Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Evaluating the Therapeutic Potential of Ublituximab in the Treatment of MS: Design, Development and Place in Therapy

Sarah-Jane Martin[1,2], Melanie Guenette[1], Jiwon Oh[1]

[1]Division of Neurology, Department of Medicine, St Michael's Hospital, Toronto, Canada; [2]University of Glasgow, Glasgow, UK

Correspondence: Jiwon Oh, Email jiwon.oh@unityhealth.to

Abstract: B cells are critical to the pathogenesis of multiple sclerosis (MS), an autoimmune disease of the central nervous system. B cell depletion using anti-CD20 monoclonal antibodies (mAbs) has proven to be an extremely successful treatment strategy, with profound suppression of both clinical and radiological evidence of focal inflammatory disease. Several anti-CD20 mAbs are now licensed for use in MS, with ublituximab being the latest to gain regulatory approval. The unique properties of each of the anti-CD20 mAb may result in nuanced differences in timing, duration and depth of B cell depletion, with the potential for such differences to have a clinical relevance to both drug efficacy and adverse effects. In this review, we summarize the design, development, and current place in MS therapy for ublituximab.

Keywords: multiple sclerosis, ublituximab, B-cell therapy, anti-CD20 monoclonal antibody

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). The prevalence of MS varies, and ranges from 8.6 per 100,000 in South East Asia to 142.8 per 100,000 in Europe and 290 per 100,000 in Canada.[1,2] Individuals often present in the 3rd decade of life, and traditionally accrue disability in their 5th or 6th decade.[3] As such, a diagnosis of MS can have significant physical and psychological implications for an individual and their family and economic implications for society as a whole.[4,5]

Increasing availability and use of disease modifying treatments (DMTs) has revolutionised the clinical management of MS.[6] One of the most successful categories of DMT are IgG1 monoclonal antibodies (mAbs) that target the transmembrane antigen CD20 expressed on B cells. Indeed, the efficacy of B-cell depleting therapy (BCDT) has inferred insights into the pathology of the disease.[7–9] The traditional view that MS is predominantly a T cell mediated disease has been replaced with a realisation that bi-directional interactions likely occur between several different immune cells, within both systemic and CNS immune compartments, and that B cells play an integral part in both compartments.[7,9,10]

B cells have many potential roles that extend beyond antibody production, including antigen presentation, release of cytokines and stimulation of T cells.[9] Through these mechanisms, they exert a net pro- or anti-inflammatory affect. Pro-inflammatory B cells stimulate pro-inflammatory T cells and are a source of inflammatory cytokines, including interleukin-6 (IL-6), tumour necrosis factor (TNF) and granulocyte-macrophage colony stimulating factor (GM-CSF).[9,10] Pro-inflammatory functions may be partially offset by anti-inflammatory functions of B regulatory cells (Bregs), such as secretion of interleukin-10 (IL-10). Whilst the success of BCDT demonstrates that B cells are critical to the pathogenesis of MS, B cell depletion is non-specific, targeting both pro- and anti-inflammatory B cells, and much remains to be elucidated on the complex role of B cells in many aspects of MS pathophysiology.

Anti-CD20 mAbs can induce B cell death via either direct or indirect mechanisms. Direct mechanisms involve cross-linking-induced apoptosis. Indirect mechanisms include binding C1q and activating the classical complement pathway –

Received: 1 April 2024
Accepted: 10 July 2024
Published: 16 July 2024

known as complement-dependent cytotoxicity (CDC) and fragmented crystallised gamma receptor (FcyR)-mediated phagocytosis by Natural Killer (NK) cells, macrophages or neutrophils – known as antibody-dependent cellular cytotoxicity (ADCC).[11] As CD20 is not expressed on stem cells (pro-B cells), full reconstitution occurs on cessation of treatment. Whilst CD20 is also absent from plasmablasts or plasma cells, immunoglobulin levels may decline over time in some individuals.[12]

Traditionally, anti-CD20 mAbs are described as type I or type II. Both types activate ADCC equally but differ in whether they also trigger direct cell death or CDC. Type I mAb primarily activates CDC, only weakly triggering direct cell death. Type II mAb primarily triggers direct cell death and only weakly activates CDC.[13] Animal models suggest that functions mediated through the FcyR (ADCC) may be of greater relevance to the success of anti-CD20 therapy, but it is unclear if such differences translate to humans. In humans, a better response to rituximab has been demonstrated in individuals who are homozygous for certain Fc allelic variants that bind the antibody with higher affinity compared with those that bind with low affinity.[14]

