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REVIEW

Ofatumumab: A Novel Anti-CD20 Monoclonal Antibody for Multiple Sclerosis: A Review of Clinical Considerations

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Abstract

Multiple sclerosis (MS), an autoimmune central nervous system disease responsible for significant morbidity and mortality worldwide, remains imperfectly understood and treated clinically. Recent advances in treating MS have come in the form of new immunomodulatory agents. Of these, anti-CD20 monoclonal antibodies (mAbs) have exhibited particular promise in treating relapsing–remitting multiple sclerosis (RRMS), the early stage of the disease where the adaptive immune system facilitates an autoimmune attack against myelin. The depletion of CD20 positive B cells in patients with RRMS has been associated with decreased symptoms, disease progression, and lesions on MRI, as well as a more favorable side effect profile relative to other immunomodulatory therapies for MS. Of the anti-CD20 mAbs available for use in MS, one of the newest is ofatumumab, a fully human anti-CD20 IgG1κ, sold under the trade name Kesimpta. The present investigation reviews the efficacy and safety of ofatumumab for MS, highlighting the role that B cells play in the initial inflammatory stage of MS and their depletion in decreasing clinical symptoms, T2-enhancing MRI lesions, and progression to the immune-independent phase of MS.

Keywords Multiple sclerosis · Monoclonal antibody · CD20 · Autoimmunity · B cells · Neurodegeneration · Antibody-dependent cytotoxicity

Introduction

Multiple sclerosis (MS) is an antigen-specific, cell-mediated chronic autoimmune disease of the central nervous system (CNS). The disease is characterized by immune infiltration, progressive demyelination, and subsequent axonal loss, leading to a coterie of degenerative neurological symptoms, including, but not limited to, optic neuritis, partial myelitis, sensory disturbances, and internuclear ophthalmoplegia. While the exact inciting cause of the body's autoreactivity in MS is not fully understood, it is has been linked to genetic, environmental, and infectious factors [1–3]. In MS, the adaptive immune system's attack on the myelin of CNS neurons is eventually augmented by the innate immune cells of the CNS (microglia, astrocytes) via cytokine-mediated activation and self-antigen presentation within the inflammatory milieu [4]. Thus, the early, relapsing–remitting inflammatory stage of the disease, which is often clinically silent, precedes the "immune-independent" progressive stage of the disease, where the morbidity of the disease becomes apparent.

Limited success in treating progressive multiple sclerosis (PMS) contrasts with noted success in treating the earlier, immune-mediated stage with various immunomodulatory therapies [5, 6]. Among the FDA-approved medications for the treatment of relapsing–remitting multiple sclerosis (RRMS), such as interferon-β, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, and alemtuzumab, anti-B cell monoclonal antibodies (mAbs) show particular promise in decreasing relapses and diminishing neural inflammation, as measured by T1- or T2-gadolinium-enhanced MRI [7]. The increasing appreciation

Key points
- Recent advances in treating MS have come in the form of new immunomodulatory agents.
- Of the anti-CD20 mAbs available for use in MS, one of the newest is ofatumumab.
- The recommended dose schedule for ofatumumab is 20 mg subcutaneously, pre-filled automatically injecting syringe at weeks 0, 1, and 2.
- Randomized control trials of ofatumumab support its superiority to certain disease-modifying therapies (DMTs).

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of the role of B cells in antigen presentation, antibody production, cytokine release, and the formation of ectopic CNS germinal centers has made these cells attractive targets for treatment [8]. One surface protein located on both proinflammatory and anti-inflammatory B cells and a small subset of T cells is CD20, whose exact function is unknown [9]. Because CD20 is expressed throughout B cell development through the mature naïve to memory B cell stage, but is lost when the B cell becomes a plasmablast, CD20 represents a promising immunomodulatory target for depleting the memory B cells that are thought to contribute heavily to the pathology of MS and are likely responsible for the characteristic monoclonal bands observed in the cerebrospinal fluid of MS patients [10].

