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# Profile of Ofatumumab in the Treatment of Multiple Sclerosis: Design, Development and Place in Therapy

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**Abstract:** Targeting B cells through monoclonal antibodies against CD20 has emerged as a highly effective strategy in managing disease activity in patients with relapsing forms of multiple sclerosis. This efficacy was initially demonstrated with rituximab and further affirmed with ocrelizumab. Ofatumumab is the first fully human IgG1 monoclonal antibody (mAb) approved for the treatment of MS. It is characterized by its convenient self-administered regimen of once-monthly subcutaneous injections. Its human antibody nature contributes to a significantly lower risk of immunogenicity compared to rituximab. Clinical trials have consistently shown its effectiveness in significantly reducing annualized relapse rates, MRI-detected lesion activity, and disability progression when compared to teriflunomide, a standard therapy for MS. Additionally, ofatumumab exhibits a manageable tolerability profile, with adverse events primarily comprising infections and injection-related reactions. This review describes ofatumumab pharmacology, core clinical trial data and clinical efficacy in addition to safety issues.

**Keywords:** ofatumumab, multiple sclerosis, relapsing remitting multiple sclerosis, anti- CD20 monoclonal antibodies, disease modifying therapeutics, safety

## Introduction

Multiple sclerosis (MS) is an autoimmune pathology characterized by demyelination within the central nervous system (CNS) encompasses inflammatory and neurodegenerative processes. Approximately 2.8 million individuals worldwide are affected by MS.[1] It is classified into three principal subtypes: relapsing-remitting MS (RRMS), progressive MS, and clinically isolated syndromes (CIS). The predominant subtype is RRMS, accounting for 85% of cases at onset.[2] Approximately 10–15% of patients are diagnosed with primary progressive MS (PPMS), which exhibits gradual clinical decline from the onset of disease.[3] In 2010, the estimated prevalence of MS among the adult demographic in the United States stood at 309 cases per 100,000 individuals. By 2017, this prevalence was projected to increase, with estimates ranging from 337 to 362 cases per 100,000 individuals.[4,5] Concurrently, treatment options for MS have expanded, with a growing number of disease modifying therapies (DMT) for MS in the modern era.

While T cells have traditionally been viewed as key players in the inflammatory demyelination seen in MS, recent evidence indicates that B cells also play a significant role in the disease development. B cells contribute to MS pathogenesis through various mechanisms, including antigen presentation to T cells, production of pro-inflammatory cytokines and chemokines enhancing inflammation, oligodendrocyte and neuronal damage, and formation of ectopic lymphoid aggregates in the meninges. These actions of B cells may contribute to both MS relapses and disease progression. This is further highlighted by clinical trials demonstrating the high efficacy of anti-CD20 monoclonal antibodies in reducing new relapsing disease activity.[6] The initial anti-CD20 therapy showing efficacy for MS was the

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chimeric antibody Rituximab. While not approved by the FDA for MS, it had been frequently prescribed off-label, especially in cases resistant to conventional therapies. Following the successful clinical trials of ocrelizumab, ofatumumab, the first fully human anti-CD20 monoclonal antibody, was developed as a subcutaneous, self-administered monthly injection. By targeting a unique CD20 epitope, it achieves consistent, near-complete B-cell reduction which is thought to enhance its effectiveness in controlling the disease. In August 2020, the FDA granted approval for ofatumumab as a therapeutic option for all forms of relapsing MS, encompassing CIS, active SPMS, and RRMS.[7] This review discusses the development of ofatumumab, emphasizing its mechanism of action, which involves targeted B-cell depletion, alongside its demonstrated efficacy and safety in clinical trials. Additionally, it underscores ofatumumab's role as a novel therapeutic option, particularly in comparison to existing multiple sclerosis therapies.

## The Role of B Cells and T Cells in MS Pathogenesis

Historically, MS was regarded as a T-cell-mediated condition. Biopsy and autopsy analyses have shown macrophages and CD3+ T cells as the primary infiltrating cells in demyelinating plaques, with a minority represented by plasma cells.[8] Flow cytometry studies revealed a prevalence of CD8+ T cells over CD4+ T cells in active MS lesions.[9] However, it is now recognized that B cells play a significant role in disease pathogenesis. B cells, classified as regulatory B cells (secreting interleukin (IL)-6, IL-10, IL-35) and pro-inflammatory B cells (secreting IL-6, IL-12, IL-15, granulocyte macrophage-colony stimulating factor (GM-CSF), tumor necrosis factor (TNF)-alpha), contribute to T-cell polarization and antigen processing through major histocompatibility complex and CD80/CD86 activation, augmenting inflammation. These B cell actions may contribute to both MS relapses and disease progression.[10]

CD20, a transmembrane, non-glycosylated phosphoprotein, is expressed primarily on the cell surface throughout various stages of the B-cell life cycle.[11] It consists of four transmembrane helices and two extracellular loops. While it is predominantly expressed on B cells, a small subset of CD3+ T cells also exhibits CD20 on their surface. CD20+ T cells, notably present in the blood and CSF of MS patients, exhibit a proinflammatory phenotype, comprising CD8+ T cells with an effector memory T cell signature.[12] This relatively selective expression on the surface of certain B cell populations has made the depletion of CD20+ cells a promising therapeutic approach.

