REVIEW ARTICLE

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Anti-CD20 treatment in multiple sclerosis

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Abstract

Introduction and Objective. Multiple sclerosis (MS) is a chronic inflammatory disease affecting the central nervous system, and leading to damage to nerve cells. Recent findings have underlined the importance of B lymphocytes in MS pathogenesis, the role of which includes the expression of the CD20 antigen. The aim of this scoping review is to summarize current data on immunological basis, clinical efficacy, and future perspectives of MS treatment options using anti-CD20 antibodies.

Review Methods. A comprehensive literature review was conducted using the PubMed database and ClinicalTrials.gov website, with a particular focus on studies related to anti-CD20 monoclonal antibodies in MS treatment, published between 2018–2025.

Brief description of the state of knowledge. Anti-CD20 therapies, such as rituximab, ocrelizumab, ofatumumab and ublituximab, successfully reduce relapse rates, disability progression, and MRI disease activity by depleting pathogenic B cells in some specific mechanisms of action, including ADCC, CDC, and ADCP. Despite high efficacy, some adverse events may occur. Injection related reactions, infections and hypogammaglobulinemia are most frequently identified. Some cases of cancers have been also been reported, which suggest the need for long-term observational studies. Moreover, reduced vaccination responses observed following prolonged B cell depletion, address the importance of optimal immunization prior to treatment initiation, and individualization of the approach to MS patients.

Summary. Anti-CD20 medications constitute a significant step in MS treatment, effectively tackling pathogenic mechanisms mediated by B cells; however, their long-term impact on human immune system require ongoing evaluation studies. Clinical trials comparing different anti-CD20 drugs are being held currently, and their results may prove to be crucial for optimizing patients' outcomes.

Key words

multiple sclerosis, rituximab, demyelinating diseases

INTRODUCTION AND OBJECTIVE

Multiple sclerosis (MS) is a chronic disease which presents in four clinical forms (Fig. 1) that negatively impacts the central nervous system (CNS). Typical features of the illness include inflammation, demyelination, gliosis, and neuronal death. MS attacks primarily target myelinated axons in the CNS, leading to harmful effects on myelin and axons [1].

Clinical relapse occurs when new or recurring neurological symptoms remain for more than 24 hours without concomitant sickness, followed by a total of 30 days of stability or improvement. MS affects approximately 2.9 million

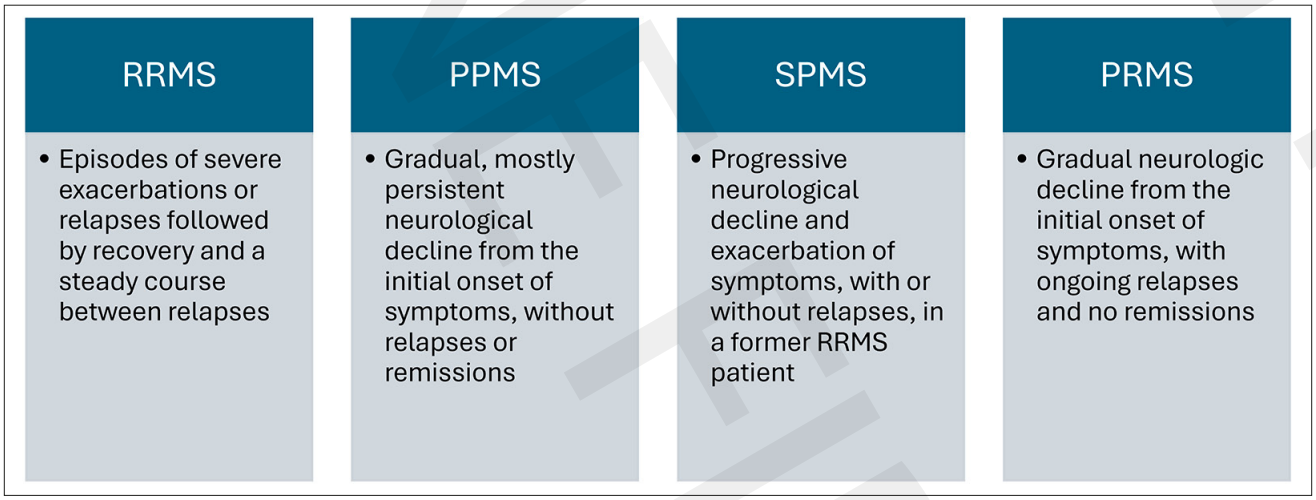

Figure 1. Clinical forms of MS. PPMS, primary progressive multiple sclerosis; PRMS, progressive-relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

