REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 3, pages: 235–242
DOI: 10.5603/PJNNS.a2023.0022

ISSN: 0028-3843, e-ISSN: 1897-4260

Targeting CD20 in multiple sclerosis — review of current treatment strategies

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ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS) that mostly manifests as irreversible disability. The aetiopathogenesis of MS is still unclear, although it was initially thought to be primarily mediated by T-cells.

Research into the immune concepts of MS pathophysiology in recent years has led to a shift in the understanding of its origin i.e. from a T-cell-mediated to a B-cell-mediated molecular background. Thus, the use of B-cell-selective therapies, such as anti-CD20 antibody therapy, as expanded therapeutic options for MS is now strongly supported.

This review provides an up-to-date discussion on the use of anti-CD20 targeted therapy in MS treatment. We present a rationale for its use and summarise the results of the main clinical trials showing the efficacy and safety of rituximab, ocrelizumab, ofatumumab, and ublituximab. Future directions that show selectivity to a broader population of lymphocytes, such as the use of anti-CD19 targeted antibodies, as well as the concept of extended interval dosing (EID) of anti-CD20 drugs, are also discussed in this review.

Key words: multiple sclerosis, targeting CD20, ofatumumab, ocrelizumab, ublituximab, rituximab, extended interval dosing

(*Neurol Neurochir Pol 2023; 57 (3): 235–242*)

Introduction

Multiple sclerosis (MS) is one of the most common autoimmune inflammatory diseases of the central nervous system (CNS) and is characterised by the accumulation of irreversible disability. The most common form of the disease, relapsing-remitting multiple sclerosis (RRMS), is characterised by the appearance of new or worsening neurological symptoms (relapses), which last for at least 24 hours. In the early stages of the disease, complete resolution of neurological defects is observed; however, after some time, the symptoms can become permanent.

Gradually, MS symptoms become more severe, and patients suffer from serious neurological deficits, including physical, psychological, and cognitive deficits. Nevertheless, there is no specific course of the disease, as it can vary from patient to patient. Other forms of MS, including primary progressive MS (PPMS), secondary progressive (steady worsening after RRMS; SPMS), and progressive-relapsing MS (PRMS), are characterised by a particularly intensive accumulation of disability [1]. Therefore, effective early treatment is crucial to prevent disability progression and reduce relapse risk.

The aetiopathogenesis of MS is still not fully clear. Nevertheless, excessive activation of the immune system is known to be responsible for the destruction of myelin and, consequently, axonal (neuronal) failure. For many years, the essential component of the immune system attacking myelin was considered to be CD4+ lymphocytes. As a result, many drugs used in the treatment of MS, such as interferons, teriflunomide, or natalizumab, decrease the activity of CD4+ cells and reduce the risk of relapses and disease progression [2, 3]. However, a profound decrease in the immune response can increase the risk of serious infections or even anticancer responses.

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Received: 30.08.2022 Accepted: 27.01.2023 Early publication date: 31.03.2023

In recent years, a growing body of evidence has emerged showing that the picture of the abnormal immune response in MS is far more complicated. An important role in the process of neuronal and myelin damage is played by B lymphocytes, or B cells [4, 5]. The involvement of these cells in MS pathology is supported by the existence of oligoclonal bands in the cerebrospinal fluid, as well as by the detection of myelin-targeted antibodies, which are responsible for myelin damage and neuronal loss. Currently, in the treatment of MS, we have some CD20-targeted antibodies at our disposal, including rituximab, ocrelizumab, and ofatumumab. Some others are still under investigation e.g. ublituximab and inebilizumab (MEDI-551, an antibody that binds to CD19, which is a surface antigen expressed on a broader range of B cells than CD20).

In this review, our aims were to describe the role of B lymphocytes in MS pathology, to present the latest data regarding the efficacy and safety of the currently available CD20-targeted drugs, and to indicate the future perspective of the use of such drugs.