The available mAbs for targeting CD20 include rituximab, ocrelizumab, and ofatumumab. The recent development of mouse chimeric mAb (rituximab), humanized mAb (ocrelizumab), and fully human anti-CD20 IgG1κ (ofatumumab) heralds an increasingly favorable side effect profile for this class of drugs in the treatment of MS; indeed, some anti-CD20 mAbs have already been shown to provide a more favorable side effect profile relative to some other historically used multiple sclerosis disease-modifying therapies (DMTs), such as interferon-β and teriflunomide [11, 12]. Intravenously administered anti-CD20 mAbs have been associated with infusion reactions, anemia, increased risk for progressive multifocal leukoencephalopathy (PML), and thrombocytopenia; however, safety protocols, including premedication with antihistamines, anti-pyretics, and glucocorticoids, can be used to manage symptomatic infusion reactions [13]. Notably, ofatumumab represents the first anti-CD20 mAb for multiple sclerosis that can be subcutaneously administered via auto-injector pen, increasing treatment accessibility relative to other intravenously administered multiple sclerosis DMTs [14].

Relative to other anti-CD20 pharmacological agents, ofatumumab binds two novel epitopes on CD20 to trigger antibody-mediated cell lysis (ADCC) and complement-mediated cell lysis (CDC) of B cells [15]. Among these two mechanisms, CDC is more prominent. In contrast to other anti-CD20 agents, ofatumumab is not internalized from the cell surface and shows relatively slower off-rate kinetics than rituximab. It is possible that the binding of novel CD20 epitopes and favorable kinetics could result in the superiority of ofatumumab relative to rituximab and other anti-CD20 mAb agents in decreasing relapse symptoms and T2 gadolinium-enhancing brain lesions on MRI, but more research is needed comparing these mAbs head to head in MS patients [7]. As our understanding of multiple sclerosis's pathophysiology, progression, and natural history increases, humanized mAbs, such as ofatumumab, show particular promise in reducing the characteristic inflammatory infiltrates of multiple sclerosis while minimizing potential adverse effects.

Multiple Sclerosis Pathophysiology and Treatment Rationale

Traditionally, multiple sclerosis was thought to be mediated by T cells without the involvement of B cells or antibodies. In reality, the demyelination present in MS lesions involved B cells and antibodies working together with the T cells [16]. The T- and B-cell autoimmune-mediate neurodegeneration in multiple sclerosis is typically defined by inflammatory demyelination with axonal transection. Typically, the disease manifests in young adults and leads to a decline in their physical ability, cognition, and quality of life. Diagnosis by the 2017 McDonald criteria requires radiographic and laboratory findings, including MRI T2 lesions and CSF oligoclonal bands, respectively [17]. Although the risk factors for the development of multiple sclerosis are multifactorial, there is a conspicuous genetic risk factor in possession of the HLA-DRB*15:01 allele in the class II major histocompatibility complex. Other inheritable risk factors include the IL2RA and IL7R genes. Environmental factors like vitamin D and ultraviolet radiation are thought to reduce the risk of MS development. They may be related to the fact that MS is more prevalent at higher latitudes. It is thought that vitamin D, which is linked to other autoimmune diseases, can suppress the immune system by influencing both B- and T-cell proliferation [18].

MS is categorized into three subtypes. These subtypes include relapsing–remitting MS (RRMS), progressive MS (PMS), and clinically isolated syndrome (CIS). Most of those diagnosed with MS have RRMS, defined by transient episodes of disease activity with new or expanding CNS lesions [13]. MS affects approximately 900,000 individuals in the USA, with a prevalence of 5 to 300 per 100,000 people [19]. Prevalence increases at higher latitudes and varies according to gender, so women are more likely to be affected by multiple sclerosis than men. Life expectancy is around 7 years less than the general population (75.9 years vs. 83.4 years). Besides anti-CD20 monoclonal antibodies, several drugs are available for relapsing–remitting multiple sclerosis, such as interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate receptor modulators, fumarates, and cladribine [17]. Recent insight into B cells' role in the disease has spurred the development of treatments with anti-CD20 monoclonal antibodies [20].