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individuals globally and is most commonly diagnosed in women between the ages of 20 – 50. White race in general, and specifically people of Northern European ancestry, are more likely to develop the condition, which increases in prevalence as one goes farther from the Equator. However, several locations have seen a surge in MS cases, for example, Iraq, with a prevalence of 4.4 per 100,000 [1–3].

The aim of this scoping is to summarise the currently available evidence on anti-cluster-of-differentiation (CD)-20 therapy in MS, with particular focus on immunological background, clinical efficacy, possible safety concerns, and future prospects. The topic is especially relevant, taking into account rapidly developing treatment options, as well as ongoing studies on frequently used MS medicines.

B lymphocytes and their function. B cells go through many developmental phases. Firstly, they arise from the lymphoid progenitor lineage. Then, they develop into pro-B cells, which by multiplying and reorganizing immunoglobulin κ light chains, result in formation of immature B cells. These cells experience a process of negative selection, which aims to eliminate auto-reactive clones. After leaving the bone marrow, B cell lymphocytes transform in secondary lymphoid organs into mature B cells. They then mature into different types of cells, such as plasmablasts (PBs), memory B cells and plasma cells (PCs). Negative selection eliminates clones with dysfunctional B cell receptor (BCR) modifications or strong affinity for auto-antigens, potentially leading to immune-mediated illness. A balanced interplay between cell proliferation and death ensures stable levels of memory B lymphocytes and PCs in the bone marrow [1, 2].

B cells contribute to humoral and cellular immunity in the adaptive immune system, as well as in the innate-adaptive immunological interface. B cells express BCRs and Toll-like receptors, which identify pathogen components. Antigen exposure, in addition to information from T cells, stimulates B cells activation and maturation into PCs that secrete protective antibodies. However, self-antibodies responsible for autoimmune disorders may also be produced [3].

B lymphocytes in MS. At first, researchers were linking T lymphocytes, especially CD4+ and CD8+, with MS pathogenesis; however, this approach has changed recently. It is thought that B lymphocytes have a more significant role while various immune cells contribute to CNS failure. When it comes to B cells, there are several ways in which they contribute to MS. Firstly, they act as antigen-presenting cells (APCs), crucial for T cell stimulation [4]. B cells are effective APCs that express class-II major histocompatibility complex (MHC class II), capable of binding free, as well as embedded in the membrane antigens. They are known for presenting antigens and activating T cells more efficiently than APCs of non-B-cell origin [5].

In terms of MS pathogenesis CD80 and CD86 are relevant proteins which are expressed on the outside layer of the cell and trigger interaction with T cells and their activation – which is a crucial aspect of the immune response in MS.

The evidence suggests that the autoimmune reaction begins with Th cells entering the CNS, followed by B lymphocytes infiltrating the afflicted area. B lymphocytes differentiate into PCs responsible for autoantibodies production that target structural and functional parts of neurons. Moreover, B cells may contribute to promoting Th cells translocation towards demyelinating lesions. Disease-causing B and T cells are able to penetrate the blood-brain barrier by activating certain chemokine receptors, cytokines that promote inflammation and adhesion molecules, leading to CNS disease in MS individuals. The specific processes, however, are still uncertain [4].

Studies revealed that MS is linked with elevated concentrations of B cells and PBs in cerebrospinal fluid (CSF). CSF PBs levels correlate with intrathecal immunoglobulin G (IgG) production and magnetic resonance imaging (MRI)-detected inflammatory parenchymal disease status, indicating inflammation in CNS [6]. Moreover, it was revealed by deep sequencing of IgG heavy chain variable regions that B cells respond actively in the periphery, implying that immunological responses and developmental processes take place simultaneously in the peripheral and CNS [7].