In recent years, anti-CD20 mAbs have become widely available for use in the treatment of MS and include rituximab, ocrelizumab, ofatumumab, and most recently, ublituximab. Ublituximab differs from pre-existing anti-CD20 mAbs in its design and mechanism of action. This may have clinical implications for administration, speed of B-cell depletion and reconstitution, and potential adverse effects, with clinically meaningful benefits for patients. In this review, we aim to summarize the design, development, and current place in MS therapy for ublituximab. Information on our search strategy is summarized in Supplementary Table 1.

Ublituximab: Drug Development

Design of Drug

Ublituximab (TG-1101, TG Therapeutics, New York, NY) is a novel, murine/human chimeric, IgG1 kappa monoclonal antibody with a unique binding site on the large extracellular loop of CD20 (residues 168–171 and 158–159).[15] The molecular weight of the antibody is approximately 147kDa.[16]

Ublituximab has been glyco-engineered with a low fructose content of the Fc region. This selectively enhances affinity for the FcyIIIa (CD16) receptor, significantly enhancing CD20 depletion through ADCC, particularly in cells with low CD20 expression.[17] As a result, in contrast to rituximab and ofatumumab, ublituximab achieves B cell depletion primarily through ADCC by natural killer (NK) cells. Like ublituximab, ocrelizumab exhibits higher levels of ADCC compared with CDC, but this is less pronounced than for ublituximab.[17,18]

Phase I and II Studies

Ublituximab is administered as an intravenous (IV) infusion and was initially designed for use in patients with relapsed chronic lymphocytic leukaemia (CLL). A phase I, first-in-human, open-label, non-controlled study of ublituximab in 21 individuals with CLL was conducted in 2010.[19] Participants received weekly doses ranging from 5 to 450mg over four weeks (4-week cumulative dose range 75 to 1650mg). Ublituximab induced profound and sustained lymphocyte depletion within a week, particularly at higher doses.

A phase I /II trial of ublituximab in rituximab-relapsed or refractory B-cell malignancies consisted of an induction (with doses ranging from 450 to 1200mg administered weekly for four weeks), followed by maintenance infusions (at the same dose) monthly for three months, then every three months for 2 years.[15] Infusion times ranged from 4 hours to 90 minutes. The study reported an overall response rate (ORR) of 45% (13% complete response, 32% partial response). Higher doses did not increase the ORR but did result in a slightly higher incidence of haematological adverse effects (grade 3 neutropenia, anaemia, and thrombocytopenia). Hence, 900mg was selected as the recommended phase II dose.

A phase II, 48-week, placebo-controlled trial conducted in individuals with relapsing MS (RMS) was reported in 2020.[20] Adults with RMS (as per 2010 McDonald criteria) and an expanded disability status score (EDSS) of 0–5.5 were eligible. Forty-nine participants were randomized to either ublituximab, or placebo followed by ublituximab, at a ratio of 3:1. Participants received an initial infusion of 150mg ublituximab, followed by either 450 or 600mg at day 15 and week 24, with infusion times ranging from 1 to 3 hours. Premedication with oral antihistamine and oral corticosteroids was

administered before each infusion. Forty-five individuals completed 48 weeks. The phase II study met its primary endpoint (>95% depletion from baseline of anti-CD19+ B cells) in all individuals (at both doses) and concluded that ublituximab could be safely infused in as little as 1 hour.

Based on these results, phase III RCTs in MS were designed with a dosing regimen of 150mg ublituximab followed by 450mg ublituximab at day 15 and then 24-week intervals.

Phase III Studies

ULTIMATE I (NCT03277261) and ULTIMATE II (NCT03277248) were identical, phase 3, randomized, multi-centre, double-blind, active-control studies that evaluated the efficacy and safety of ublituximab versus teriflunomide in people with RMS (see Table 1).[21] Both studies had a duration of 96-weeks. Inclusion criteria were adults 18–55 years, with a diagnosis of RMS (according to McDonald 2010 criteria) and at least 2 relapses in the previous 2 years, or at least one relapse with at least one gadolinium enhancing lesion within the last year. EDSS had to be between 0 and 5.5 at screening, with neurological stability in the 30 days prior.