## Anti-CD20 Monoclonal Antibodies (mAbs) and Role in MS

Anti-CD20 antibodies selectively target memory B cells in MS while sparing plasma cells, which do not express CD20. These therapies rapidly and nearly completely deplete circulating CD20+ B cells but have limited effects on B cells in secondary lymphoid organs. In MS patients, peripheral B cells show abnormal pro-inflammatory cytokine responses, including heightened secretion of lymphotoxin-α, TNF-alpha, IL-6, and GM-CSF. As a result, B-cell depletion significantly reduces pro-inflammatory activity in CD4+ and CD8+ T cells offering robust control of clinical relapses and focal inflammatory disease activity.[6]

The mechanisms underlying B cell depletion by anti-CD20 mAbs are influenced by their molecular structure and epitope-binding patterns, resulting in three distinct pathways: direct induction of cell death, complement-dependent cytotoxicity (CDC), and antibody-dependent cellular cytotoxicity (ADCC). ADCC involves the recognition of antibodies by Fc-gamma receptors present on immune effector cells such as natural killer cells and macrophages, leading to either direct cytotoxicity or phagocytosis. Although all anti-CD20 mAbs can induce the translocation of CD20 into lipid rafts, which allows for greater activation of complement proteins, the relative level of CDC activity varies between them.[12] CDC potency by anti-CD20 mAbs is influenced by the "off rate", which signifies the rate at which a ligand dissociates from the complex with a biomolecule over a set duration. Another critical factor influencing CDC potency seems to be the specific region of the target molecule they bind to. Both factors contribute to the activity of each anti-CD20 mAb in activating complement and inducing cell lysis. Ofatumumab exhibits a slower "off-rate" when compared to rituximab, thus markedly enhancing CDC.[13] Also, due to its greater potency and affinity for B cells, it binds to a unique CD20 epitope achieving nearly complete B-cell depletion at a lower concentration compared to other anti-CD20 mAb.

## Mechanism of B Cell Depletion of Ofatumumab

Ofatumumab, with a molecular weight of approximately 146 kDa, is the first fully human IgG1 mAb approved for the treatment of MS. It binds to discontinuous sequences of the small (amino-acid residues 74–80) and large (amino-acid residues 145–161) extracellular loops of CD20.[14] Ofatumumab is a high-affinity mAb whose epitope on CD20 is distinct from rituximab's target.[15] Unlike ocrelizumab or rituximab, ofatumumab's binding epitope situated near the plasma membrane facilitates Fc-mediated complement binding in close proximity to the cell surface. This characteristic may enhance the effectiveness of CDC initiated by ofatumumab causing more active CDC-dependent B-cell lysis compared to that induced by rituximab and ocrelizumab.[10,12] Ofatumumab has showed higher complement-dependent B-cell lysis in vitro when compared to ocrelizumab (77.1% versus 7.1%) after a 2-hour exposure and continued to effectively induce CDC even with delayed complement addition. This increased potency in CDC is believed to explain why ofatumumab is effective at lower doses, unlike rituximab, ocrelizumab, and ublituximab.[12]

Despite no relevant difference in ADCC activity of ofatumumab compared to ocrelizumab, in vitro investigations have demonstrated that ofatumumab exhibits an approximately two-fold higher ADCC activity compared to rituximab.[12] Moreover, it demonstrates superior binding affinity to the cell membrane and displays a slower dissociation rate from CD20 in comparison to rituximab resulting in efficient B-cell lysis and thus suppression of inflammatory activity.[12]

A summary of Ofatumumab characteristics and other anti CD20 is shown in Table 1.

## The 20 Mg Subcutaneous Dosing Regimen of Ofatumumab

Ofatumumab is administered via subcutaneous (SC) injection at a dose of 20 mg weekly for three doses, then 20 mg monthly starting at week 4. It is mainly absorbed via the lymphatic system and has an estimated steady-state volume of distribution of 5.42 L. Subcutaneous administration may offer enhanced targeting of B cells within the lymphatic circulatory system compared to intravenous (IV) administration, as suggested by studies conducted in a human CD20 transgenic mouse model.[16] This direct access to the lymphatic system allows for a lower dose of drug to achieve CD20+ cell depletion.[7] Indeed, a pre-clinical comparative study showed that subcutaneous ofatumumab demonstrates superior efficiency compared to IV ocrelizumab in targeting lymphoid organs. Specifically, it exhibits a 20-fold higher depleting potency on circulating B cells and comparable potency on non-circulating B cells.[16]

The efficacy of the 20-mg dosage of ofatumumab compared to other doses was assessed by a pharmacokinetic-pharmacodynamic (PKPD) model combining data from Phase 2 and Phase 3 trials of ofatumumab in RRMS. It established a correlation between B-cell counts and ofatumumab concentration. It revealed that both the 20-mg and 40-