Addressing B cells in MS was initially motivated by the identification of abnormal antibodies production in CNS, such as oligoclonal bands (OCB) in CSF, accelerated Ig synthesis, detection of Ig and complement in demyelinating lesions. CSF OCB in patients are usually persistent, which is assumed to be a result of both continuous CNS inflammation and immune memory; however, there are examples of OCB disappearance after receiving treatment [8]. The OCB target antigens have been thought to be important for the pathophysiology of MS. According to the most widely accepted explanation, IgG in OCB targets viruses and/or myelin autoantigens that may cause direct or indirect CNS injury through molecular mimicry [9].

The pathophysiological relevance of specific antibody production in MS requires further investigation. There is no obvious link between antibody levels and disease severity, and none of the isolated antibodies are specific to MS [6].

Mechanisms of action of anti-CD20 therapies. B cell depletion treatment, which targets the CD20 receptor, has been utilized for systemic autoimmune disorders, affecting many immunological systems. Among the Food and Drug Administration (FDA)-approved disease modifying therapies, (DMTs) for MS, anti-CD20-mediated B cell depletion has been demonstrated as effective and reasonably secure.

Anti-CD20 monoclonal antibodies (mAbs) are therapeutics binding to the transmembrane phosphoprotein called CD20 antigen, which is expressed by some forms of B cell lineage [7, 10]. Figure 2 shows hematopoiesis demonstrating B cell lineage development, including particular forms of B cells that express CD20 [5]. The exact physiological function of CD20 antigen remains unclear, although it is believed to play a role in B cell differentiation, growth, and calcium flux control [11, 12]. The antigen is present on more than 90% of B cells and on the small group of T cells. mAbs attach to the CD20 cells leading to the death of B cells in different ways, which will be described later. Some components of the B cell lineage, which are CD20-negative (pro-B cells, PBs, and antibody-secreting PCs), remain unaffected [4, 10].

There are two categories Anti-CD20 antibodies. Type I causes CD20 reorganization into lipid rafts, which promotes the recruitment and activation of complement proteins. This leads to high complement-dependent cytotoxicity (CDC). In type II, on the contrary, antibodies do not reorganize into lipid rafts and, as a consequence, CDC is low. Nevertheless,