Participant baseline characteristics are outlined in Table 2. Whilst largely comparable across studies of widely approved anti-CD20 mAbs, the OPERA cohorts had a higher proportion of treatment-naïve patients compared to ULTIMATE and ASCELOPIOS cohorts. When comparing ULTIMATE and ASCELEPIOS cohorts (which used identical active comparators), the ULTIMATE cohorts were slightly younger, had a shorter disease duration and were more likely to be treatment naive compared with cohorts in the ASCLEPIOS study of ofatumumab versus teriflunomide.[22] This may, at least in part, explain why there was not a difference observed between ublituximab and teriflunomide in CDP, whereas both ocrelizumab and ofatumumab demonstrated evidence of a decrease in CDP vs active comparator in the pivotal Phase III clinical trials.

Participants were randomized at a 1:1 ratio to receive IV ublituximab and oral placebo or oral teriflunomide 14mg daily and IV placebo. Oral antihistamine and oral dexamethasone (or equivalent steroid) were administered before each dose of IV ublituximab or IV placebo. Five hundred and forty-nine participants were randomised in ULTIMATE I (N = 274 to ublituximab; N = 275 to teriflunomide) and 545 in ULTIMATE II (N = 272 to ublituximab; N = 273 to teriflunomide).

The primary endpoint of both studies was annualised relapse rate (ARR). Secondary endpoints were defined in a hierarchical analysis (meaning that failure to meet an endpoint automatically nullified subsequent secondary endpoint results) and included total number of gadolinium-enhancing (Gd+) lesions by week 96; total number of new or enlarging T2 hyperintense lesions by week 96; time to confirmed disability worsening at 12-weeks (CDW-12), pre-specified pooled analysis across the two trials; number of participants with no evidence of disease activity (NEDA) between weeks 24–96, as defined by no clinical relapses, no MRI-activity and no worsening disability (NEDA-3); number of participants with impaired cognitive status (defined as a ≥4 point decrease in Symbol Digit Modalities Test (SDMT) compared with baseline); percentage change in brain volume from baseline to week 96.

Both studies met their primary end point. In ULTIMATE I, ARR was 0.08 on ublituximab versus 0.19 on teriflunomide, rate ratio 0.41, $p < 0.001$. In ULTIMATE II, ARR was 0.09 on ublituximab versus 0.18 on teriflunomide, rate ratio 0.51, $p = 0.002$.

Both studies met two of their secondary endpoints. Total number of Gd+ lesions on ublituximab was 0.02 versus 0.49 on teriflunomide, rate ratio 0.03, $p < 0.001$, in ULTIMATE I, and 0.01 on ublituximab versus 0.25 on teriflunomide, rate ratio 0.04, $p < 0.001$, in ULTIMATE II. New/enlarging T2 lesions on ublituximab were 0.21 compared with 2.79 on teriflunomide in ULTIMATE I, rate ratio 0.08, $p < 0.001$, and 0.28 compared with 2.83 in ULTIMATE II, rate ratio 0.10, $p < 0.001$. Pre-specified pooled analysis found that CDW-12 was not significantly different between trial groups. As a result, subsequent secondary endpoints were considered non-significant. Possible explanations for the lack of a difference in CDW-12 between ublituximab and teriflunomide may relate to the fact that teriflunomide in ULTIMATE I and II was associated with numerically lower rates of disability worsening than reported in previous phase III RCTs (3-month CDW on teriflunomide 5.9% in ULTIMATE compared with 15% in ASCLEPIOS, see Table 2).[22] In addition, low ARR in both groups may have led to lower rates of relapse-associated disability worsening.

NEDA-3 rates on ublituximab were 44.6% (ULTIMATE I) and 43.0% (ULTIMATE II) compared with 15.0% and 11.4% on teriflunomide. Rates of NEDA are not directly comparable across phase III RCTs. The majority of studies report NEDA between 0 and 96 weeks. In contrast, in ULTIMATE I and II, NEDA-3 was calculated specifically between weeks 24 and 96,

Table 1 Summary of the Two Phase III RCTs for Ublituximab: ULTIMATE I and ULTIMATE II