**Table 1** Summary of Anti-CD20 Characteristics

| Anti-CD20 / Characteristic | Ofatumumab | Rituximab | Ocrelizumab | Ublituximab |
|---|---|---|---|---|
| Structure and type | Fully human monoclonal antibody (IgG1) | Chimeric IgG1 | Humanized IgG1 | Glycoengineered chimeric IgG1 |
| Route of administration | Subcutaneous: home self-administration | Intravenous | Intravenous | Intravenous |
| Dosage | 20 mg at weeks 0, 1, and 2, followed by subsequent dosing of 20 mg once monthly starting at week 4 | 1 g once every 2 weeks for 2 doses; then repeat 1 g once every 6 to 12 months | 300 mg once on day 1, followed by 300 mg once 2 weeks later; subsequent doses of 600 mg are administered once every 6 months | 150 mg once on day 1, followed by 450 mg once 2 weeks later; subsequent doses of 450 mg are administered once every 24 weeks |
| Primary mode of action | CDC>ADCC | CDC>ADCC | ADCC>CDC | ADCC>CDC |

**Abbreviations**: IgG, immunoglobulin G; ADCC, antibody-dependent cell cytotoxicity; CDC, complement-dependent cytotoxicity.

mg subcutaneous doses administered monthly resulted in a rapid decline and almost complete depletion of B-cells.[17] Lower doses of ofatumumab (1, 2, 5, or 10 mg) failed to achieve comparable levels of B cell depletion.[17]

## Pharmacokinetics and Pharmacodynamics

Ofatumumab's steady-state half-life is approximately 16 days.[18] A subcutaneous dose of 20 mg every 4 weeks leads to a mean maximum plasma concentration (Cmax) of 1.43 mcg/mL at steady state. After subcutaneous administration, it is believed to be absorbed via the lymphatic system. The volume of distribution at steady state is estimated to be 5.42 L following subcutaneous administration of repeated ofatumumab 20 mg dose.[19]

The pharmacodynamic properties of ofatumumab are notable for its effective B cell depletion, as evidenced by findings from both Phase II and Phase III trials.

In the phase II APLIOS study, the majority of recipients exhibited a B cell count of less than 10 cells/μL by day 14, with over 95% of patients maintaining this reduction until the end of the study.[20] Phase III trials of subcutaneous ofatumumab further demonstrated a rapid and sustained decrease in B cell count across all patient subgroups, with 94% of patients reaching a count below 10 cells/μL by study week 4.[7] The median time to B cell recovery post-treatment discontinuation, defined as the time to return to B-cell count of 40 cells/μL (LLN), was approximately 24.6 weeks, with pharmacokinetic modeling suggesting a range of 23 to 40 weeks.[7]

These results were similar to a phase 2 randomized, placebo-controlled trial, in which patients received either ofatumumab IV infusions (100 mg, 300 mg, or 700 mg) or placebo two weeks apart.[21] IV ofatumumab treatment led to significant decrease in CD19+ cell counts in peripheral blood across all three dosage levels. Median CD19+ cell counts dropped to zero within one week of initiating ofatumumab. Recovery began around 12 to 16 weeks after treatment in the ofatumumab 100-mg group, approximately 20 weeks in some patients in the ofatumumab 300-mg group, while all patients in the ofatumumab 700-mg group experienced continuous and complete suppression of CD19+ cells by week 24.[21]

A dose-dependent reduction was also observed in the MIRROR study. B cell reduction was more pronounced in the 60-mg dose administered every 4 weeks, leading to B cell levels decreasing to less than 2% of baseline levels at maximum depletion.[22] The median time to B-cell repletion time was 11 months in patients receiving ofatumumab at doses of 3 mg and 30 mg every 12 weeks, and around 14 months for those receiving 60 mg every 12 or 4 weeks. Despite all dosage groups exhibiting similar rates of B-cell repopulation, the higher-dose groups experienced a delayed time to onset of repopulation. By the end of the study, B-cell repletion was achieved by 64% to 74% of patients across the ofatumumab groups.

Pharmacokinetic-pharmacodynamic (PKPD) model simulations have demonstrated that ofatumumab-mediated B cell depletion does not vary with patient weight, age, or initial B-cell count. The percentage of patients falling below a certain B-cell level remained consistent regardless of body weight.[17] The model projected a median time of approximately 23 weeks for B-cell counts to return to lower limit of normal after discontinuation of medication following 2 years of medication administration.[17] Across all weight categories, the estimated time for B-cell repletion to reach the lower limit of normal ranged between 18 and 29 weeks following the last dose.[17]

## Efficacy of Ofatumumab in Clinical Trials

Ofatumumab has demonstrated strong efficacy in rheumatoid arthritis, and initial studies showed that IV ofatumumab, administered in doses up to 1000 mg, was clinically effective for patients unresponsive to at least one disease-modifying antirheumatic therapy.[23] A subsequent study found that subcutaneous injections of up to 60 mg led to prolonged B-cell depletion and were well tolerated in patients previously treated with methotrexate.[24]

The initial investigations in rheumatoid arthritis patients provided the rationale for the dosing regimen used in ofatumumab's clinical trials for RMS. Multiple studies have showed ofatumumab's clinical efficacy in RMS. These are summarized in Table 2.