Ofatumumab Overview

Ofatumumab is a fully human monoclonal antibody with sufficient activity in vivo at plasma concentrations of 5 to 10 μg/mL [20, 21]. It was first generated by

immunizing human immunoglobulin transgenic HCo7 and KM mice with human CD20-expressing NS/0 cells [21]. Besides multiple sclerosis, it is currently approved for treating refractory chronic lymphocytic leukemia. In addition, it is also being tested for use in a subcutaneous dosing regimen rather than intravenous formulation, which is the application approach used by most anti-CD20 monoclonal antibodies. One limitation of anti-CD20 monoclonal antibodies is the possibility of failure in depleting some B cells in the central nervous system parenchyma or meninges, or indeed plasma cells anywhere else in the body. These residual cells are a source of underlying progressive disease activity [22, 23]. Despite this, these limitations may play a role in the favorable safety profile of these monoclonal antibodies. Therapies that target the immune system more broadly may not have this limitation but may have a less favorable safety profile due to more extensive patient immunosuppression (Table 1) [20].

Therapeutic monoclonal antibodies are used to treat a broad spectrum of clinical conditions, including transplant rejection, cancer, autoimmune conditions, and the prevention of viral infections [21]. Specifically, several are used to treat hematological malignancies of the B-cell lineage, such as rituximab, and anti-CD20 monoclonal antibody [16, 24]. Ofatumumab is unique in that its therapeutic effector mechanism involved in destroying CD20-positive tumor cells is through complement-dependent cytotoxicity along with antibody-dependent cellular toxicity, giving it the ability to treat low CD20-expressing malignancies [15, 25, 26]. It has been shown in vivo that while antibody-dependent cellular toxicity predominates at lower antibody-binding levels, complement-dependent cytotoxicity becomes active at higher antibody-binding levels [21]. Cells that do not possess CD20 and are spared from lysis include stem cells or pro-B cells, many plasmablasts, and plasma cells which produce antibodies [20].

Dosage

Ofatumumab may be administered intravenously or via subcutaneous, self-administered autoinjector. Injection of ofatumumab represented a shift in the treatment options for MS. The ability to administer home care, as opposed to inpatient management, allows for more widespread use of the drug, as shown by both nurse and patient preference for the Sensoready® auto-injector pen compared to previous administration methods [27]. The recommended dose schedule for ofatumumab is 20 mg subcutaneous, pre-filled automatically injecting syringe at weeks 0, 1, and 2. After this time, a monthly administration of 20 mg subcutaneous, pre-filled syringe at week 4 becomes the maintenance dose [14]. In a study comparing ofatumumab with the recommended dosage schedule of once daily teriflunomide 14 mg, ofatumumab demonstrated a reduced relapse rate and reduced occurrence of lesions in patients recently diagnosed with MS and had no previous treatment [14]. Personalized dosage adjustments in patients with hepatic or renal insufficiency taking ofatumumab have not been studied; however, in patients who have experienced an infusion reaction, dosage adjustments may be made based on the grading of the infusion reaction; some sources recommend decreasing the infusion rate by 50% following resolution of a grade 1 or 2 infusion reactions (rash, urticaria, dyspnea, etc.), or using an infusion rate of 12 mL/h in the case of grade 3 or 4 infusion reactions (bronchospasm, hypotension, etc.) [14, 28]. In the case of evidence of hepatitis B or progressive multifocal leukoencephalopathy reactivation, ofatumumab should be discontinued immediately.

Adverse Effects

Using the phase III (ASCLEPIOS I and II) trials, in which 946 patients received treatment with ofatumumab, 83.6% of participants (791 patients) reported an adverse event

Table 1 Timeline for development of anti-CD20 monoclonal antibodies used for multiple sclerosis

Drug; structure	FDA initial approval use (year of approval); side effects
Rituximab (Rituxan) Chimeric M*o*Ab	Non-Hodgkin's lymphoma (1997) Side effects: emesis, oliguria, anemia, arrhythmia
Ocrelizumab (Ocrevus) Humanized M*o*Ab	Relapsing–remitting and primary progressive multiple sclerosis (2017) Side effects: colitis, back pain, bloating, vertigo, emesis
Obinutuzumab (Gazyva) Humanized MoAb	Chronic lymphocytic leukemia (2013) Side effects: ecchymosis, hepatitis, headache, diarrhea
Ublituximab (Briumvi) Chimeric MoAb	Relapsing–remitting multiple sclerosis (2022) Side effects: vertigo, insomnia, hematuria
Ofatumumab (Arzerra) Fully human MoAb	Chronic lymphocytic leukemia (2009) Side effects: rash, progressive multifocal leukoencephalopathy