Our *modus operandi* involved searching the PubMed database from 1970 to the present. Clinical trial registries were also searched for appropriate data. Key words searched for were "CD20", "rituximab", "ocrelizumab", "ofatumumab", "ublituximab", "multiple sclerosis", "RMS", "RRMS", "SPMS", and "randomised clinical trial". Records were limited to those in the English language. The search was last updated on 5 January 2023.

B lymphocytes in MS

Research into the pathology associated with MS has been ongoing for many years. Initially, attention was focused on the role of T lymphocytes, including CD4+ and CD8+ lymphocytes, with consideration given to subtypes releasing IL-17 or granulocyte-macrophage colony-stimulating factor (GM-CSF) [6, 7]. These cells were believed to play a crucial role in demyelination and neuronal damage. In recent years, attention has been drawn to a shift in thinking regarding the pathogenesis of MS.

It now appears that CNS damage results from multiple types of immune cells, with a more significant than expected role played by B lymphocytes [8, 9]. In patients with MS, B lymphocytes have been shown to be an important component of inflammatory infiltrates, especially in active demyelinating lesions with predominantly perivascular localisation [10, 11]. The concept of B-cell-mediated pathogenesis of MS was prompted by the finding of impaired antibody production in the CNS (presence of anti-myelin antibodies), the presence of oligoclonal bands in the cerebrospinal fluid (CSF), the detection of antibodies in inflammatory lesions, and, above all, the clinical confirmation of the high clinical effectiveness of antibodies directed against CD20, the most reliable marker of B lymphocytes [12].

In MS, increased numbers of B cells and plasmablasts (PB) have been observed in the CSF. Most B lymphocytes present the phenotype of memory cells and short-lived PB [13]. It is worth noting that CSF PB numbers in MS patients are correlated with intrathecal IgG synthesis and inflammatory parenchymal disease activity as revealed by MRI, in other words, CNS inflammation.

It should be noted however, that antibodies directed against CD20 do not cover the entire population of B lymphocytes suspected to be involved in the pathogenesis of MS. Plasma cells, as well as plasmablasts, which are responsible for the production of antibodies and whose presence and number in inflammatory infiltrates correlate with the severity of inflammatory processes in the CNS, do not present CD20 antigens, i.e. they are not targeted by anti-CD20 antibodies [14].

B lymphocytes can contribute to MS in multiple ways. Subsets of B lymphocytes may produce cytokines with pro- (which secrete TNFα, GM-CSF, IL-6, IL-12, and IL-15) and anti-inflammatory (which secrete IL-10 and IL-35) properties [5]. Furthermore, they are antigen-presenting cells pivotal for T-cell activation. B cells can also express CD80 and CD86 antigens on their surface, which play a crucial role in the T-cell activation observed in MS [15].

The available data indicates that the initial step of the autoimmune reaction may be the attraction of Th cells into the CNS followed by secondary infiltration of the affected region by B lymphocytes. Finally, B lymphocytes undergo differentiation into plasma cells that are able to produce autoantibodies, thus directly contributing to the demyelination of neurons, which is strongly facilitated in conditions of increased inflammation. Antibodies produced by B lymphocytes in the CNS are directed against various structural, but also other functional, elements of neurons. Previous studies have identified antibodies directed against myelin basic protein (MBP), proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG), inwards rectifying potassium channel (Kir) 4.1, a calcium-activated chloride-channel protein called 'anoctamin 2' (ANO2), and many other antigens [16–19]. The role of B cells is also postulated to be linked with the trafficking of Th cells to demyelinating lesions. This action of B cells could form a 'vicious circle' of inflammation and lead to intense accumulation of different inflammatory mediators in the CNS.

