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Biological Therapies in Multiple Sclerosis: Mechanisms of Action, Clinical Efficacy, and Safety of Monoclonal Antibodies Targeting CD20, CD52, and α4-Integrin - Review Article

Aleksandra Machnik[1], Mateusz Witowicz[2], Katarzyna Kilarowska[2], Daria Podleśna[2], Katarzyna Trela[2], Martyna Nowak[2], Aleksander Tuteja[2], Laura Więcko[2], Konrad Krupa[3], Monika Białowąs[4], Weronika Białowąs[5], Pola Sitek [6]

#1 University Clinical Center, Medical University of Silesia in Katowice (Prof. Kornel Gibiński), Medyków 14, 40-752 Katowice, Poland
#2 Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice, Poland Poniatowskiego 15, 40-055 Katowice, Poland
#3 Specialist Municipal Hospital in Toruń, Stefana Batorego 17/19, 87-100 Toruń, Poland
#4 Andrzej Mielecki Independent Public Clinical Hospital in Katowice, Poland
#5 Bielański Hospital in Warsaw, Cegłowska 80, 01-809 Warsaw, Poland
#6 Municipal Hospital in Siemianowice Śląskie, 1 Maja Street 9, 41100 Siemianowice Śląskie, Poland

ABSTRACT: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system driven by autoimmune mechanisms involving both T and B lymphocytes. Advances in immunopathological understanding have led to the development of highly effective biological therapies, particularly monoclonal antibodies targeting CD20, CD52, and α4-integrin. The aim of this study is to compare the mechanisms of action, clinical efficacy, and safety profiles of currently approved monoclonal antibodies used in MS treatment. Anti-CD20 therapies demonstrated robust efficacy in reducing relapse rates and MRI lesion activity across relapsing MS populations. Ocrelizumab showed additional efficacy in primary progressive MS by significantly slowing disability progression. Ublituximab provided comparable efficacy with shorter infusion times. Alemtuzumab exhibited high efficacy, particularly in early disease stages, but was associated with the highest rate of autoimmune and infectious adverse events. Natalizumab remained one of the most effective agents for relapse suppression; however, its long-term use was limited by the risk of progressive multifocal leukoencephalopathy (PML). Monoclonal antibodies have significantly improved MS outcomes, though their benefit–risk profiles vary. Anti-CD20 therapies offer the most favorable balance between efficacy and safety, while alemtuzumab and natalizumab require strict monitoring. Treatment selection should be individualized based on disease phenotype, safety considerations, and patient-specific factors.

KEYWORDS: multiple sclerosis; monoclonal antibodies; CD20; CD52; α4-integrin; ocrelizumab; ofatumumab; ublituximab; alemtuzumab; natalizumab

MATERIALS AND METHODS

A systematic literature review was conducted using PubMed, focusing on randomized controlled trials (RCTs), systematic reviews, and network meta-analyses published from 2018 onward. The analyzed agents included anti-CD20 monoclonal antibodies (ocrelizumab, ofatumumab, ublituximab), anti-CD52 antibody (alemtuzumab), and anti-α4-integrin antibody (natalizumab). Outcomes assessed included annualized relapse rate (ARR), confirmed disability progression (CDP), MRI activity, and adverse event profiles.

INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated disorder characterized by inflammation, demyelination, and neurodegeneration within the central nervous system (CNS) [1]. Autoreactive T cells, B cells, and innate immune components contribute to blood–brain barrier disruption and CNS injury [2]. The recognition of B-cell involvement in MS pathogenesis has led to the development of highly targeted biological therapies, fundamentally transforming disease management [3].