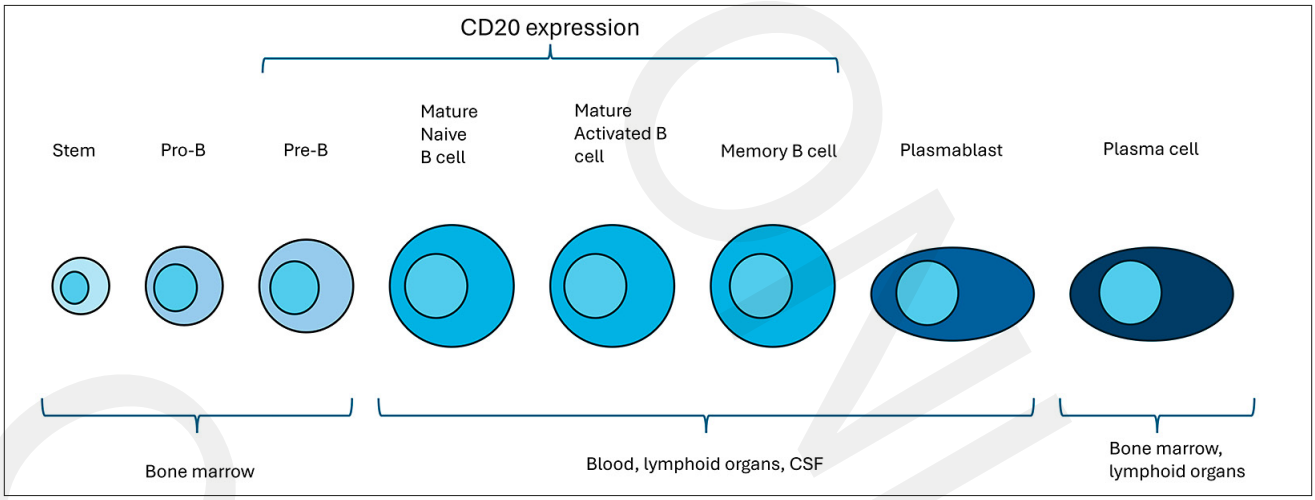

Figure 2. B cell lineage development, including particular forms of B cells that express CD20 and their place of origin. CSF, cerebrospinal fluid

in this case, B cell death may be caused in a direct, non-apoptotic way [13].

mAbs aimed at specific targets eliminate the intended cells in at least four known mechanisms. Besides the above-mentioned CDC, researchers have distinguished antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and programmed cell death. As far as anti-CD20 mAbs are concerned, B cell depletion is primarily prompted by ADCC, CDC, and ADCP [5].

Anti-CD20 mAbs are administered by slow intravenous (IV) infusion, which leads to significant reduction of CD20 B cells in a short time [5]. This reduction usually reaches its lowest point after eight weeks of treatment and may persist for weeks or months, in line with the dose and specific properties of the anti-CD20 mAb. Following the therapy, B cells begin to regenerate within the bone marrow and spleen. To prevent interference from anti-CD20 mAbs, levels of B cells are often measured using CD19 cells, which overlap with CD20 cells during differentiation [14]. From all anti-CD20 mAbs, only type I are authorized in MS. Nevertheless, some preclinical findings indicate that type II antibodies might serve as a therapeutic option in the future. This review includes only type I mAbs approved for MS treatment or promising mAbs in ongoing clinical trials [13].

Efficacy of anti-CD20 therapies

Rituximab (RTX). Although widely used in medical settings, RTX has not been approved for MS, and only a limited number of studies have evaluated its role in MS. It is a hybrid murine-human IgG1 κ mAb which induces more CDC than ADCC [4]. Besides in MS, RTX is frequently utilized in haematological and autoimmune disorders, such as chronic lymphatic leukemia, rheumatoid arthritis, and granulomatosis with polyangiitis, and non-Hodgkin's lymphoma (NHL) [7].

RTX is administered IV in MS, and as a prevention of infusion-related side-effects, pre-medication with drugs such as diphenhydramine or corticosteroids should always be prescribed [15]. The initial dose is 1,000 mg, and the same dose is given on day 15, with subsequent doses given every six months [4]. Hauser et al. [16] performed an important trial investigating RTX's effectiveness in individuals with RRMS. The trial was a phase II, double-blind, placebo-controlled study of RTX which assessed the number of gadolinium-enhancing (Gd-enhancing) brain MRI lesions at weeks 12, 16, 20, and 24, following two IV doses of 1,000 mg RTX administered on days one and 15 [16].

Compared with those receiving placebo, individuals treated with RTX experienced considerably fewer relapses at week 24 (14.5% vs. 34.3%) and week 48 (20.3% vs. 40.0%) [16]. Another study conducted by Svenningsson et al. aimed to compare the safety and therapeutic effectiveness of RTX and dimethyl fumarate (DF) in RRMS patients. It was a multicentre, rater-blinded, active-comparator, phase 3, randomized controlled trial in 200 participants divided into two treatment groups: group 1 received IV RTX 1,000 mg initially, then 500 mg every six months, while group 2 received oral DF 240 mg twice daily. RTX was shown to be more effective than DF in relapse prevention during a 24-month period (3% vs. 16%, respectively) [17].

Several clinical trials are currently underway on the treatment of MS with RTX, demonstrating its potential. For example, the DanNORMS [15] study is investigating whether RTX treatment is comparable in terms of efficacy to ocrelizumab (OCR) in patients with active MS. The main outcome is the proportion of patients without new or growing white matter lesions on brain MRI scans between months six and 24. The assessment of efficacy and safety endpoints are being conducted with use of clinical evaluations, MRI, and blood samples, as well as experimental biomarkers [18]. Other ongoing clinical trials comparing the efficacy of RTX with the efficacy of OCR include the TRIO trial and OVERLORD-MS trial. To date, however, no results have been posted.