A placebo-controlled Phase 2 study, evaluating two infusions of ofatumumab two weeks apart, with doses ranging from 100 mg to 700 mg, led to a notable suppression of new brain lesions by over 99% ($p < 0.001$) in the initial 24 weeks after ofatumumab administration across all doses.[21]

**Table 2** Summary of Ofatumumab Clinical Trials

| Clinical Study | Study Design | Participants demographics | Dose | Outcomes | Results | Adverse Events |
|---|---|---|---|---|---|---|
| MIRROR[22] | Phase 2b, multicenter, randomized, double-blind, placebo-controlled study | Total of 231 patients (67% Female sex, 97%White) | Subcutaneous dose of 3, 30, or 60 mg q12w or 60 mg q4w vs placebo; 24 weeks | Cumulative number of new gadolinium-enhancing (GdE) brain lesions at week 12 | 65% reduction in the mean rate of cumulative new GdE lesions (rate ratio 0.35, 95% confidence interval [CI] 0.221–0.548, $p < 0.001$)<br>Dose-dependent CD19 B-cell depletion | Mild to moderate in severity, no death.<br>≤2% AEs leading to withdrawal<br>SAEs: Injection-related reactions (IRRs) |
| ASCLEPIOS I and II[25] | double-blind, double-dummy, phase 3 trials | Total of 1882 patients<br>927 in ASCLEPIOS I (68% female sex) and 955 in ASCLEPIOS II (67% female sex) | Subcutaneous ofatumumab (20 mg every 4 weeks) or oral teriflunomide (14 mg daily) for up to 30 months | Annualized relapse rate (ARR)<br>3-or 6-month CDW; 6-month CDI, Number of Gd + lesions per T1-weighted MRI<br>Annualized rate of new or enlarging lesions on T2-weighted MRI, sNFL at month 3, Change in brain volume | ASCLEPIOS I:<br>ARR 0.11 with ofatumumab and 0.22 with teriflunomide (95% CI, −0.16 to −0.06; P<0.001)<br>ASCLEPIOS II ARR 0.10 and 0.25 (95% CI, −0.20 to −0.09; P<0.001)<br>CDW 10.9% with ofatumumab and 15.0% with teriflunomide (HR, 0.66; P=0.002) at 3 months and 8.1% and 12.0%, at 6 months (HR 0.68; P=0.01)<br>CDI at 6 months 11.0% and 8.1% (HR, 1.35; P=0.09) | IRR 20.2% in the ofatumumab group and in 15.0% in the teriflunomide group |
| APLIOS[20] | Randomized, open-label, multicenter, parallel-group, 12-week, phase-2 study | Total of 284 patients (70.1% female sex, 96.8% white, 90.1% not Hispanic or Latino) | Subcutaneous ofatumumab 20 mg every 4 weeks (q4w) | Area under the plasma concentration–time curve over the dosing interval and maximum plasma concentration ($C_{max}$)<br>Depletion of CD19+ B cells and MRI parameters (including new or persistent Gd + T1 lesions) | Abdominal administration of bioequivalence to that via PFS<br>99.1% depletion of B cells at day 14<br>Reduced of mean number of new/persisting Gd + T1 lesions from 1.5 at baseline to 0.8, 0.3, and 0.1 by Weeks 4, 8, and 12, respectively | AEs leading to study-drug discontinuation: 0.4% with no deaths occurred<br>Mild to moderate AE mainly IRR |
| APOLITOS[26] | 24-week, double-blind, placebo-controlled core-part followed by an open-label extension-part | 64 patients from Japan and Russia | Subcutaneous ofatumumab 20 mg q4w or placebo; total duration 48 weeks | Number of Gd + T1 lesions per scan over 24 weeks<br>Consistency of efficacy at weeks 12, 16, 20, and 24 | Reduced Gd + T1 lesions with ofatumumab versus placebo by 93.6% ($p < 0.001$)<br>Reduced annualized T2 lesion and relapse rate versus placebo by week 24 | lower incidence of AE with ofatumumab versus placebo (69.8% vs 81.0%). No deaths, opportunistic infections, or malignancies |
| ALITHIOS[27] | Open-label, Phase 3b extension of ASCLEPIOS I/II, APLIOS, APOLITOS | Total of 1969 patients (68.3% female sex) in the safety set, and 1882 in the efficacy set | Subcutaneous 20 mg q4w for up to 6 years | ARR; 3/6mCDW, mean number of Gd + T1 lesions, neT2 lesions per year; sNfL concentration and NEDA-3 status | 44% fewer relapses<br>96.4% and 82.7% reductions in MRI lesions (Gd+ T1 and neT2)<br>24.5% and 21.6% fewer 3- and 6-month CDW events | Overall rates of AEs and serious AEs consistent between the core Phase III trials |

**Abbreviations**: AE, adverse event; SAE, serious adverse event; SC, subcutaneous; ARR, annualized relapse rate; CDW, confirmed disability worsening; GdE/ Gd +, gadolinium-enhancing; IRR, injection-related reaction; MRI, magnetic resonance ratio; PFS, pre-filled syringe; q4w, every 4 weeks; q12w, every 12 weeks; neT2, new/enlarging T2; NEDA-3, No evidence of disease activity with three components; sNFL, Serum neurofilament light chain, HR: Hazard Ratio.