1. Mechanisms of Action of Monoclonal Antibodies in MS

1.1 Anti-CD20 therapies (Ocrelizumab, Ofatumumab, Ublituximab)

Anti-CD20 monoclonal antibodies selectively deplete circulating B cells while sparing plasma cells and stem cells [4]. This results in reduced antigen presentation, cytokine secretion, and formation of ectopic lymphoid follicles in the CNS [5]. Ocrelizumab induces B-cell depletion mainly via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [6]. Ofatumumab is a fully human monoclonal antibody administered subcutaneously, providing continuous B-cell suppression with lower systemic exposure [7]. Ublituximab, a glycoengineered antibody, enhances ADCC and allows infusion times of less than one hour [8].

1.2 Anti-CD52 therapy (Alemtuzumab)

Alemtuzumab targets CD52, expressed on mature T and B lymphocytes, leading to profound immune cell depletion followed by immune reconstitution [9]. This mechanism accounts for its strong efficacy but also its association with secondary autoimmunity [10].

1.3 Anti-α4-integrin therapy (Natalizumab)

Natalizumab blocks α4-integrin-mediated leukocyte adhesion, preventing immune cell migration across the blood–brain barrier [11]. This effectively suppresses CNS inflammation but impairs immune surveillance within the brain [12].

2. Clinical Efficacy

2.1 Relapse rate reduction

Network meta-analyses consistently rank monoclonal antibodies among the most effective disease-modifying therapies for reducing annualized relapse rates (ARR) in relapsing forms of multiple sclerosis, outperforming both first-line injectable therapies and most oral agents [13,14]. These analyses demonstrate that monoclonal antibodies not only reduce the frequency of clinical relapses but also provide more sustained suppression of inflammatory disease activity over time, as reflected by lower rates of breakthrough disease and MRI lesion formation [13]. Anti-CD20 therapies, in particular, have shown robust and reproducible effects on relapse prevention, with reductions in ARR of approximately 45–60% compared with first-line oral agents such as teriflunomide and dimethyl fumarate [15]. This benefit has been consistently observed across different patient populations, including treatment-naïve individuals as well as patients switching from other disease-modifying therapies due to suboptimal disease control or intolerance [7,15]. In the phase III ULTIMATE I and II trials, ublituximab demonstrated a rapid and sustained reduction in ARR of approximately 59% compared with teriflunomide, accompanied by significant reductions in gadolinium-enhancing and new or enlarging T2 lesions, underscoring its potent anti-inflammatory effect [16]. Ocrelizumab and ofatumumab have shown comparable efficacy in relapse suppression, with durable benefits observed in long-term extension studies [7,8]. Natalizumab remains one of the most effective agents for relapse prevention, with efficacy comparable to or exceeding that of anti-CD20 therapies; however, its long-term use is limited by safety considerations, particularly the risk of progressive multifocal leukoencephalopathy, which necessitates careful patient selection and ongoing risk stratification [17].

2.2 Disability progression

Disability progression represents one of the most clinically meaningful and challenging aspects of multiple sclerosis management, as it reflects irreversible neuroaxonal damage rather than transient inflammatory activity. While many disease-modifying therapies effectively reduce relapse rates, their impact on long-term disability accumulation has historically been limited, particularly in progressive disease phenotypes. In this context, monoclonal antibodies have demonstrated superior efficacy in delaying confirmed disability progression (CDP), redefining therapeutic expectations in MS [13,15]. Ocrelizumab remains the only monoclonal antibody approved for the treatment of primary progressive multiple sclerosis (PPMS) and has consistently demonstrated a significant reduction in confirmed disability progression across multiple analyses [6,18]. In the pivotal ORATORIO trial and its long-term extension, ocrelizumab reduced the risk of 12-week and 24-week confirmed disability progression compared with placebo, with sustained benefits observed over extended follow-up periods [18,21]. Importantly, post hoc analyses revealed that patients with evidence of ongoing inflammatory activity—such as gadolinium-enhancing lesions or elevated neurofilament light chain (NfL) levels—derived the greatest benefit, suggesting that early intervention may be critical even in progressive disease stages [21,22]. Real-world