	ULTIMATE I (NCT03277261)[21]		**ULTIMATE II (NCT03277248)**[21]	
Study date	September 2017 - October 2018			
Inclusion criteria	Adults 18–55 years, with RMS (McDonald 2010 criteria) and ≥2 relapses in the previous 2 years, or ≥1 relapse with at least one Gad+ lesion within the last year. EDSS 0–5.5 at screening, with neurological stability in the 30 days prior.			
Study design	1:1 randomisation: - IV ublituximab and oral placebo or - Oral teriflunomide 14mg daily and IV placebo *Oral antihistamine and oral dexamethasone (or equivalent steroid) were administered before IV ublituximab/placebo.			
Median follow-up	95 weeks		95 weeks	
Primary endpoint	Annualised relapse rate (ARR)		Annualised relapse rate (ARR)	
Secondary endpoint hierarchical analysis	1. Total number of Gad+ lesions by week 96 2. Total number of new or enlarging T2 hyperintense lesions by week 96 3. Confirmed disability worsening (CDW) at 12-weeks (data pooled across the two trials) 4. Number of participants with no evidence of disease activity (NEDA) from weeks 24–96 5. Number of participants with impaired cognitive status (defined as a ≥ point decrease in Symbol Digit Modalities Test (SDMT) compared with baseline) 6. Percentage change in brain volume from baseline to week 96			
Study populations	N=549		N=545	
	Ublituximab group (UBL) (N=274)	Teriflunomide group (TER) (N=275)	Ublituximab group (UBL) (N=272)	Teriflunomide group (TER) (N=273)
Age (mean, SD)	36.2 (8.2)	37.0 (9.6)	34.5 (8.8)	36.2 (9.0)
Female sex (%)	61.3	65.3	65.4	64.7
RRMS subtype (%)	97.4	98.5	98.5	98.2
Trial completed (%)	87.6	91.6	93.4	87.5
Primary endpoint results	ARR: UBL 0.08 vs TER 0.19, RR 0.41, p<0.001		ARR: UBL 0.09 vs TER 0.18, RR 0.51, p=0.002	

Secondary endpoint results	• Gad+ lesions: UBL 0.02 vs TER 0.49, RR 0.03, p<0.001 • New/enlarging T2 lesions: UBL 0.21 vs TER 2.79, RR 0.08, p<0.001 • CDW-12 weeks from pooled analysis: Not significantly different between trial groups – thereafter all further endpoints non-significant • NEDA-3: UBL 44.6% vs TER 15.0% • Cognitive impairment: UBL 29.2% vs TER 31.8% • Percentage change in brain volume: N.S.		• Gad+ lesions: UBL 0.01 vs TER 0.25, RR 0.04 p<0.001 • New/enlarging T2 lesions: UBL 0.28 vs TER 2.83, RR 0.10, p<0.001 • NEDA-3: UBL 43.0% vs TER 11.4% • Cognitive impairment UBL 29.0% vs TER 31.6% • Percentage change in brain volume N.S.	
	Ublituximab group (N=273)	Teriflunomide group (N=275)	Ublituximab group (N-272)	Teriflunomide group (N=273)
Any adverse event	235 (86.1%)	245 (89.1%)	251 (92.3%)	256 (93.8%)
Serious adverse event	31 (11.4%)	19 (6.9%)	28 (10.3%)	21 (7.7%)
Discontinuation of treatment due to adverse event	18 (16.6%)	2 (0.7%)	5 (1.8%)	2 (0.7%)
Infection	135 (49.5%)	133 (48.4%)	169 (62.1%)	165 (60.4%)
Serious infection	15 (5.5%)	6 (2.2%)	12 (4.4%)	10 (3.7%)
Infusion related reaction	120 (44%)	19 (6.9%)	140 (51.5%)	48 (17.6%)
Deaths*	2 (0.7%)	0	1 (0.4%)	0

Note: *The three deaths among ublituximab recipients included one as a result of pneumonia, one as a result of encephalitis following measles and one as a result of salpingitis after an ectopic pregnancy.
Abbreviations: RMS, relapsing MS; Gad+, gadolinium enhancing lesion; RR, rate ratio; N.S., non-significant.

https://doi.org/10.2147/DDDT.S388410

Table 2 Table Summarising the Phase III RCTs of the Anti-CD20 mAbs, Rituximab, Ocrelizumab, Ofatumumab and Ublituximab