The MIRROR study further showed the effectiveness of ofatumumab in reducing new brain MRI lesions through subcutaneous administration, even at lower doses that do not fully deplete B cells. While the absence of an active comparator warrants cautious interpretation, this study provided evidence for a reduction in inflammatory MRI lesions in RMS. In this phase 2b trial, participants were randomly assigned to receive placebo or various doses of ofatumumab (3 mg, 30 mg, or 60 mg every 12 weeks, or 60 mg every 4 weeks) for 12 weeks. Ofatumumab treatment led to a rapid and dose-dependent depletion of B-cells, which was associated with improved efficacy outcomes. Primary analysis showed a 65% decrease in the mean rate of cumulative new gadolinium-enhancing (GdE) lesions across all ofatumumab groups compared to placebo (rate ratio 0.35, 95% confidence interval [CI] 0.221–0.548, $p < 0.001$).[22] Post hoc analysis revealed a reduction ranging from 71% to 92% in the mean rate of cumulative new GdE lesions from weeks 4 to 12 across ofatumumab groups, with ≥90% suppression observed at cumulative doses ≥30 mg over 12 weeks (0.08 [95% CI 0.044–0.162] to 0.10 [95% CI 0.056–0.187]).[22] The maximum benefit was seen with a cumulative dose of 60 mg of ofatumumab over 12 weeks, with no further lesion suppression noted at higher doses. Surprisingly, the ofatumumab 3-mg every 12 weeks lowered circulating B-cell levels to around 25% of baseline.[22] However, optimal suppression of MRI-visible lesion activity (≥90% reduction) was only achieved with B-cell levels depleted to approximately 32 cells/μL.[22]

The efficacy of ofatumumab was demonstrated in RRMS patients from Japan and Russia in the APOLITOS trial. Ofatumumab reduced the number of Gd+ T1 lesions by 93.6% compared to placebo ($p < 0.001$), with consistent results across both regions.[26] The annualized relapse rate (ARR) for MRI-confirmed relapses was lower in the ofatumumab than in the placebo group with 58.0% rate reduction. Patients on placebo during the first 24 weeks were allowed to transition to an ofatumumab open-label extension for weeks 24 to 48. For patients who switched to ofatumumab, the annualized rate of non-enhancing T2 (neT2) lesions decreased from 12.080 between baseline and Week 24, to 0.813 between week 24 and week 48. Additionally, ARR dropped from 0.684 to 0.083 after transitioning to ofatumumab.[26]

Approval for subcutaneous ofatumumab in patients with RMS was granted by the FDA following the results of phase 3 clinical trials ASCLEPIOS I and ASCLEPIOS II. These trials assessed the efficacy and safety of subcutaneous ofatumumab compared to oral teriflunomide in RMS and formed the basis for this approval. In ASCLEPIOS I, the annualized relapse rates in the ofatumumab and teriflunomide groups were 0.11 and 0.22, respectively (difference, −0.11; 95% confidence interval [CI], −0.16 to −0.06; P< 0.001) and 0.10 and 0.25 (difference, −0.15; 95% CI, −0.20 to −0.09; P < 0.001) in ASCLEPIOS II, demonstrating a significantly lower relapse rate with ofatumumab in both trials.[25] A prespecified meta-analysis of both trials revealed lower percentages of patients experiencing confirmed disability worsening at 3 and 6 months with ofatumumab compared to teriflunomide (hazard ratio 0.66, p=0.002 at 3 months; hazard ratio 0.68, p=0.01 at 6 months), though there was no significant difference in confirmed disability improvement between the groups.[25] Ofatumumab also outperformed teriflunomide in suppressing lesion activity on MRI. Specifically, in ASCLEPIOS I, the mean number of gadolinium-enhancing lesions per T1-weighted MRI scan was 0.01 with ofatumumab and 0.45 with teriflunomide, while in ASCLEPIOS II, these numbers were 0.03 and 0.51, respectively.[25]

Additionally, in both trials, ofatumumab resulted in lower mean numbers of new or enlarging lesions per year on T2-weighted MRI compared to teriflunomide. It also led to reductions in serum concentrations of neurofilament light chain, a marker of neuroaxonal damage, but changes in brain volume did not significantly differ between the two treatments.

Although clinical trial design, comparator arms, and recruitment paradigms differ across trials of B cell therapies in MS, efficacy results from ASCLEPIOS I and II are comparable to those of clinical trials of other B cell depleting therapies like ocrelizumab and ublituximab. Clinical trials of ocrelizumab have shown significant efficacy in reducing confirmed disability progression and MRI markers in RMS and PPMS, with this effect persisting in open-label extension periods.[28–30] Despite the similar efficacy profiles between both medications, ofatumumab has not been associated with confirmed disability improvement and reduced rates of brain volume loss. However, it is important to note that comparison across B cell depleting trials should be done with caution or not at all as trial design, recruitment, and comparator arms may differ. No head-to-head B cell depleting therapy trials exist in MS, and further research is necessary.

Longer-term efficacy and safety of ofatumumab in RMS was evaluated in the ALITHIOS study supporting a favorable benefit–risk profile. Over up to 3.5 years of follow-up, ofatumumab exhibited sustained tolerability with no new safety concerns, alongside further reduction in relapse rates compared to ASCLEPIOS I/II.[27] This was coupled with near-complete suppression of MRI lesions and minimal risk of CDW over up to 4 years.