OCR. A recombinant humanized glycosylated anti-CD20 IgG1 κ mAb, which predominantly drives ADCC. It is IV-delivered, starting with 300 mg infusions on day one and day 15, followed by 600 mg infusions every six months. For this drug, similar to RTX, pre-medication is also recommended. OCR was approved by FDA and European Medicines Agency (EMA) for primary progressive MS (PPMS), as well as relapsing forms of MS (RMS) [19].

A phase II placebo-controlled trial [20] examined the efficacy of OCR in RRMS individuals. According to the results, at week 24, patients receiving 600 mg and 1,000 mg of OCR demonstrated fewer Gd-enhancing T1 lesions than the placebo group of patients [21]. This study was followed

up by the OPERA I and OPERA II studies, which assessed OCR's efficacy in comparison with IFNβ-1a. After 96 weeks of therapy, OCR had a lower annualized relapse rate (ARR) than IFNβ-1a (0.16 vs 0.29). Moreover, treatment with OCR resulted in 40% relative risk reduction in 12-week and 24-week confirmed disease progression (CDP) risk, when compared with IFNβ-1a. In the OCR treatment groups, Gd-enhancing T1 lesions were reduced by 94% in OPERA I and 95% OPERA II, whereas new or larger T2 lesions declined by 77% and 83%, respectively. OCR also resulted in an increased number of individuals attaining absence of disease activity in comparison with IFNβ-1a, and a reduction in brain volume loss. The data remain inconclusive due to statistical processing [20].

Post hoc evaluation of the OPERA I/II trials in RMS showed that OCR prevented cognitive deterioration and improved cognitive function better than IFNβ-1a treatment [22].

As for PPMS patients, the placebo-controlled ORATORIO study [20] assessed the effectiveness of OCR. The research revealed that 32.9% of individuals given OCR and 39.3% of those on placebo achieved 12-week CDP. In comparison, a 24-week assessment showed that 29.6% of OCR and 35.7% placebo patients were observed with CDP. Between baseline and week 120, the overall volume of T2-weighted hyperintense lesions decreased in the OCR arm and increased in the placebo arm (mean percent change, -3.4 vs. 7,4; $p<0.001$) [23].

A novel OCR formulation was designed for subcutaneous (SC) administration on a twice-yearly schedule to give clinical benefit and therapeutic flexibility. The results of the OCARINA II Phase 3 Study revealed that SC formulation is non-inferior in pharmacokinetics in comparison to IV formulation, showing comparable systemic exposure to OCR. Therefore, both OCR SC and IV treatment provide similar advantages in terms of efficacy-related measures [24].

Ofatumumab (OFA). OFA is an SC, selective B-cell-depleting anti-CD20 human mAb commonly used in chronic leukemia. OFA binds to distinct regions of CD20 compared with other anti-CD20 antibodies, interacting with smaller and larger extracellular loops of CD20 receptors [25].

The approval of OFA was supported by the Phase 3 ASCLEPIOS I and II trials [26], which showed enhanced effectiveness compared to teriflunomide (TFL) and a good benefit-risk ratio. OFA significantly reduced ARR by 51% in ASCLEPIOS I and 58% in ASCLEPIOS II (both $p<0.001$), and outperformed TFL in the majority of secondary clinical and MRI studies.

To evaluate the long-term safety and benefit-risk OFA ratio in RMS, participants from OFA trials (ASCLEPIOS I/II, APLIOS, and APOLITOS) were assigned to ALITHIOS, a Phase 3b, open-label extension study, in which they maintained OFA or changed placebo/TFL to OFA. Following 3.5 years of ALITHIOS, OFA continued to show good tolerability, with rates of adverse events (AEs) and serious AEs on similar level to prior findings [26].