References	Number and Characteristics of Participants	Trial Design	Clinical Outcomes	Radiological Outcomes	Adverse Events
RITUXIMAB (RTX)					
Hawker et al, Ann Neurol. 2009.[23] NCT00087529	439 PPMS (OLYMPUS) 50% male. Median age 51 years. Mean time from symptom onset 9 years. 65% DMT naive. EDSS 2–6.5. Mean EDSS 4.8.	Phase II/III, multicentre randomized, double-blind, placebo-controlled study. 2:1 randomisation of 1000mg IV RTX every 24 weeks vs placebo. Duration - 96 weeks.	Non-significant ↓ proportion of patients with 3-month CDP on RTX vs placebo (30.2% vs 38.5%, p=0.14). Sub-analysis: Delayed CDP in patients aged < 51 years at baseline treated with RTX.	Less ↑ of T2 LV at week 96 (median increase: + 302.0 mm^3 with RTX, + 809.5 mm^3 with placebo, $p < 0.001$). Similar rate of brain atrophy between groups (median decrease: − 13.1 cm^3 with RTX vs − 14.0 cm^3 with placebo, $p = 0.62$). Sub-analysis: Delayed CDP in patients with Gd+ lesions at baseline treated with RTX.	↑ IARs with 1st infusion 67.1% RTX vs 23.1% placebo. IAR decreased to rates comparable to placebo with successive courses. ↑ serious infections 4.5% with RTX vs < 1% placebo. ↑ SAE 16.4% RTX vs 13.6% placebo.
Sveningsson A et al, Lancet Neurol 2022.[24] NCT02746744	200 RRMS/CIS (RIFUND-MS) 33% male. Mean age 33.4 years. Mean time from symptom onset 1.7 years. 96% DMT naive. EDSS 0–5.5. Mean EDSS 1.7.	Phase III, multicentre, randomized, rater-blinded active-comparator study. 1:1 randomisation of 1000mg IV RTX followed by 500mg six-monthly vs oral dimethyl fumarate (DMF) 240mg twice daily. Duration - 2 years.	Significant ↓ in the number of participants who experienced a clinical relapse on RTX versus DMF (3% vs 16%, risk ratio 0.19, p=0.006). Confirmed EDSS worsening 10% on RTX vs 5% on DMF, p=0.2.	↓ new/Gd+ T2 lesions on RTX 21% vs 37% on DMF, p=0.02.	Rate of IAR in the RTX group was 40.9 per 100 patient years. Gastrointestinal side effects in the DMF group was 47.4 per 100 patient years. Flushing side effect in the DMF group was 47.4 per 100 patient years.
→ Not licensed for use in MS.					
OCRELIZUMAB (OCZ)					
Hauser et al, NEJM 2016.[25] NCT01247324 NCT01412333	821 RRMS (OPERA I) 835 RRMS (OPERA II) Across both trials, approximately 34% male. Mean age 37.2 years. Mean time from symptom onset 6.5 years. Approximately 73% DMT naive. EDSS 0–5.5. Mean EDSS 2.8.	Identical phase III, multi-centre, randomized, double-blind, active-controlled, parallel group studies. 1:1 randomisation of 600mg IV OCZ every 24 weeks vs 44μg SC Interferon-β1a (INFβ-1a) 3 times weekly with IV placebo. Duration - 96 weeks.	↓ ARR with OCR of 46% (OPERA I) and 47% (OPERA II), $p < 0.001$ vs IFN-β1a.	↓ Gd+ lesions on OCR (94% OPERA I; 95% OPERA II, $p < 0.001$). ↓ new/enlarged T2 lesions on OCR (77% OPERA I; 83% OPERA II, $p < 0.001$) with OCR vs INFβ-1a. ↓ % brain volume loss from week 24 to 96 on OCR in OPERA I (− 0.57% vs − 0.74%, $p = 0.004$) but not in OPERA II (− 0.64% vs − 0.75%, $p = 0.09$).	↑ IARs 34% OCR vs 10% INFβ-1a or placebo. ↑ infections 56.9% with OCR (vs 54.3% INFβ-1a) in OPERA I, and 60.2% (vs 52.5% with INFβ-1a) in OPERA II → ↑ upper respiratory tract infections with OCR. No ↑ serious AE. ↑ neoplasm OCR (0.5%) vs INF-β-1a (0.2%).