Although no direct comparisons with head-to-head RCT have been conducted between ofatumumab and other DMTs (other than the ASCLEPIOS trials), the relative efficacy of ofatumumab was shown in a network meta-analysis [NMA]. Ofatumumab exhibited comparable effectiveness to other potent monoclonal antibody disease-modifying therapies (DMTs), such as alemtuzumab, natalizumab, and ocrelizumab, across key measures including ARR, time to 3-month confirmed disability progression (CDP), and time to 6-month CDP.[31]

## Safety Clinical Trials

Due to its fully human nature, ofatumumab has a low immunogenic risk profile with only 2 of 914 patients receiving ofatumumab in ASCLEPIOS I/II developed anti-drug antibodies.[25] Also, the consistent near-complete depletion of B cells observed with ofatumumab trials is thought to offer advantages not only with efficacy and aiding in disease control, but also safety by reducing the risk of severe systemic injection or infusion reactions compared to other DMTs.[7]

In the phase II MIRROR trial, adverse events (AEs) were predominantly mild to moderate, with less than or equal to 2% of patients experiencing study withdrawals, mainly secondary to decreased immunoglobulin or systemic injection-related reactions (IRRs), defined as reaction/symptoms occurring within 24 hours after injection. These comprised mainly of fever, headache, nausea, vomiting, dizziness, rash, urticaria, pruritus, chills, hypotension, tachycardia, asthenia, dyspnea, abdominal pain, diarrhea, fatigue, chest discomfort, arthralgia, myalgia, back pain, cough, bronchospasm, flushing, and hypertension. Despite the high incidence of IRRs (41%–66%), their frequency decreased substantially with subsequent dosing.[22] Serious adverse events (SAEs) were primarily injection-related, with no reported deaths.

Similarly, in the APLIOS trial, AE leading to discontinuation were rare (0.4%).[20] IRRs occurred in 25.0% of patients after the first injection, decreasing to less than 2.8% after subsequent injections.[20] Most IRR were mild to moderate, with a few severe reactions reported. Infections were reported in 20.4% of patients, with nasopharyngitis (2.8%) and rhinitis (2.5%) being the most common. Serious infections, though rare, included cases of appendicitis and pneumonia.[20]

In the ASCLEPIOS phase III trials, IRRs, nasopharyngitis, headache, and injection-site reactions were the most common adverse events. SAEs were documented in 9.1% of patients receiving ofatumumab and 7.9% receiving teriflunomide. Serious infections were infrequent but slightly higher with ofatumumab (2.5%) compared to teriflunomide (1.8%).[25] Injection-site reactions were noted in only 10.9% of patients receiving ofatumumab, with most being mild to moderate.[25] In a sub-analysis of the ASCLEPIOS study IRRs were mostly mild to moderate and occurred primarily with the first ofatumumab injection, while subsequent reactions resembled those with placebo injections in the teriflunomide arm. Following initial training, most participants self-administered injections at home.[32]

Over a 4-year follow-up in the ALITHIOS study, ofatumumab demonstrated sustained tolerability without the emergence of new safety signals. Malignancies were documented in 0.6% of all participants.[27] Among these cases, basal cell carcinoma was seen in 4 patients, while invasive breast carcinoma occurred in 2 patients across the study population. Despite these results, there has been no increased risk of invasive breast carcinoma with ofatumumab, serving as a contrast with data from ocrelizumab RCTs and case series that had suggested a possible higher incidence of breast cancer among ocrelizumab-treated patients.[28,29,33]

Although IgM levels declined, they remained above the lower limit of normal (LLN) on average. Importantly, low IgG or IgM levels were not associated with an increased incidence of serious infection. IgG levels fell below the LLN in only 1.6% of patients, mostly without treatment interruption or discontinuation.[27] Lymphocyte and neutrophil levels remained stable and above the LLN with prolonged ofatumumab use.[27] Guidelines for ofatumumab recommend monitoring the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections along with monitoring after discontinuation of therapy until B-cell repletion.[19] Discontinuation of ofatumumab therapy should be considered if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with IV immunoglobulins.

To prevent infection reactivation, it is crucial to conduct Hepatitis B virus screening, prior to treatment initiation. Vaccination with live-attenuated or live vaccines is not recommended during ofatumumab treatment and until B-cells have been replenished after discontinuation. All immunizations should adhere to guidelines, ideally administered at least 4 weeks before starting ofatumumab for live or live-attenuated vaccines. Additionally, whenever feasible, vaccinations should be administered at least 2 weeks prior to ofatumumab initiation for inactivated vaccines.

## Place in Therapy

Ofatumumab stands out as a pioneer in targeted B cell therapy, allowing for self-administration at home without the need for scheduling infusion visits. This eliminates the need for scheduled infusion visits, potentially enhancing compliance due to its ease of use, with around 95% adherence observed in both core and open-label extension studies.[34] Premedication is not necessary for ofatumumab therapy and is of a little benefit in reducing IRRs.[32]

### Long-Term Benefits of Ofatumumab as a High Efficacy Therapy in Early Disease

Recent evidence from clinical trials and real-world data indicates that early initiation of high-efficacy therapy (HET) results in superior outcomes compared to escalation strategies.[35,36] This includes better prevention of relapses, reduction of disability progression, fewer cases of conversion to SPMS, and overall preservation of brain volume and functions. It is strongly recommended to offer HET early to RMS patients who experience moderate to severe clinical attacks or have high disease activity, especially if they exhibit poor prognostic factors such as male gender, non-white ethnicity, multifocal onset, cognitive impairment, frequent relapses in the first 2–5 years after onset, heavy T2 lesion load, infratentorial lesions on MRI, spinal cord lesions on MRI, and high levels of serum neurofilament light chain.[37]