OFA therapy decreased neurofilament light chain levels but did not cause a substantial reduction in brain volume; as these are both indications of tissue injury, this discrepancy warrants further investigation. OFA's tolerance profile was largely controllable in phase III studies. Infections are a possible safety risk with OFA treatment due to its mechanism of action, historical usage in other indications, and previous experience with other anti-CD20 mAbs. However, the phase III studies did not show meaningful differences in infection rates across the groups. OFA, unlike other mAb treatments, and may be administered by patients themselves after initial training by a healthcare professional [27].

Ublituximab (UTX). UTX is the most recent FDA- and EMA-approved anti-CD20 antibody, registered for RRMS and active SPMS treatment. This chimeric anti-CD20 IgG1 κ mAb primarily promotes ADCC rather than CDC. It is IV-delivered, starting with an initial dose of 150 mg over 4 hours, then continued with 450 mg two weeks later. Maintenance infusions of 450 mg are given every 24 weeks, over the course of one hour. Pre-medication is necessary before each infusion.

Two parallel phase 3 studies with double-blind and double-dummy designs were carried out to evaluate the efficacy of UTX for RMS treatment (ULTIMATE I and II) [25]. Participants were randomly assigned to UTX or TFL groups. The adjusted ARR throughout a 96-week period in the ULTIMATE I study was 0.08 for the UTX arm and 0.19 for the TFL arm, while in the ULTIMATE II trial, the corresponding rates were similar, and amounted to 0.09 and 0.18, respectively. Regarding MRI outcomes, the ULTIMATE I study revealed that patients from the UTX group had a mean total number of 0.02 of Gd-enhancing T1 lesions, while those in the TFL group had a mean total number of 0.49. In the ULTIMATE II study, the corresponding rates amounted to 0.01 and 0.25, respectively [28].

ENHANCE is a phase 3b study with the main objective of assessing the efficacy of a modified UTX regimen in RMS patients, with results being measured by T1 Gd-enhancing lesions and pharmacokinetics changes. The trial is divided into two parts: the first is open-label and single-armed, while the second is double-blind, randomized, and placebo-controlled. It is estimated that the primary completion date will be in the first half of 2026 [29]. There are also several clinical ongoing trials aimed at, e.g., assessment of SC administration of the drug, its impact on motor functions or effects during pregnancy.

Assessment of safety and tolerability in anti-CD20 treatment

Infusion-associated AEs. The most commonly observed adverse effects of anti-CD20 therapies are infusion- or injection-related reactions (IRRs). mAbs administration leads to B cell depletion which, in turn, results in IRRs. IRRs most commonly occur within the first 24 hours after the first dose and the risk of their occurrence decreases with subsequent doses. Most reported symptoms are mild to moderate, and include rash, pruritus, throat irritation, and flushing. In order to prevent IRRs, pre-medication with drugs such as methylprednisolone, antihistamine, and antipyretics is administered. RTX and OFA may be linked with higher incidence of IRRs than OCR and UTX due to greater CDC induction, given that CDC is suggested to have a higher potential in triggering IRRs than ADCC. However, to date, no research studies comparing the incidence of IRRs in anti-CD20 drugs have been conducted [4, 30].

Førde et al. analyzed the complement-activating potential of three mAbs. The results revealed that *in vitro* exposure to OCR or OFA, but not RTX, led to complement cascade activation in whole blood from healthy donors, which

suggests that OCR appears to activate the complement to a similar extent as OFA. The findings may be useful in further research on the efficacy and side-effects of anti-CD20 treatment in MS [31].

Hypogammaglobulinemia (HGG). Long-term anti-CD20 medication can lead to HGG via delayed B cell reconstitution. B cell reconstitution to either baseline or lower limit of normal has been documented to need 24 weeks with OFA, 72 weeks (ranging from 27 – 175 weeks) with OCR, and 70 weeks (ranging from 0.1 – 75 weeks) with UTX [32, 33]. Also, Hauser et al. reported that 48 weeks after RTX withdrawal, B cell counts had recovered to only about 30.7 % of baseline values [16].