Montalban et al, NEJM 2017.[26] NCT01194570	732 PPMS (ORATORIO) 49% male. Mean age 44.6 years. Mean time from symptom onset 6.5 years. 88% DMT naive. EDSS 3–6.5. Mean EDSS 4.7.	Phase III, double-blind, randomized, placebo-controlled, parallel group study. 2:1 randomisation of 600mg IV OCZ every 24 weeks vs placebo. Duration – at least 120 weeks.	↓ proportion of patients with 3-month CDP (32.9% OCR vs 39.3% placebo, p = 0.03) and 6-month CDP (29.6% vs 35.7%, p = 0.04).	↓ 3.4% T2 lesions from baseline to week 120 (mean change, − 3.4% with OCR vs + 7.4% with placebo, p < 0.001). ↓ % loss of brain volume (− 0.90 with OCR vs − 1.09 with placebo, p = 0.02).	↑ IARs with OCR (40%) vs placebo (26%). ↑ infections with OCR (71.4%) vs placebo (69.9%) → ↑ upper respiratory tract infections with OCR. No ↑ SAE ↑ neoplasm with OCR (2.3%) vs placebo (0.8%).
→ Licensed for use in adults with relapsing or primary progressive MS by the FDA in March 2017 and by the EMA in January 2018					
OFATUMUMAB (OFT)					
Hauser et al, NEJM 2020.[22] NCT02792218 NCT02792231	927 RMS (ASCLEPIOS I) 955 RMS (ASCLEPIOS II) Across both trials, approximately 33% male. Mean age 38 years. Mean time from symptom onset 8.2 years. Approximately 40% DMT naive. EDSS 0–5.5. Mean EDSS 2.9.	Identical phase III, multi-centre, double-blind, double-dummy, active-controlled studies. 1:1 randomisation of 200mg SC OFT every 4 weeks versus 14mg PO Teriflunomide (TER) daily. Duration - 120 weeks.	↓ ARR with OFT 0.11 vs 0.22, p < 0.001 (ASCLEPIOS I); 0.10 vs 0.25, p < 0.001 (ASCLEPIOS II). ↓ proportion of patients with 3- and 6-month CDP with OFT, 10.9% and 8.1%, vs 15.0% and 12.0% with TER, p=0.002 and p=0.01. ↓sNfL with OFT of 7% at week 12 (p=0.01), 27% at week 52 and 23% at week 104 compared with TER.	↓ Gd+ lesions with OFT 97% (ASCLEPIOS I), 94% (ASCLEPIOS II). ↓ new/enlarging T2 lesions, 82% (ASCLEPIOS I) and 85% (ASCLEPIOS II). No differences in the annualized rate of brain atrophy OFT vs TER (− 0.28% vs − 0.35% (ASCLEPIOS I) and − 0.29% vs − 0.35% (ASCLEPIOS II).	Equivalent IARs with OFT (20.2%) vs TER (15.0%). Equivalent infections with OFT (51.6%) vs TER (52.7%). Equivalent % of neoplasm with OFT (0.5%) vs TER (0.4%).
→ Licensed for use in adults with relapsing forms of MS by the FDA in August 2020 and the EMA in March 2021					
UBLITUXIMAB (UBL)					
Steinman, et al, NEJM 2022.[21] NCT03277261 NCT03277248	549 MS (ULTIMATE I) 545 MS (ULTIMATE II) Across both trials, approximately 36% male. Mean age 36 years. Mean time from symptom onset 7.2 years. Approximately 55% DMT naive. EDSS 0–5.5. Mean EDSS 2.9.	Identical phase 3, multi-centre, randomized, double-blind, active-controlled studies. 1:1 randomisation of IV UBL 150mg at baseline and day 15, followed by 450mg at weeks 24 and 48 versus oral Teriflunomide (TER) 14mg daily. Duration - 96 weeks.	↓ ARR of 0.08 on UBL vs 0.19 on TER, rate ratio 0.41, p<0.001 (ULTIMATE I) and 0.09 on UBL vs 0.18 on TER, rate ratio 0.51, p=0.002 (ULTIMATE II). Non-significant ↓ proportion of patients with 3-month CDP 5.2% UBL vs 5.9% TER, p=0.51 (pooled data).	↓ Gd+ lesions on UBL of 0.02 vs 0.49 on TER, rate ratio 0.03, p<0.001 (ULTIMATE I) and 0.01 on UBL vs 0.25 on TER, rate ratio 0.03, p<0.001 (ULTIMATE II). ↓ new/enlarging T2 lesions on UBL of 0.21 vs 2.79 on TER, rate ratio 0.08, p<0.001 (ULTIMATEI) and 0.28 on UBL vs 2.83 on TER, rate ratio 0.10, p<0.001 (ULTIMATEII).	↑ IARs 47.7% UBL. ↑ infections 49.5% UBL vs 48.4 TER (ULTIMATE I) and 62.1% vs 60.4% (ULTIMATE II). ↑ SAE 31% UBL vs 19% TER (ULTIMATE I) and 28% vs 21% (ULTIMATE II). ↑ neoplasm - 0% in either group in ULTIMATE I. 2% UBL vs 1% TER (ULTIMATE II).
→ Licensed for use in relapsing MS in December 2022 (FDA) and May 2023 (EMC)					