Results previously reported from the ASCLEPIOS I/II trials and ALITHIOS were further supported by the recent data published regarding longer-term (up to 6 years) efficacy of ofatumumab. In April 2024, updated data from the ALITHIOS open-label extension study demonstrated the sustained efficacy of first line and continuous ofatumumab treatment in individuals with RMS who were recently diagnosed and treatment-naïve. The initial analysis revealed a notable reduction in the already low ARR experienced by recently diagnosed treatment naïve (RDTN) individuals with RMS who received continuous ofatumumab during the core Phase III trials. This rate was further decreased from 0.104 to 0.050 (52.0% reduction), corresponding to an adjusted ARR of one relapse per 20 years.[38] Additionally, rates of 3- and 6-month progression independent of relapse activity (PIRA) with first-line ofatumumab were lower compared to those who switched therapies highlighting the importance of initiating HET. The observed rapid increase in the proportion of participants with no evidence of disease activity (NEDA-3) with continuous first-line ofatumumab treatment was maintained up to six years. Among RDTN individuals initially randomized to teriflunomide, switching to ofatumumab resulted in improvements across several efficacy parameters, including significant reductions in ARR (71.3%) and MRI lesion activity. However, rates of 3- and 6-month confirmed disability worsening (CDW) events remained elevated compared to patients receiving continuous ofatumumab from the onset of the study, indicating that the disability-delaying efficacy of ofatumumab was not fully realized in the switch group. Nevertheless, the majority of participants across both continuous and switch groups achieved NEDA-3 status in 6 years. Subsequent analysis encompassing the entire ALITHIOS population confirmed sustained efficacy of continuous ofatumumab treatment for up to six years, including reductions in ARR and MRI lesion activity, as well as sustained reductions in CDW events relative to the switch group.[39]

Rates of AEs, serious AEs, serious infections, and malignancies remained stable over the six-year period. These long-term efficacy results up to 6 years, combined with the favorable benefit–risk profile demonstrated in the overall study population, support the use of ofatumumab as first-line therapy for RDTN people with RMS. First-line initiation of ofatumumab was associated with significantly fewer CDW events and lower rates of PIRA up to 6 years compared with participants who switched from teriflunomide to ofatumumab, demonstrating that the efficacy benefit of first-line ofatumumab in delaying disability worsening cannot be recovered in those switching from teriflunomide to ofatumumab.

Early initiation of high-efficacy therapy (HET) was also supported in another study demonstrating that early initiation of ofatumumab led to improved outcomes, providing better long-term clinical and economic outcomes compared to teriflunomide treatment from a Spanish societal perspective.[40]

The advantages of initiating ofatumumab earlier in the treatment regimen for patients diagnosed with RRMS was highlighted utilizing a discrete event simulation (DES) model grounded in real-world data from the UK National Health Service (NHS). Findings indicated initiating ofatumumab treatment earlier reduced relapse occurrences and postponed reliance on a wheelchair compared to delayed initiation. Furthermore, a higher percentage of patients who received earlier ofatumumab treatment demonstrated less severe disease progression.[41] These results emphasize the potential therapeutic advantages of initiating ofatumumab early in the treatment trajectory, potentially improving clinical outcomes for individuals with RRMS.[41]

## Economics of Ofatumumab Treatment

In addition to its favorable clinical outcomes, ofatumumab was found to be cost-effective compared to currently approved and reimbursed first-line and second-line therapies for RRMS. Both base case and sensitivity analyses demonstrated similar or better clinical, productivity, and economic outcomes for ofatumumab in comparison to other DMTs approved for RRMS in Canada.[42] This is likely related to the fact that treatment with ofatumumab resulted in patients spending more time in mild disability health states, thereby reducing the proportion of patients experiencing disease progression to states associated with greater disability, reduced caregiver burden, and decreased healthcare resource costs required for managing the disease. Furthermore, patients receiving ofatumumab experienced favorable clinical and productivity outcomes over both 10- and 15-year periods compared to those receiving moderate-efficacy DMTs, potentially positively impacting patient independence and reducing healthcare system costs.[43] Ofatumumab treatment was also shown to be less costly and more effective when compared to ocrelizumab.[44]

## Special Considerations

### Ofatumumab and COVID-19

Coronavirus Disease 2019 (COVID-19) remains a significant threat to immunosuppressed individuals despite vaccination and improved understanding of its pathophysiology and management. In addition to age, male sex, and cardiovascular comorbidities, neurologic disability and anti-CD20 therapies have been linked to severe COVID-19.[45] Patients treated with anti-CD20 therapy may be unable to mount an adequate antibody response to natural infection or vaccination.[46,47] Reduced vaccine response may contribute to a higher frequency of breakthrough infections in patients who received vaccinations while undergoing anti-CD20 therapy and neither the type DMT used during vaccination nor the antibody levels correlate with the severity of infections.[48]

The effects of early ofatumumab treatment on changes in immune cell composition and immune response to SARS-CoV-2 are not fully understood. Although a reduced humoral response can occur, it does not necessarily equate to a lack of functional immunity, as there is significant interest in the memory T-cell-mediated adaptive immune response.[47,48] Indeed, in response to SARS-CoV-2 mRNA vaccination, patients with MS on anti-CD20 therapy have reduced rates of seropositivity, but a robust T-cell receptor repertoires breadth and clonal depth as shown in a post-vaccination study.[49]