Anti-CD20 therapy may also provoke HGG secondary to the therapy, which might be explained in several possible ways. One explanation is that long-lived memory PCs remaining after B cell depletion, are not fully self-sufficient and require continuous replenishment from the CD20-positive B cell precursors [34]. Elgenidy et al. [33] examined HGG and infection rates in MS patients undergoing anti-CD20 therapy. In their analysis, which included almost 20,000 MS individuals, the overall prevalence of HGG was 11%, with RTX exhibiting the highest prevalence [33].

Several researches have examined the relationship between low IgG levels and patient demographics. In research by Mears et al. [35] that included 184 patients treated with RTX plus OCR, 22 individuals had HGG. Those affected were more likely to be above the age of 50, and to have lower baseline IgG levels [35]. Research that included MS patients after a median of five (1–6) RTX cycles also found that older age was associated with lower IgG levels, reaching below 6 g/L, although gender or history of immunosuppressive medication did not have a significant impact [36].

Infections and COVID-19 interaction. Several studies have investigated whether HGG caused by anti-CD20 therapy increases infection risk in MS patients. A retrospective study found that patients with MS receiving RTX experienced greater risk of being hospitalized, prolonged antibiotic treatment, or IV antibiotics, compared with patients who had higher IgG levels. Another study among 291 individuals treated with RTX (43.6%), OCR (48.1%), or RTX followed by OCR (8.3%), found that low IgG levels were linked with an elevated risk of severe infections [37, 38].

A meta-analysis by Elgenidy et al. [33] found that pulmonary infections were the most common type of infections, reaching a prevalence rate of 9%. Another common infection was of the urinary tract. Divided by the drug used, the top prevalence was in the OCR group (26%), followed by RTX (6%), non-specified anti-CD20 (3%), and OFA (1%). Overall prevalence was 6%, and divided by drug groups, 13% for OCR, 3% for RTX, 3% for non-specified anti-CD20, and 2% for OFA. Gastrointestinal infections were prevalent at the 2% level (OCR – 4%, OFA – 3%, RTX – 1%, non-specified anti-CD20 – 1%), skin and mucus membrane infections – 2% (subgroups division was non-significant), and herpes virus infections – 1% (subgroups division was non-significant) [33].

Anti-CD20 treatments have also been linked to a higher risk of hospitalization and severe COVID-19. A retrospective analysis of 758 individuals found no conclusive association between COVID-19 and IgG levels below 700 mg/dL, hence, HGG is rather not a contributing factor. Older, Black, non-ambulatory MS patients who have comorbidities or take glucocorticoids are more likely to be hospitalized, or die from COVID-19 [39, 40].

Malignancies. In OPERA I and II, and ORATORIO studies, OCR was associated with a greater incidence of neoplasms than the comparison and placebo groups. Furthermore, an imbalance was observed in the occurrence, with a higher incidence in breast compared to other tissues. In the ORATORIO trial, 2.3% (11 of 486) of patients who had OCR reported neoplasms, compared to 0.8% (2 of 239) who received placebo. Among 11 cases in the OCR group, four were breast cancer. During the open label extension, two additional neoplasms were identified (one basal cell skin carcinoma and one squamous cell carcinoma). There were four neoplasms in total (0.5% of the patients receiving OCR) in OPERA trials, including two invasive ductal breast carcinomas. Patients taking IFNβ-1a developed two neoplasms (0.2%): mantle-cell lymphoma and squamous-cell carcinoma of the chest, with five more neoplasms recorded during the open-label extension, two of which were breast cancers.

Further studies are required to clarify the disparity in the incidence of breast cancer. Patients receiving anti-CD20 antibodies should follow age-appropriate breast cancer screening protocols [20, 23].

In ASCLEPIOS trials neoplasms were found in 0.5% of patients treated with OFA (one case each of invasive breast carcinoma [BCC], recurrent NHL, malignant melanoma *in situ,* and two instances of basal cell carcinoma), compared with 0.4% of individuals on TFL. In the concurrent ASCLEPIOS studies, there were two incidences of BCC and one case each of cervical cancer and fibrosarcoma. Research on the link between cancer risk and DMTs indicated that RTX has a comparable prevalence of neoplasms as the general population. RTX treatment was most commonly associated with invasive tumours such as breast, colon, melanoma, and non-melanoma skin cancer, with no observed imbalance among the different subtypes of invasive malignancies [25, 41].