Conversely, in MS, the pathophysiological role of individual antibody production needs to be clarified. Specifically, no clear correlation has been demonstrated between antibody titres and disease severity [20]. It is worth noting that among the isolated antibodies, none are strictly specific for MS. However, their occurrence correlates with disease activity e.g. the number of demyelinating foci lesions, indicating that in individual patients, a certain unique specificity may be expected. In addition, there is a lack of research into the nature of stimuli that trigger B-cell influx into the CNS and the mechanism of B-cell accumulation in specific CNS regions [21].

However, these doubts do not change the fact that inhibition of CD20+ cell activity will effectively slow disease progression, regardless of the antigenic spectrum of antibodies produced. Accordingly, the role of B lymphocytes as antigen-presenting cells and cells that induce overactivity of T cells is becoming increasingly important. Recent studies have shown that the involvement of B lymphocytes in CNS damage in the course of MS is not only limited to the production of antibodies directed against structural elements of myelin, glial cells, or neurons, but also involves the activation of T lymphocytes. This phenomenon is related to the activity of B lymphocytes as antigen-presenting cells, and their action includes the effective presentation of soluble and membrane-bound antigens [22].

The predominant mechanism by which CD20-blocking antibodies exert their therapeutic effect is still unclear. Protection against relapses is achieved within 1–2 months of administration depending on the agent used, which is faster than the effect on antibody production or plasma cell counts [23]. It is speculated that the reduced function of B lymphocytes as antigen-presenting cells, as well as a reduced influx of B lymphocytes across the blood–brain barrier, may lead to a local decrease in antibody production in the CNS [8]. In addition, B lymphocytes in MS have a disturbed cytokine production profile, with excessive production of proinflammatory cytokines such as IL-6, TNFα, or lymphotoxin alpha, and a concomitant deficiency in inhibitory cytokines, including TGFβ. The disturbed profile of cytokine production results in an excessive activation of Th1 or Th17 cells, leading to processes associated with myelin and neuronal damage [5]. An important element affecting the effectiveness of drugs targeting CD20 is the profile of B lymphocytes reconstituted after treatment. Reconstituted B lymphocytes produce fewer proinflammatory cytokines, such as TNFα, IL-6, or GM-CSF, and more IL-10. The change in the profile of B lymphocytes also appears to reduce the proinflammatory response of T lymphocytes [15, 24]. This phenomenon seems very important in terms of the long-term suppression of the pathological inflammatory response in MS.

CD20-targeted drugs in MS

Due to evidence of B lymphocyte involvement in MS-related pathology, a decision was made to use anti-CD20 monoclonal antibody medication for MS treatment. Currently used anti-CD20 agents include ocrelizumab, ofatumumab, and rituximab (off-label). The last of the CD20 ligands currently being assessed by the FDA and the EMA is ublituximab. CD20 is a surface antigen present on B lymphocytes at different stages of maturation, from pre-B cells to naïve and memory B cells, and is involved in the generation of T-cell-independent antibody responses [25]. The binding of anti-CD20 antibodies to the antigen leads to the activation of mechanisms that result in a profound decrease in the number of B lymphocytes. Usually, these mechanisms are antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Available drugs targeting CD20 do not act identically in this regard. Ocrelizumab and ublituximab are drugs with a dominant ADCC effect involving NK cells (natural killer cells), whereas rituximab and ofatumumab have a dominant CDC effect with activation of the C1q component of the classical complement pathway [26, 27]. A decrease in CD20+ cell levels below 10% is considered to be therapeutic and correlates with clinical efficacy. However, in clinical practice and clinical trials, the reduction in B lymphocytes (measured as CD19+ cells) is usually more profound, reaching as low as less than 1% [28]. Current clinically used antibodies directed against CD20 have different structures and some differences in binding sites. However, their efficacy in reducing CD20+ cell levels appears to be similar.

Rituximab

Rituximab (RTX) is a chimeric (mouse–human) anti-CD20 antibody used in the off-label treatment of MS. As mentioned above, the drug's mechanism of action is mainly based on the activation of CDC. In addition to its use in MS, RTX is widely used in haematological disorders and autoimmune diseases such as B-cell lymphomas (e.g. non-Hodgkin's lymphoma, chronic lymphatic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis) (SmPC Mabthera).