All may present with infusion reaction, tumor lysis syndrome, and immunosuppression

occurring within 100 days of drug administration [29]. Infection was the leading adverse event, with 51.6% of patients reporting nasopharyngitis, upper respiratory tract infection, or urinary tract infection [29]. In addition to infection, systemic injection reactions, defined as symptoms occurring within 24 h of injection, were also reported. These symptoms included but were not limited to fever, headache, nausea, vomiting, rash, urticaria, hypotension, flushing, chest discomfort, and arthralgia [29]. Instances of neoplasms were also reported, with five total cases in the ofatumumab group (0.5%). Neoplasms reported included two instances of basal-cell carcinoma, one case of malignant melanoma, one case of recurrent non-Hodgkin's lymphoma, and one case of invasive breast carcinoma [29].

Concerning the effects of ofatumumab on pregnancy and fetal development, a study on cynomolgus monkeys showed no association between drug administration and maternal or embryo toxicity [30]. The development and growth of the exposed offspring were also not affected [30]. The presence of ofatumumab in breastmilk has not been extensively studied. Still, a study on rituximab, a comparable anti-CD20 monoclonal antibody, demonstrated very low levels of transfer to the infant with limited absorption by the infant [31].

Yet another complication of anti B-cell therapy is hypogammaglobulinemia, though anti-CD20 monoclonal antibodies do not disrupt the function of mature plasma cells. In ocrelizumab, yet another anti-CD20 monoclonal antibody, the majority of patients remained above the lower limit of normal for IgG (94.9%) and IgM (70.5%) over 5 years of therapy [32]. In one meta-analysis examining ofatumumab versus similar anti B-cell therapies, these agents were significantly associated with decreased IgG levels; additionally, decreased IgG levels were not significantly associated with an increased risk or severity of infection in treated groups [33].

Ofatumumab in Relapsing–Remitting MS

Preliminary clinical trials have shown beneficial effects of ofatumumab in relapsing–remitting multiple sclerosis, such as reduction in new brain lesion formation on MRI, reduction in rates of clinical relapse, and prolonged duration of efficacy with no evidence of rebound activity after stopping the treatment. Furthermore, a favorable safety profile was noted [34]. High-dose, intravenous ofatumumab used as an RRMS treatment in phase II randomized, double-blind placebo-controlled trial has shown no serious adverse effects, with decreased relapse incidence relative to placebo observed (19% vs. 25%) [35]. In phase II, placebo-controlled, randomized, manufacturer-sponsored MIRROR study, the effects of varying doses of subcutaneous ofatumumab in patients with RRMS were measured through the rate of new gadolinium-enhancing T1 brain lesions detected via MRI [36]. Patients were divided into groups of differing medication dosages, including placebo, 3 mg, 30 mg, and 60 mg. A 65% reduction in the rate of new brain lesions was seen when comparing any of the ofatumumab-receiving groups to the placebo group, supporting the efficacy of subcutaneous ofatumumab [36].

Another systematic review of over 30 randomized controlled trials compared ofatumumab to other monoclonal antibody treatments available for RMS, mainly analyzing the safety profiles of each drug [37]. No statistically significant difference was seen in the rate of infections among monoclonal antibody treatments used when compared to each other; however, compared to placebo, ofatumumab did have an increased risk of infection [37].