Vaccination. Vaccines different from the Bacillus Calmette-Guérin (BCG) vaccine primarily provide protection by boosting the production of antibodies and memory B cells. T cell responses are also significantly increased. As a result, there is fear that B cell depletion would impede the vaccination response.

Research found that patients using RTX for autoimmune illnesses had a lower antibody response to two doses of the mRNA COVID-19 vaccination compared to healthy controls (29% vs. 92%), with the interval since the last injection being a key predictor of response. Importantly, T cell responses remained intact. In another study of RTX-treated MS patients, B cell count was identified as an important determinant influencing vaccination response [42, 43].

Vaccination response was studied in the VELOCE phase III trial to investigate how OCR affects patients who were randomly assigned to receive OCR or to a control group without immunotherapy or IFN-β therapy. In the OCR group, vaccines were administered 12 weeks following infusion, and responses to antigens, including pneumococcal polysaccharide vaccine (PPSV-23), tetanus toxoid, and influenza were assessed. Patients who had received a

seasonal influenza vaccination, PPSV-23 within five years, or tetanus toxoid within two years during enrollment, were excluded. Eight weeks after vaccination, 23.9% of OCR-treated patients showed positive reaction to tetanus toxoid, compared with 54.5% in the control group, resulting in a treatment difference of -30.7%. OCR-treated patients with peripheral B cell depletion showed reduced humoral responses to T-cell-dependent and T-cell-independent stimuli. Nonetheless, seroprotection or a substantial increase in antibody levels were the outcomes of vaccination in OCR patients [44]. In another trial, only 25% of patients treated with OCR had measurable protective IgG levels eight weeks after receiving COVID-19 mRNA vaccine, a response that was not maintained at 24 or 36 weeks [45]. Another study demonstrated a progressive increase in the proportion of individuals with antibody response after each booster dosage. Following four booster vaccinations, 90% of OCR-treated patients had an antibody response [46]. Research found that both RTX and OCR lowered antibody levels by 21-fold and 20-fold, respectively, when compared to untreated individuals. However, comparison of OCR and RTX in the study was limited due to differences in the interval between the last infusion and vaccination across groups, as well as the observed relationship between time since last infusion and antibody response [47]. Thus, vaccination should be administered at least four to six weeks before anti-CD20 infusion to ensure a proper immune response.

CONCLUSIONS

Anti-CD20 mAbs have significantly improved the therapeutic approach to MS, with a substantial success in lowering relapse rates, disability progression and MRI activity, taking into consideration various MS clinical forms. By selectively targeting CD20 B cells, these therapies inhibit key immune mechanisms that cause demyelination and neurodegeneration, including antigen presentation, cytokine secretion, and autoreactive T cell activation.

There is growing evidence confirming the high efficacy of RTX, OCR, OFA and UTX in relapsing and progressive forms of MS. Their mechanisms of action, based on a sustained reduction in B cell numbers through ADCC, CDC, and apoptosis induction, have been shown to be effective in alleviating inflammation in the CNS. Importantly, SC formulations remain an important improvement in MS treatment because of better accessibility and IRRs reduction. Nonetheless, anti-CD20 treatment may be linked with AEs, which include the above-mentioned IRRs, infections, and gradual Ig depletion. Moreover, cases of breast and skin cancer have been reported, which highlights the need for long-term pharmacovigilance. Another challenge involves the reduced vaccination response after prolonged B cell depletion, necessitating optimal immunization scheduling prior to the beginning of treatment.

Long-term studies and data will be important for a full comprehension of the safety profile of persistent B cell depletion, immune system reconstitution, and chances for secondary autoimmunity. Currently, there are ongoing clinical trials intending to compare different anti-CD20 drugs in terms of safety and efficacy.

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