One of the first clinical trials to evaluate the efficacy and safety of RTX in MS was an open-label, 72-week clinical trial in which 1.0 g of RTX was administered on days 1 and 15 of treatment and then at 6-monthly intervals in adult patients with RRMS [29]. The use of RTX was shown to be associated with a reduction in the annualised relapse rate (ARR) from 1.27 at baseline to 0.18 at week 72 of treatment, with the proportion of patients without relapses exceeding 80% (80.8%). However, the high rate of infusion-related allergic reactions was noteworthy (65.4%).

Subsequent studies confirmed the initial observations. The double-blind, placebo-controlled HERMES study, which used RTX in 69 RRMS patients at a dose of 1.0 g on days 1 and 15 of treatment, showed that, starting at week 12 of follow-up, there was a significant reduction in both the number of Gadolinium-enhancing (Gd+) lesions (by more than 90%) and the risk of relapse [20.3% (RTX) *vs.* 40% (PBO)] at week 48 of follow-up [RR 1.9 (1.1–3.2), p = 0.04]. Infusion-related adverse events were common following the first infusion (in more than 90% of patients) and most likely reflected cytokine release syndrome. However, during the next dose, their frequency did not differ from the placebo [30]. In contrast, the OLYMPUS study, which was also a double-blind, placebo-controlled trial using RTX in 439 adult patients with PPMS, with a modified regimen (two infusions of RTX at a dose of 1.0 g every two weeks or placebo every 24 weeks until week 96) showed no significant difference in terms of confirmed disability progression (CDP12 — time

to confirmed disease progression sustained for 12 weeks; hazard ratio (HR) 0.77, 95% confidence interval (CI): 0.55–1.07, p = 0.1442). However, subgroup analysis indicated a significant effect in a population of younger patients (50 years or younger) with active disease [with active Gd+ lesions present; HR 0.33 (95% CI: 0.14–0.79, p = 0.0088)] [31].

Although the results of the study were disappointing to some extent, they did indicate a direction for further research on a subpopulation of younger patients with active disease (with active Gd+ lesions). As in previous studies, infusion-related side effects occurred primarily after the first dose of the drug. The tolerability of RTX treatment appears to be good. A retrospective analysis of MS patients adhering to treatment, based on data from a Swedish multiple sclerosis registry, showed much the lowest dropout rate to be from RTX therapy (3%) compared to other agents such as IFNsβ (53%), fingolimod (38%), dimethyl fumarate (32%), and natalizumab (29%) [32].

The long-term efficacy and safety of RTX use in patients with relapsing multiple sclerosis with active disease were evaluated in a double-blind, placebo-controlled, randomised, single-centre study. Participants were followed up for three years. The primary endpoint was the number of participants with no evidence of disease activity (NEDA). At the end of the study, 44% of RTX-treated patients showed NEDA, compared to 19.23% of the placebo-treated group (p = 0.049). More than two new lesions, relapses and/or sustained accumulation of disability, defined as treatment failure, was smaller in RTX--treated patients than in placebo-treated patients (37.04% *vs.* 69.23%, p = 0.019). Furthermore, the time to treatment failure was longer in RTX-treated patients than in placebo-treated patients (23.32 months *vs.* 11.29 months, p = 0.027). More infusion-related reactions were observed in the RTX-administered group than in the control group. No differences in serious adverse events between the groups were observed [33].

Ocrelizumab

Ocrelizumab (OCR) is the first anti-CD20 drug registered for the treatment of MS. The drug has received a positive recommendation from both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with RRMS as well as PPMS. Due to structural differences compared to RTX (i.e. slightly different target site, humanised antibody), OCR is a drug that exerts its effects primarily through an ADCC mechanism.

