receiving anti-CD20 therapy [1,2,22,23,25,26]

COVID-19 and Anti-CD20 Therapy

Accumulating evidence from international MS registries indicates that anti-CD20 therapies, particularly rituximab and ocrelizumab, may be associated with an increased risk of severe COVID-19 outcomes. Patients receiving these agents have shown higher rates of hospitalization and intensive care admission than patients treated with several other disease-modifying therapies. In addition, anti-CD20-mediated B-cell depletion attenuates humoral responses following SARS-CoV-2 vaccination. Consequently, vaccination should preferably be scheduled before treatment initiation or, whenever possible, at an appropriate interval before the next treatment cycle to maximize immunogenicity. [1,22–24]

Patient Monitoring

Safe administration of anti-CD20 therapy requires regular clinical and laboratory monitoring. Baseline assessment should include a complete blood count, serum immunoglobulin concentrations, HBV, HCV and HIV screening, and verification of vaccination status. During treatment, periodic monitoring of blood counts and immunoglobulin levels is recommended, together with surveillance for recurrent infections and progressive hypogammaglobulinemia. Routine age-appropriate cancer screening should also be maintained. [1,4,13–23]

Risk-Minimization Strategies

Several strategies have been proposed to reduce treatment-related toxicity while preserving clinical efficacy. Extended-interval dosing of ocrelizumab has emerged as a promising approach that may reduce cumulative immunosuppression and limit immunoglobulin decline without compromising disease control in carefully selected patients. Treatment de-escalation may also be considered in older individuals with prolonged disease stability, although such decisions should always be individualized and supported by close clinical and MRI follow-up. [4,9,11,12,25]

Summary

Anti-CD20 monoclonal antibodies remain among the most effective disease-modifying therapies for multiple sclerosis and demonstrate an overall favorable safety profile. Administration-related reactions, infections, hypogammaglobulinemia, and reduced vaccine responsiveness constitute the principal safety concerns. Appropriate patient selection, structured laboratory monitoring, timely vaccination, and individualized risk-minimization strategies allow these therapies to be used safely over the long term while maintaining substantial clinical benefit. [1,2,4,13–25]

The Role of Anti-CD20 Therapy in Contemporary Multiple Sclerosis Treatment Guidelines

During the past decade, therapeutic strategies for multiple sclerosis have shifted from the traditional escalation paradigm toward an early high-efficacy treatment approach. This concept aims to suppress inflammatory disease activity at the earliest possible stage, thereby preventing irreversible neuroaxonal injury and long-term disability accumulation. Anti-CD20 monoclonal antibodies now represent one of the key components of this strategy because of their consistently demonstrated efficacy across randomized clinical trials and real-world studies. [2,4,9–18,25]

Individualized Treatment Decisions

Current international recommendations emphasize that treatment selection should be individualized and based on disease activity, prognostic factors, age, comorbidities, reproductive plans, patient preferences, and safety considerations. For patients with highly active disease or unfavorable prognostic markers, anti-CD20 therapies are increasingly recommended as first-line high-efficacy treatment. [1,2,4,13–18,25]

Prevention and Monitoring

Infection prevention and structured safety monitoring have become essential elements of modern MS management. Vaccination status should be reviewed before treatment initiation, with influenza, pneumococcal, hepatitis B, and SARS-CoV-2 vaccination administered whenever feasible before B-cell depletion. During therapy, regular monitoring of complete blood count, serum immunoglobulins, infectious complications, and long-term safety parameters is recommended. [1,19–23]

Special Clinical Situations

Anti-CD20 therapies may offer additional advantages in patients with coexisting autoimmune diseases, particularly rheumatoid arthritis, in whom rituximab has established efficacy. Management of such patients requires interdisciplinary cooperation and individualized therapeutic planning. Emerging evidence also supports treatment individualization through extended-interval dosing in carefully selected patients with stable disease. [10,17,18,25,26]

Summary

Anti-CD20 monoclonal antibodies have become a cornerstone of contemporary multiple sclerosis management. Their high efficacy, favorable long-term benefit-risk profile, and expanding real-world evidence have firmly established these agents within current international treatment guidelines. Ongoing safety monitoring, vaccination strategies, and individualized patient care remain fundamental to optimizing therapeutic outcomes. [1,2,4,19,22,25]

Conclusions

Anti-CD20 monoclonal antibodies have fundamentally transformed the therapeutic landscape of multiple sclerosis by establishing B-cell depletion as one of the most effective treatment strategies for both relapsing and, in the case of ocrelizumab, primary progressive disease. Over the past decade, accumulating evidence from randomized clinical trials, long-term extension studies, and real-world cohorts has consistently demonstrated their ability to reduce relapse activity, suppress MRI disease activity, delay disability progression, and improve long-term clinical outcomes.

Although rituximab, ocrelizumab, ofatumumab, and ublituximab differ in molecular structure, route of administration, regulatory approval, and pharmacological characteristics, they share a common mechanism of selectively targeting CD20-positive B lymphocytes while preserving hematopoietic stem cells and plasma cells. Their favorable efficacy-to-safety profile has established anti-CD20 therapy as a cornerstone of contemporary high-efficacy treatment strategies for multiple sclerosis.

Despite these therapeutic advances, long-term B-cell depletion requires careful patient selection and continuous safety monitoring. Infections, hypogammaglobulinemia, reduced vaccine responsiveness, and other treatment-related adverse events highlight the importance of individualized risk assessment, regular laboratory surveillance, vaccination planning, and appropriate preventive measures throughout therapy. Increasing attention is also being directed toward treatment optimization through personalized dosing strategies, extended-interval administration, and de-escalation approaches in selected patients with stable disease.

Future research should focus on identifying biomarkers predicting treatment response, optimizing individualized therapeutic strategies, and defining the long-term safety of prolonged B-cell depletion. Further comparative effectiveness studies and real-world observational data will continue to refine the position of individual anti-CD20 agents within rapidly evolving treatment algorithms.

In conclusion, anti-CD20 monoclonal antibodies represent one of the greatest therapeutic advances in the management of multiple sclerosis. Their high clinical efficacy, durable disease control, and generally acceptable safety profile make them an essential component of modern MS treatment. Continued improvements in patient monitoring, preventive strategies, and personalized treatment approaches are expected to further enhance both the safety and long-term effectiveness of this therapeutic class.

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