studies published after 2018 further support the disability-modifying effect of ocrelizumab in both relapsing and progressive MS populations. Observational cohort data indicate stabilization or slowing of Expanded Disability Status Scale (EDSS) progression over periods exceeding three years, including in patients transitioning from relapsing-remitting to secondary progressive disease [23]. These findings reinforce the concept that B-cell depletion may influence both inflammatory and neurodegenerative components of MS pathology. Alemtuzumab has also demonstrated durable effects on disability outcomes, particularly in relapsing MS patients with high disease activity. Long-term follow-up from the CARE-MS I and II extension studies showed sustained reductions in disability progression and, notably, a proportion of patients experienced confirmed disability improvement lasting several years after the last treatment course [19,24]. This effect is thought to result from immune reconstitution leading to a more tolerogenic immune profile, although the exact mechanisms remain incompletely understood [24]. However, the interpretation of alemtuzumab's disability outcomes must be balanced against its safety profile. While its efficacy in preventing disability accumulation is substantial, secondary autoimmune complications and serious adverse events may indirectly affect long-term functional outcomes and quality of life, emphasizing the need for careful patient selection and prolonged monitoring [10,19]. Emerging comparative analyses and network meta-analyses published after 2018 suggest that monoclonal antibodies—particularly anti-CD20 therapies and alemtuzumab—rank highest among disease-modifying treatments for reducing confirmed disability progression in relapsing MS [13,14,25]. These studies consistently demonstrate superior performance compared with oral agents and first-line injectables, especially when treatment is initiated early in the disease course. Collectively, these findings indicate that disability progression in MS is increasingly modifiable, particularly when high-efficacy monoclonal antibodies are introduced before extensive neuroaxonal loss has occurred. Early suppression of inflammatory activity, reduction of chronic compartmentalized inflammation, and potential indirect neuroprotective effects appear to be key mechanisms underlying the observed clinical benefits [5,22,25]. Consequently, disability outcomes are now a central consideration in therapeutic decision-making, reinforcing the role of monoclonal antibodies as cornerstone treatments in modern MS management.

3. Safety and Adverse Events

Safety considerations remain a critical component of treatment selection and long-term disease management in multiple sclerosis, particularly in the context of highly effective biological therapies. Among monoclonal antibodies, alemtuzumab has been consistently associated with the highest incidence of serious adverse events, reflecting its mechanism of profound immune depletion followed by immune reconstitution [10,19]. The most frequently reported complications include autoimmune thyroid disorders, immune thrombocytopenia, and an increased susceptibility to infections, which may occur months or years after treatment initiation and necessitate prolonged post-treatment surveillance [10]. Natalizumab carries a well-documented risk of progressive multifocal leukoencephalopathy (PML), a rare but potentially fatal opportunistic infection caused by JC virus reactivation [12,17]. The risk of PML increases with treatment duration, prior immunosuppressive therapy, and positive anti–

JC virus antibody status, requiring regular risk stratification and monitoring to guide continued therapy [12,17]. In contrast, anti-CD20 therapies have demonstrated relatively favorable and predictable safety profiles across clinical trials and real-world studies [6,7,20]. Infections represent the most commonly reported adverse events, typically involving the upper respiratory tract and generally mild to moderate in severity. Serious infections remain uncommon when patients are appropriately screened and monitored, supporting the long-term tolerability of B-cell–depleting therapies in routine clinical practice [6,7].