The two largest phase III trials using OCR in adult patients with RRMS were the two identical, double-blind OPERA I and OPERA II trials, in which more than 800 patients (in each trial) were randomised to receive OCR (300 mg on days 1 and 15 of therapy followed by 600 mg every 24 weeks) or the active comparator, IFNβ 1α, s.c. at a dose of 44 μg (three times weekly). After 96 weeks of treatment, there was a statistically significant difference in favour of OCR in terms of ARR (0.29 for IFN1β *vs.* 0.16 OCR, p < 0.001 for both studies). At the same time, almost complete protection was observed in terms of Gd+ lesions [OPERA I — 0.02 *vs.* 0.29 (= 94%), p < 0.001; OPERA II — 0.02 *vs.* 0.42; p < 0.001 — 95% reduction] and in terms of the number of new Gd+ lesions [OPERA I — 0.32 *vs.* 1.41 (= 77%), p < 0.001; OPERA II — 0.33 *vs.* 1.90 (= 83%), p < 0.001]. Additionally, the use of OCR was shown to be associated with a c.30–40% reduction in the risk of 24-week CDP [OPERA I — 5.9% *vs.* 9.5% (= 38%), p = 0.03; OPERA II — 7.9% *vs.* 11.5% (= 31%), p = 0.003].

These results clearly demonstrated the usefulness of OCR and its significant advantage over the active comparator (IFNβ 1a). An interesting observation was the weaker functional effect (progression of disability) compared to almost complete protection in the context of new demyelinating lesions. However, this phenomenon was not explained [34].

The long-term efficacy and safety of OCR in relapsing MS were assessed over the course of 6.5 years (336 weeks) in the double-blind period (DBP) and open-label extension (OLE) period of the OPERA I and OPERA II studies, wherein the influence of OCR administration (compared to IFN) on time to EDSS ≥ 6.0, confirmed for ≥ 24 and ≥ 48 weeks, was assessed [35]. The risk of requiring a walking aid confirmed for ≥ 24 weeks was 34% lower in patients who initiated OCR treatment over 6.5 years earlier [HR (DBP + OLE) 0.66, 95% CI: 0.45–0.95, p = 0.024]. Furthermore, over 6.5 years, the risk of requiring a walking aid at ≥ 48 weeks was 46% lower in patients who initiated OCR treatment earlier compared to those who started it later [HR (DBP + OLE) 0.54, 95% CI: 0.35–0.83, p = 0.004].

A continuation of the set of studies with OCR was a double-blind, placebo-controlled phase III study in 732 adult patients with PPMS (the ORATORIO trial). OCR was administered intravenously at a dose of 300 mg on days 1 and 15 and then repeated every 24 weeks. OCR was shown to result in a moderate but statistically significant reduction in the risk of disability progression (12-week CDP — 24% reduction, OCR — 32.9% *vs.* PBO — 39.3%, and 24-week CDP — 25% reduction, OCR — 29.6% *vs.* PBO — 35.7%). Similarly to RTX, the effect of OCR was most pronounced in the younger subpopulation (under 45 years) [36].

The safety profile of OCR is quite similar to that of RTX, and as in the case of RTX, the most common adverse reactions observed in clinical trials were drug-related reactions associated with cytokine release, especially after the first dose of OCR. Pruritus and redness of the skin and hot flushes were the most common. However, the incidence of these changes was significantly lower than with RTX, probably due to premedication, including antipyretics and antihistamines. It is worth mentioning that OCR has been discontinued in patients with rheumatoid arthritis due to an increased risk of opportunistic infections. The older age of patients and the concomitant use of other immunosuppressive drugs were the most likely causes of these infections [23, 28].