Clinical Trials and Evidence: Ofatumumab

A randomized, double-blind, placebo-controlled study with class II evidence was one of the first trials to look at the safety and efficacy of ofatumumab for patients with relapsing–remitting multiple sclerosis (RRMS) [35]. Thirty-six patients completed the study and were assigned to receive either 2 IV infusions of ofatumumab or a placebo 2 weeks apart. Ofatumumab doses were either 100, 300, or 700 mg. After 24 weeks, treatment groups were switched to start receiving a placebo, and placebo groups began receiving ofatumumab. In the 700-mg ofatumumab groups, not a single patient had any MRI lesions or experienced any relapses, whereas 8 of the 12 patients who received a placebo had at least one new T1-weighted gadolinium-enhancing (GdE) lesion. However, one patient from the 100-mg ofatumumab group also developed a new T1 GdE lesion. Overall, including all treatment groups from weeks –24, there was a 99% reduction in the total number of T1 GdE lesions ($p < 0.001$). Safety-wise, researchers found that ofatumumab was well tolerated, and infection rates were similar to those of the placebo groups. However, the only consistent treatment adverse event was infusion-related reactions such as rash, often occurring during the first dose.

The phase III ASCLEPIOS I and II trials, published in the *New England Journal of Medicine*, evaluated the efficacy and safety of ofatumumab in 1882 patients, across 37 countries, with RRMS [29]. In these trials, ofatumumab was compared to teriflunomide, a pyrimidine synthesis inhibitor and commonly used oral medication for MS. The results showed that ofatumumab reduced the annual relapse rate (ARR) by 50.5% (0.11 to 0.22) compared to teriflunomide, meeting the study's primary endpoint. Additionally, ofatumumab was superior to teriflunomide in reducing the number of new or enlarging T2 lesions (82% lower) and gadolinium-enhancing T1 lesions (97% lower) on MRI scans.

The safety profile of ofatumumab was similar to teriflunomide's; however, ofatumumab yielded a higher percentage of injection-related systemic reactions (20.2% ofatumumab vs. 15.0% teriflunomide).

The MIRROR Study, a phase 2b double-blind trial, compared the efficacy and safety of ofatumumab to placebo, in 232 patients with relapsing–remitting MS [36]. Patients were assigned to either 3, 30, or 60 mg subcutaneous ofatumumab every 12 weeks, 60 mg every 4 weeks, or placebo, all for a 24-week treatment. The study's primary endpoint was the number of gadolinium-enhancing lesions on MRI scans. The results showed that ofatumumab reduced new lesions by at least 65% in all dose groups ($p < 0.001$) and ≥ 90% in drug doses 30 mg or greater after 12 weeks. Although not necessary for an ample treatment outcome, dose-dependent CD19 b-cell reduction occurred. Similar to other studies, injection-related reactions, although not severe, occurred in 52% of ofatumumab patients, compared to only 15% of patients receiving a placebo.

Finally, a meta-analysis looked at 82 randomized controlled trials. It measured the annualized relapse rate (ARR) as well as confirmed disability progression (CDP) for ofatumumab versus other very effective monoclonal antibodies that are frequently used in the treatment of MS [6]. Measuring the ARR using 30 trials, ofatumumab was statistically significantly superior to common first-line agents such as teriflunomide and dimethyl fumarate. However, there was no statistical significance differentiating ofatumumab concerning cladribine, natalizumab, ocrelizumab, or alemtuzumab on ARR. Using 20 trials, the authors also measured CDP at 3 and 6 months. They found that ofatumumab had statistically significantly less disease progression at 3 months than teriflunomide, fingolimod, and glatiramer acetate. At 6 months, ofatumumab was again superior to teriflunomide. At both 3 and 6 months, ofatumumab was just as effective in reducing disease progression as other monoclonal antibody therapies such as alemtuzumab, ocrelizumab, and natalizumab (Table 2). In different review, ofatumumab was found superior to ublituximab in decreasing lesion volume over time as measured by MRI T2; however, ofatumumab was found inferior to ocrelizumab on imaging [38].

In the rapidly expanding field of immunotherapy monoclonal antibodies, there are multiple CD20 B-cell depleting antibodies, including rituximab, ocrelizumab, and ublituximab, in addition to ofatumumab. While side effect profiles largely resemble each other and therapeutic efficacy for the treatment of multiple sclerosis does not vary largely, investigation of these advantages and disadvantages of these antibodies does show differences based on route of administration, kinetics, and initial dosage [38]. In a review of phase III clinical trials examining these monoclonal antibodies, it appears infection risk is increased in rituximab, ocrelizumab, and ublituximab relative to ofatumumab; however, ofatumumab was found to be inferior to ublituximab from the perspective of decreasing annual relapse rate [38]. In sum, randomized control trials of ofatumumab appear to support its superiority to certain disease-modifying therapies (DMTs) such as dimethyl fumarate, teriflunomide, fingolimod, glatiramer acetate, interferon α-1a, and interferon β-1b, as well as other anti-CD20 B-cell depleting MoAbs in the prevention of new lesions and/or disease progression in patients with relapsing–remitting multiple sclerosis.