Data from the phase 3 ALITHIOS study, comparing ofatumumab to teriflunomide in MS, revealed that out of 1703 patients, 245 (14.3%) reported COVID-19 disease. Among them, 44.1% experienced a mild course, while 46.5% had a moderate course.[50] Severe or life-threatening disease was observed in only 9% of cases, resulting in two deaths. The overall fatal outcome (0.8%) and hospitalization rate (9.4%) due to COVID-19 were lower than those reported in the MS general population general.[50] Breakthrough COVID-19 infections occurred in 1.5% of fully vaccinated participants, all of whom recovered.[50]

Regarding the response to COVID-19 vaccination while on ofatumumab treatment, a recent study examining immune cell alterations in MS patients treated with ofatumumab after receiving a third vaccination against SARS-CoV-2 showed that antibody titers and neutralization capacity against SARS-CoV-2 variants were reduced, while the cellular immune response remained strong, characterized by a robust T helper 1 profile (Th1).[51] While antibody titers are generally low, some people still mount a sizable titer, as evidenced by a case report from the ASCLEPIOS-extension study showing a robust IgM and IgG response against the spike protein after contracting COVID-19, despite experiencing complete depletion of B cells after receiving ofatumumab treatment for 42 months.[52] Interestingly, the levels of anti-SARS-CoV-2 IgG antibodies remained positive three months after the initial infection.[52] This suggests that individuals with MS undergoing ofatumumab treatment may still be capable of mounting an effective immune response to SARS-CoV-2 infection and potentially to COVID-19 vaccines as well.

The interim results from the KYRIOS study shed light on the impact of concurrent ofatumumab treatment on the immune response post-initial and booster SARS-CoV-2 mRNA vaccination. This study revealed that patients undergoing ofatumumab treatment were indeed capable of mounting immune responses following SARS-CoV-2 mRNA vaccination. While the T-cell response appeared unaffected by ofatumumab treatment, a reduction was noted in the humoral response among these patients.[53] This adds further information to previous reports that despite receiving ofatumumab, individuals with MS can

still generate an immune response to SARS-CoV-2 mRNA vaccination. Upon assessing the response following booster vaccination, it was found that patients under continuous ofatumumab treatment exhibited antibody titers comparable to those in the control group. Remarkably, three out of four patients seroconverted after receiving their booster vaccine while on stable ofatumumab treatment. Additionally, an increase in neutralizing antibody titers post-booster was observed in patients who initially received their vaccination while on stable ofatumumab treatment, indicating successful immune memory cell development. These results underscore the importance of booster vaccination in ofatumumab-treated patients, as it enhances the immune response regardless of their treatment status during the initial vaccination.[54]

While the end of the pandemic has significantly reduced the immediate risk of SARS-CoV-2 in the population, it remains crucial to continue analyzing the rates of severe COVID-19 disease and vaccine responses which can have broader implications for responding to other viral infections and enhancing future vaccination strategies.

### Ofatumumab and Pregnancy

To date, only limited evidence is available on most DMTs in pregnancy. A comprehensive study that examined the impact of IV ofatumumab on pregnancy, childbirth, and lactation in cynomolgus monkeys revealed no signs of maternal or embryotoxicity, and offspring development remained unaffected. However, B-cell depletion occurred in both maternal animals and their offspring. Though these effects were generally reversible there were three perinatal deaths in the high-dose group due to infections that were presumably consequences of immunosuppression.[55]

Results from the Novartis Safety Database in women exposed to ofatumumab during pregnancy or 6 months prior to last menstrual period reports 30 known outcomes, among these 16 live births, 8 induced abortions, 5 spontaneous abortions, and 1 ectopic pregnancy. None of the 16 live births reported any birth defects/congenital anomalies or serious infections.[56]

The US Food and Drug Administration (FDA) concludes that there is currently insufficient data to make a recommendation. It recommends avoidance of ofatumumab treatment during pregnancy. The European Medicines Agency and FDA recommends that women of reproductive potential use effective contraception while receiving ofatumumab and for at least 6 months after the last dose. Early interruption of treatment in case of unplanned or expected pregnancy may pose a low risk of fetal exposure.[57] The risk of relapse during pregnancy is generally reduced, and the longer-lasting efficacy of anti-CD20 therapies, demonstrated in extended dosing interval studies,[58] provides ongoing protection during pregnancy. Although limited studies in pregnancy have been conducted so far, early discontinuation of ofatumumab might prevent neonatal B-cell depletion or fetal abnormalities. Further studies are necessary to elucidate the risks.

## Conclusion

Anti-CD20 treatments have revolutionized MS therapy, offering novel mechanisms of action that target underlying disease processes. Ofatumumab represents a significant advancement in the treatment landscape of MS allowing for convenient in-home dosing, which enhances patient compliance. While ofatumumab may differ in safety or tolerability from other CD20-targeting therapies, head-to-head trials comparing anti-CD20 medications are still lacking. Additionally, while ocrelizumab has demonstrated efficacy in PPMS, it remains unclear whether similar benefits can be extrapolated to ofatumumab. Future studies should aim to explore this potential and further establish the comparative efficacy and safety profiles of ofatumumab in the MS treatment landscape.

## Disclosure

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