Ofatumumab

Another drug registered by the FDA (2020) and the EMA (2021) targeting CD20 is ofatumumab. This is a fully human IgG1 antibody suspected to have reduced immunogenicity compared to chimeric rituximab and ocrelizumab. It is postulated that the mechanism of action on B lymphocytes is mainly based on CDC. An additional advantage of ofatumumab is that it can be administered subcutaneously. In addition to MS, the drug is also registered for the treatment of chronic lymphocytic leukaemia.

The primary evidence for the efficacy of ofatumumab comes from two methodologically identical, double-blind, randomised trials (ASCLEPIOS I and II) comparing the efficacy and safety of ofatumumab (20 mg every four weeks after 20 mg loading doses on days 1, 7, and 14) *vs.* teriflunomide (14 mg daily) [37].

Both studies showed that, compared to teriflunomide, the use of ofatumumab was associated with a reduced risk of relapse (ARRs were 0.11 and 0.22, respectively, in ASCLEPIOS I [RR 0.49 (95% CI — 0.37 to 0.65), $p < 0.001$] and 0.10 and 0.25 in ASCLEPIOS II [RR 0.42 (0.31 to 0.56), $p < 0.001$)]. In addition, there was a significantly better inhibitory effect of ofatumumab on the progression of disability confirmed at six months [8.1% and 12.0%, respectively (HR 0.68 (95% CI — 0.50 to 0.92), $p = 0.01$]. A very strong effect of ofatumumab was also observed in terms of inflammatory parameters on MRI, in terms of the number of Gd+ lesions on T1-weighted MRI [ASCLEPIOS I — Rate ratio 0.03, (95% CI) (0.01 to 0.05) $p < 0.001$; ASCLEPIOS II — Rate ratio 0.06 (95% CI) (0.04 to 0.10), $p < 0.001$], as well as in terms of new or enlarging lesions on T2-weighted MRI [ASCLEPIOS I — Rate ratio 0.18 (95% CI) (0.15 to 0.22), $p < 0.001$; ASCLEPIOS II — Rate ratio 0.15 (95% CI) (0.13 to 0.19), $p < 0.001$]. The safety profile of ofatumumab was very favourable, with the most common changes associated with the first administration of the drug (e.g. headache, flushing) (14.4% and 7.5% ofatumumab *vs.* placebo injections, respectively). In both studies, other adverse effects, particularly those leading to treatment discontinuation, occurred in 5% of both the ofatumumab and teriflunomide groups.

Additional data pertaining to the long-term safety of ofatumumab comes from the ALTHIOS study, which was a phase IIIb, open-label, long-term safety study. Patients completing the ASCLEPIOS I/II, APLIOS, or APOLITOS trials could enter ALITHIOS [38]. The safety and tolerability of ofatumumab were assessed in RMS patients after extended treatment for up to 3.5 years. A total of 1,650 patients (83.8%) reported ≥ 1 adverse event, and 191 (9.7%) had ≥ 1 serious adverse event. No opportunistic infections or progressive multifocal leukoencephalopathy events were identified; the risk of malignancies was very low (0.55%, 11/1,969).

Ublituximab

The last of the CD20 ligands currently being evaluated by both the FDA and EMA is ublituximab. Unlike the recently registered ofatumumab, but similarly to ocrelizumab and rituximab, ublituximab is a chimeric antibody with different binding sites on CD20 and a mechanism based mainly on ADCC [39].

The main results regarding treatment efficacy have come from the ULTIMATE I and II studies. As with other CD20 ligands, these were double-blind, controlled phase III studies, with teriflunomide as an active comparator. The results were not published as full text but have been presented as conference reports. In both studies, ublituximab was administered as an intravenous infusion of 450 mg UTX via a one-hour *i.v.* infusion every 24 weeks (following a 150 mg UTX infusion on day 1) or 14 mg oral teriflunomide once a day.