Abbreviations: AE, adverse event; CDP, confirmed disability progression; Gd+, gadolinium enhancing lesion; IAR, infusion associated reaction; IV, intravenous; LV, lesion volume; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SAE, serious adverse event; SC, subcutaneous; sNfL, serum neurofilament light chain.

thereby removing cases of early disease activity on ublituximab, prior to the drug being fully effective. This may skew results towards achieving higher rates of NEDA-3. However, differences also exist in how NEDA is defined, and ASCLEPIOS reported NEDA-4 rates (NEDA-3 in addition to rates of brain volume change of greater than −0.4%/year) for ofatumumab between weeks 0 and 96.[22]

Cognitive impairment on SDMT was detected in 29.2% and 29.0% on ublituximab and 31.8% and 31.6% on teriflunomide. Finally, percentage change in brain volume was reported to be not significantly different between groups. Similar results were reported in the ASCLEPIOS study which found no significant difference in brain atrophy rates between ofatumumab and teriflunomide.[22] The reasons for the lack of a difference in rate of brain atrophy between ublituximab and teriflunomide are not clear, but since brain atrophy is a non-specific measure that is reflective of both MS disease processes as well as many other biological and physiologic factors, the lack of an observed difference in brain atrophy between ublituximab and teriflunomide is not necessarily reflective of a lack of a difference in efficacy on MS-related disease processes, particularly taking into account the clear differences observed in clinical and other MRI measures.

Pharmacokinetics and Pharmacodynamics

Steady State Levels, Half-Life and Elimination

Ublituximab shows linear pharmacokinetics over a dose range of 150–600mg (ie, exposure increases in a dose-proportional manner).[27] In phase II studies, the median maximum serum ublituximab concentration (Cmax) ratio of week 24 to day 1 was 3.04, in keeping with a three-fold increase in dose and indicative of no accumulation of drug. Similarly, the Cmax ratio of week 48 to week 24 was 1, also suggesting lack of significant drug accumulation.[27] In the clinical trials, pharmacokinetics did not significantly vary with age, sex, body weight or mild renal or hepatic impairment in individuals under 65 years old. The expected metabolic pathway for ublituximab is degradation to small peptides and amino acids by ubiquitous proteolytic enzymes.[16] The half-life is reported to be 21.8 days (90% confidence interval 21.4–22.1) and the median time to reach steady state is 15.5 weeks.[27]

Notably, existing pharmacokinetic studies of ublituximab and other antiCD20 mAbs have largely been conducted in younger individuals without comorbidities. There is a dearth of studies in individuals over the age of 65 with significant comorbidities, which should be an area of future investigation.

Lymphocyte Depletion and Repopulation

In the phase II RCT of ublituximab in people with RMS, CD19+ B cells were reduced by 96% (from 7.3% to 0.2%)[28] at 2 hours following an initial 150mg dose of ublituximab and remained consistently depleted to week 48.[27] Pooled post-hoc analyses of the phase III RCTs also demonstrated a mean decrease in CD19+ B cells of 96% in the 24 hours following initial infusion that remained constant through to 96-week follow-up (24-weeks following the last infusion).[27]

Further analyses of peripheral blood mononuclear cells (PBMCs) from ublituximab recipients in the phase II study revealed significant reductions in the proportions of CD3+ total T cells (from 45% to 29%) and CD56+ NK cells (from approximately 6% to 2%) by day 2, alongside the rapid and profound depletion of CD19+ B cells.[28] This may be partially explained by an early efflux of myeloid cells from the bone marrow altering the relative proportions of different cell types.