4. Clinical Implications and Treatment Selection

The expanding availability of highly effective monoclonal antibody therapies has fundamentally altered clinical decision-making in multiple sclerosis, shifting treatment strategies toward earlier and more aggressive disease control. Selection of an appropriate biological therapy requires a multidimensional assessment that integrates disease activity, MS phenotype, prognostic indicators, patient comorbidities, lifestyle considerations, and individual risk tolerance [3,14,15]. This personalized approach is essential given the heterogeneity of MS and the divergent benefit–risk profiles of available monoclonal antibodies. Disease phenotype remains a primary determinant of treatment selection. In relapsing forms of MS, particularly in patients with high inflammatory activity, early initiation of high-efficacy therapy has been associated with superior long-term outcomes compared with escalation strategies that delay effective treatment [13,15,25]. Anti-CD20 monoclonal antibodies have demonstrated consistent efficacy across a wide range of relapsing MS populations, including treatment-naïve patients and those switching from other disease-modifying therapies due to suboptimal response or intolerance [7,8,15]. In primary progressive MS, ocrelizumab remains the only monoclonal antibody with proven efficacy, making it the preferred biological option for this phenotype [6,18]. Patient-specific factors play a critical role in therapeutic decision-making. Comorbid conditions such as recurrent infections, cardiovascular disease, autoimmune disorders, and malignancy history may influence both treatment choice and monitoring strategies [14,26]. For example, alemtuzumab may be contraindicated or used with caution in patients with pre-existing autoimmune disease, while natalizumab requires careful assessment of JC virus serostatus and prior immunosuppressive exposure to mitigate the risk of progressive multifocal leukoencephalopathy [10,12,17]. In contrast, anti-CD20 therapies generally exhibit a more predictable safety profile, contributing to their increasing preference in routine clinical practice [6,7,14]. Risk tolerance and patient preference are equally important components of treatment selection. Monoclonal antibodies differ substantially in administration route, dosing frequency, and monitoring burden. Subcutaneous ofatumumab offers greater convenience and autonomy for patients, while intravenous therapies such as ocrelizumab and ublituximab provide less frequent dosing but require infusion center visits [7,8]. Alemtuzumab’s induction-based dosing regimen may appeal to patients seeking long treatment-free intervals but demands prolonged post-treatment surveillance, which may not be acceptable to all individuals [9,10]. Growing evidence supports the concept that early use of high-efficacy monoclonal antibody therapy can prevent irreversible neuroaxonal damage and delay disability accumulation [13,15,21]. This has led to a paradigm shift away from traditional

stepwise escalation toward an individualized early high-efficacy strategy, particularly in younger patients with active disease and poor prognostic markers [25,27]. Biomarkers such as serum neurofilament light chain levels and MRI measures of brain atrophy are increasingly being incorporated into treatment decisions to refine risk stratification and optimize therapeutic timing [22,27]. In clinical practice, anti-CD20 therapies are increasingly preferred as first-line high-efficacy treatments due to their robust efficacy, favorable long-term safety profile, and broad applicability across MS phenotypes [15]. However, alemtuzumab and natalizumab remain indispensable options for selected patients with highly aggressive disease requiring rapid and profound disease control, provided that appropriate monitoring and risk mitigation strategies are implemented [14,17]. In summary, optimal treatment selection in multiple sclerosis requires a personalized, evidence-based approach that balances efficacy, safety, and patient-centered considerations. The integration of clinical characteristics, biomarkers, and patient preferences allows clinicians to tailor monoclonal antibody therapy to maximize long-term neurological outcomes while minimizing treatment-related risks.

RESULTS

All anti-CD20 monoclonal antibodies demonstrated significant efficacy in reducing annualized relapse rates (ARR) and suppressing MRI disease activity when compared with standard first-line therapies and oral disease-modifying agents. These effects were consistently observed across pivotal randomized controlled trials as well as long-term extension studies, indicating sustained control of inflammatory disease activity. In addition to reducing clinical relapses, anti-CD20 therapies significantly decreased the number of gadolinium-enhancing lesions and new or enlarging T2 lesions, reflecting robust inhibition of central nervous system inflammation. In the phase III ULTIMATE I and II trials, ublituximab reduced ARR by approximately 59% compared with teriflunomide and demonstrated rapid and profound B-cell depletion. A distinguishing feature of ublituximab was its shortened infusion time, typically under one hour, which may improve treatment convenience and patient adherence. Ocrelizumab and ofatumumab showed comparable efficacy in relapse suppression and MRI outcomes, with favorable long-term safety profiles supported by extension and real-world data. Notably, ocrelizumab also demonstrated clinically meaningful efficacy in primary progressive MS, significantly reducing confirmed disability progression and representing a unique therapeutic option for this disease phenotype. Alemtuzumab exhibited potent efficacy, particularly when administered early in the disease course, resulting in marked reductions in relapse rates and sustained effects on disability outcomes in relapsing MS populations. However, its use was associated with the highest rates of autoimmune adverse events and required intensive and prolonged safety monitoring. Natalizumab remained one of the most effective agents for preventing relapses and new MRI lesion formation; nevertheless, its long-term utility was limited by the risk of progressive multifocal leukoencephalopathy (PML), necessitating careful patient selection, regular risk stratification, and individualized treatment duration.