Over a 96-week follow-up period, ublituximab was shown to be associated with no relapses in 86.7% (ULTIMATE I) and 87.5% (ULTIMATE II) of MS patients. In addition, ublituximab was associated with a significant reduction in the risk of developing a relapse compared to teriflunomide (ULTIMATE I: HR 0.50; 95% CI: 0.33–0.75; $p = 0.0007$; ULTIMATE II: HR 0.43, 95% CI: 0.28–0.65, $p < 0.0001$) [40].

The ULITMATE study showed an acceptable safety profile for the drug. Infusion-related adverse events occurred in 47.7% (ublituximab) and 12.2% (placebo) of patients and, as with ocrelizumab or rituximab, these adverse events were mostly associated with the first infusion. A severe anaphylactic reaction was observed in one patient [41].

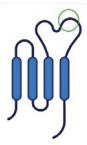
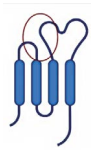
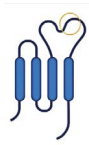
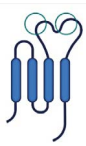
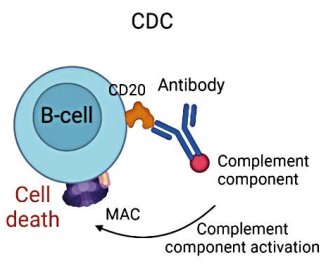
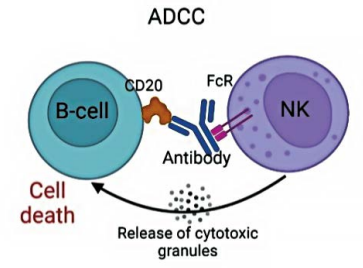
At the time of writing, full results have not yet been published, but the preliminary data indicates similar efficacy and safety profiles for ublituximab compared to other drugs belonging to the CD20 ligand group. Long-term data regarding efficacy and safety is not available for ublituximab. An OLE study of ublituximab in subjects with relapsing multiple sclerosis is ongoing. This study is planned to be completed in October 2023 (clinicaltrials.gov, NCT04130997) (Tab. 1).

Future directions

In clinical practice, in addition to the drugs used for the treatment of MS, other anti-CD20 molecules are available for the treatment of haematological diseases or treatment-resistant autoimmune conditions. These include veltuzumab, obinutuzumab, tositumomab, and ibritumomab; however, to date (based on ClinicalTrials.gov), there is no data regarding their efficacy in MS.

Another therapeutic option being considered for the treatment of MS is blocking the CD19 antigen. Similar to CD20, the CD19 antigen is localised on B lymphocytes but, unlike CD-20, CD19 is also localised on younger forms (early pro-B cells) and on plasmablasts and plasma cells, which are responsible for antibody production [42]. It is therefore postulated that antibodies

Table 1. Biological, pharmacological and clinical characteristics of anti-CD20 antibodies used in multiple sclerosis treatment