Conclusion

MS remains a complex, incompletely understood disease. Progress in understanding the pathophysiology and natural history of the disease has accelerated the development of immunomodulatory therapies that target cell-mediated autoimmunity. In contrast to the more generalized immunosuppressive agents used for treating inflammatory stage RRMS, MoAbs-targeting CD20 cells have distinguished themselves in clinical trials for their ability to reduce symptoms on the Expanded Disability Status Scale (EDSS) and T2 gadolinium-enhanced MRI lesions. With

Table 2 Ofatumumab versus other B-cell modulators for multiple sclerosis

Study	Findings
Sorensen et al. (2014) Randomized control trial	36 patients with relapsing–remitting multiple sclerosis receiving 700 mg ofatumumab experienced a 99% reduction ($p < 0.001$) in new T1-weighted gadolinium-enhancing (GdE) lesions relative to placebo control during weeks 8–24 of the 24-week treatment regimen
Hauser et al. (2020) Randomized control trial	In 1886 multiple sclerosis patients, ofatumumab was superior to teriflunomide in reducing annual relapse rate (11% reduction), new or enlarging T2 lesions (82% reduction), and number of gadolinium-enhancing T1 lesions (97% lower)
Bar-Or et al. (2019) Randomized control trial	In 232 patients with relapsing–remitting multiple sclerosis, subcutaneous ofatumumab reduced new gadolinium-enhancing lesions on MRI by ≥ 90% in drug doses 30 mg or greater after 12 weeks relative to placebo control
Samjoo et al. (2020) Meta-analysis	Across 82 randomized control trials comparing ofatumumab to other effective monoclonal antibodies frequently used for MS, at 3 and 6 months of treatment, ofatumumab demonstrated similar efficacy as measured by confirmed disability progression and annualized relapse rate relative to natalizumab, alemtuzumab, and ocrelizumab

the advent of ofatumumab, a subcutaneous, fully humanized anti-CD20 is now a treatment option for RRMS.

Although anti-CD20 therapy represents a promising new tool for treating RRMS, progressive multiple sclerosis (PMS), associated with immune-independent mitochondrial injury, oxidative stress, and tissue hypoxia, is poorly treated with immunomodulatory therapy. Although anti-CD20 therapy has exhibited limited success in patients with PMS, early treatment of the disease, in the inflammatory stage, remains the highest yield target. The clinical findings of anti-CD20 therapy concord with the role of B cells in the natural history of the disease, where B cells are the antigen-presenting cells driving the activation and development of self-reactive T cells, which also play a central role in the initiation and flares of RRMS. B cells that have crossed the blood–brain barrier and reside in the meninges in ectopic lymphoid follicles may underlie the difficulty in depleting B cells in later disease. Early treatment of RRMS patients necessitates expeditious screening and detection. The initial complaint crossing the clinical detection threshold is often followed by a lengthy period of relapsing–remitting disease, where symptoms are clinically silent.

August, 2020, saw the FDA's approval of ofatumumab (trade name Kesimpta) for treating CIS, RRMS, and secondary PMS. Thus, ofatumumab is one of the newest treatment options for patients with multiple sclerosis. With the drug being in its relative infancy in terms of clinical availability, there is a lack of research on the long-term outcomes of using this drug for MS. More clinical trials are needed to follow ofatumumab through long-term disease progression. With a disease as heterogeneous as MS, effective therapy of patient may require a combination of several different DMTs, with the end goal being no evidence of disease activity (NEDA). It may be that new MoAbs, such as ofatumumab, will be key tools for achieving NEDA in future MS patients.

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Declarations

Ethics Approval This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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