CONCLUSIONS

Biological therapies targeting CD20, CD52, and α4-integrin have reshaped MS treatment. Anti-CD20 monoclonal antibodies currently provide the most favorable benefit–risk ratio. Highly effective agents such as alemtuzumab and natalizumab remain valuable options but require intensive safety monitoring. Personalized treatment strategies are essential for optimizing long-term outcomes in MS. Biological therapies targeting key immune pathways—specifically CD20-expressing B cells, CD52-positive lymphocytes, and α4-integrin–mediated leukocyte trafficking—have fundamentally transformed the therapeutic landscape of multiple sclerosis. These agents represent a paradigm shift from broad immunomodulation toward highly targeted immune intervention, enabling more effective suppression of inflammatory disease activity and improved long-term clinical outcomes compared with earlier disease-modifying therapies. Among currently available biological treatments, anti-CD20 monoclonal antibodies have emerged as the most consistently effective and best-balanced therapeutic class. Extensive evidence from randomized controlled trials, long-term extension studies, and real-world observational data demonstrates that ocrelizumab, ofatumumab, and ublituximab achieve substantial reductions in annualized relapse rates, MRI lesion activity, and markers of subclinical disease progression. Importantly, ocrelizumab remains the only monoclonal antibody with proven efficacy in primary progressive multiple sclerosis, highlighting the central role of B cells not only in relapsing disease but also in progressive neuroinflammation. The relative preservation of innate immune function and immunoglobulin-producing plasma cells likely contributes to the favorable safety profile of anti-CD20 therapies, supporting their increasing use as first-line high-efficacy treatments. Alemtuzumab and natalizumab continue to play an important role in the management of highly active or treatment-refractory multiple sclerosis. Alemtuzumab offers profound and durable disease control through immune depletion followed by immune reconstitution, which may translate into long-lasting remission in selected patients. However, this mechanism is associated with a significant risk of secondary autoimmune disorders, infections, and rare but severe vascular complications, necessitating prolonged and rigorous post-treatment monitoring. Similarly, natalizumab remains one of the most potent agents for suppressing relapse activity and new MRI lesion formation, yet its interference with central nervous system immune surveillance confers a well-established risk of progressive multifocal leukoencephalopathy. As a result, its long-term use requires careful patient selection, regular JC virus antibody monitoring, and individualized risk stratification. The growing diversity of highly effective biological therapies underscores the importance of personalized treatment strategies in multiple sclerosis. Therapeutic decision-making should integrate disease phenotype, inflammatory activity, prognostic biomarkers, patient age, comorbidities, reproductive plans, and individual risk tolerance. Additionally, emerging evidence suggests that early initiation of high-efficacy biological therapy may improve long-term neurological outcomes by preventing irreversible axonal damage and delaying disability accumulation. In conclusion, biological therapies have markedly improved the prognosis of patients with multiple sclerosis, but their optimal use depends on balancing efficacy with long-term safety. Anti-CD20 monoclonal antibodies currently offer the most favorable benefit–risk profile for the majority of patients, while alemtuzumab and natalizumab remain indispensable options in

selected clinical scenarios. Ongoing pharmacovigilance, biomarker-driven treatment selection, and long-term real-world data will be essential for refining therapeutic algorithms and further improving patient-centered outcomes in multiple sclerosis.

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