Antibody	Rituximab	Ofatumumab	Ocrelizumab	Ublituximab
Structure	Chimeric	Human	Humanised	Chimeric
Target epitope of CD20				
Primary mechanism of action				
Important clinical endpoints				
Symptomatic results	ARR reduction from 1.27 at baseline to 0.18 at week 72 in RRMS [29] ARR not reduced compared to PBO at week 48 in RRMS (0.37 *vs.* 0.72) [30]	ARR reduction compared to teriflunomide in RRMS at EOS (median 86 weeks) (0.11 *vs.* 0.22 — ASCLEPIOS I and 0.10 *vs.* 0.25 — ASCLEPIOS II) [37]	Reduction of CDP in PPMS (at week 24 CDP for OCR — 29.6% *vs.* PBO — 35.7%; OLYMPUS [36] Reduction compared to IFN-β1a in RRMS (0.16 *vs.* 0.29 at week 96 — OPERA I and II) [34]	Full data not available Nearly 86.7% of RMS patients free of relapse at week 96 (ULTIMATE I) and 87.5% (ULTIMATE II) [40]
MRI results	Reduction of T2 lesion volume compared to baseline (from 8,566.4 mm^3 at baseline by 272.7 mm^3 at week 72 in RRMS [29] Reduction of Gd+ lesions from 1.31 at baseline to 0 at week 72 in RRMS [29] Reduction of T2 compared to PBO (–175 mm^3 *vs.* +418 mm^3) at week 36 in RRMS [30] Reduction of Gd+ lesions compared to PBO at weeks 12, 16, 20, 24, and 48 in RRMS (0.5 *vs.* 5.5) [30]	Reduction of mean number of Gd+ lesions compared to teriflunomide at EOS (median 86 weeks) in RRMS (0.01 *vs.* 0.45) (ASCLEPIOS I and 0.03 *vs.* 0.51) (ASCLEPIOS II) [37] Reduction of new or lesions on T2 compared to teriflunomide at EOS (median 86 weeks) in RRMS (ASCLEPIOS I — 0.72 *vs.* 4.0; ASCLEPIOS II — 0.64 *vs.* 4.15) [37]	Reduction of mean percent change in total volume of lesions on T2 compared to placebo in PPMS (–3.37 *vs.* +7.43 from baseline to week 120; OLYMPUS) [36] Reduction of mean no. of Gd+ lesions compared to IFN-β1a in RRMS at week 96 (OPERA I — 0.02 *vs.* 0.29; OPERA II — 0.02 *vs.* 4.2) [34] Reduction of number of new Gd+ lesions compared to IFN-β1a in RRMS at week 96 (OPERA I — 0.32 *vs.* 1.41; OPERA II — 0.33 *vs.* 1.9) [34]	Full data not available Mean number of lesions per scan per participant: 0.282 for ublituximab + oral placebo *vs.* 2.831 for teriflunomide + IV placebo in RMS at week 96 (ULTIMATE I) [40, 41]

directed against CD19 may be more potent in modifying immune activity. Conversely, this effect may also be associated with a poorer safety profile than that of anti-CD20 antibodies due to its more potent suppression of the immune system.

The results of a phase I trial using inebilizumab (MEDI-551), a humanised IgG1κ monoclonal antibody directed against the CD19 antigen, for the treatment of MS are now available [43]. During a 24-week follow-up period, the use of inebilizumab was shown to lead to an effective reduction in B-lymphocyte counts, with an acceptable safety profile and a reduced risk of new Gd+ lesions. However, these results should be regarded as preliminary.

Extended interval dosing

The high efficacy of anti-CD20 drugs used in MS has led to increased consideration of the option of increasing the dosing interval for patients with good disease control achieved with standard dosing [44]. The concept of extended interval dosing (EID) is related to observations that the use of anti-CD20 drugs results in prolonged immunosuppression, which in turn is associated with maintaining clinical activity. Currently available data indicates that ocrelizumab can take more than six months to repopulate B lymphocytes and, in some cases, more than 12 months. Furthermore, no significant differences

in treatment efficacy have been found when comparing the effectiveness of standard dosing to EID. Similarly, encouraging findings were also obtained for another highly active drug (not acting on CD20), natalizumab [45]. However, the issue requires further study, especially since most of the available clinical data is from phase III trials with standard dosing, and there is relatively limited long-term data [46].

Conclusions

The importance of drugs directed against CD20 in the treatment of MS is not in doubt. Clinical evidence indicates that these agents are highly effective in various forms of MS. Although the full mechanism of their high clinical efficacy is not yet fully understood, it is mainly related to their effect on the number and function of B lymphocytes. Currently used agents include ocrelizumab, ofatumumab, and rituximab (off-label). In addition, promising data also exists for ublituximab, which is presently being evaluated by the registration agencies (FDA and EMA). Despite the relatively modest data supporting the long-term efficacy of anti-CD20 antibodies, they represent an important therapeutic option in the treatment of MS.

Conflicts of interest: *None.*
Funding: *None.*

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