While the percentage of total NK cells and T cells normalised by week 2, changes within NK and T cell subpopulations appeared longer-lasting.[28] $CD56^{lo}$ NK cells (that express high levels of CD16) were disproportionally depleted following exposure to drug, whilst $CD56^{hi}$ NK cells (with relatively lower expression of CD16) were not. The percentage of CD56+ NK cells normalised by week 2, and the ratio of $CD56^{lo}$: $CD56^{hi}$ had normalised at week 24. Analysis of T cell subsets over the 24-week study period revealed a gradual differential loss of effector and central memory (but not naive) CD8+ T cells. This is in keeping with prior literature demonstrating that CD20+ T cells are primarily CD8+ T memory cells.[29] Further, there was a significant decline in the percentage of Th1 CD4+ T cells and significant increase in the percentage of Tregs over the 24-week period suggesting a favourable shift in the T cell profile following treatment with ublituximab.[28]

Safety

In the phase II study of ublituximab in MS, there were no adverse-event (AE) related discontinuations and a single grade 3 AE (fatigue).[20] The most common grade 1 or 2 AEs were infusion-related reactions (58%), arthralgia (15%), nausea (15%) and upper respiratory tract infection (15%). AEs were most common on the day of the first infusion. Infusion-related reactions did not increase with higher doses or shorter infusion times.

In the pooled analysis of ULTIMATE I and II, 486 of 545 who received ublituximab (89.2%) and 501 of 548 (91.4%) who received teriflunomide reported at least one AE.[21] The most common AEs in the ublituximab arm mirrored those seen in phase II trials and included infusion-related reactions (47.7%), headache (34.3%), nasopharyngitis (18.3%), pyrexia (13.9%) and nausea (10.6%). Grade 3 or higher AEs were recorded in 116 participants who received ublituximab (21.3%) and in 77 who received teriflunomide (14.1%). Serious AEs occurred in 59 individuals who received ublituximab (10.8%) and in 40 who received teriflunomide (7.3%). Three deaths occurred in ublituximab recipients: one pneumonia; one encephalitis after measles; and one salpingitis after ectopic pregnancy.

Infections occurred in 304 participants who received ublituximab (55.8%) and 298 who received teriflunomide (54.4%).[21] Most infections were mild respiratory tract infections or nasopharyngitis. Serious infections occurred in 5% of ublituximab and included pneumonia (3 individuals), COVID-19 pneumonia (2 individuals) and CNS enteroviral infection (2 individuals). Serious infections occurred in 2.9% of teriflunomide recipients and included urinary tract infection (2 individuals) and COVID-19 pneumonia (1 individual). No opportunistic infections were reported. To date, no cases of progressive multifocal leukoencephalopathy (PML) have been reported in individuals receiving ublituximab for MS.

Infusion-related reactions, including pyrexia, headache, and chills, occurred in 47.7% on ublituximab and mostly at initial infusion (43.3%). Grade 3 or higher infusion-related reactions occurred in 2.8%. One participant had anaphylaxis during a second infusion, and one had a decrease in lymphocytes at initial infusion. Six participants (1.1%) discontinued ublituximab due to infusion-related reactions.

Immunoglobulin Depletion

In ULTIMATE I/II, 6.5% of patients on ublituximab had IgG levels below the lower limit of normal (LLN) at week 96, compared with 4.9% on teriflunomide.[21] A greater proportion of participants treated with ublituximab had IgM levels below the LNN (20.9%) compared with teriflunomide (4.9%). IgA levels did not differ between the groups.

Immunogenicity

Anti-Drug Antibody

Serum samples from participants who received ublituximab in the phase III RCTs were tested for anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) during the 96-week treatment period.[30] Of the 543 participants who received the drug, 17.8% tested positive for ADA at baseline and 86.5% tested positive at any subsequent time point. About 2.4% tested positive for NAbs at baseline and 6.4% at any subsequent time point. Development of treatment-emergent ADA and NAbs peaked at week 24 and declined thereafter. The development of ADAs or NAbs had no perceived effect on B cell depletion or the safety or efficacy of the drug and was not associated with differences in baseline characteristics of the participants (such as age, sex, race, BMI, etc).[30] Reported rates of ublituximab ADA are higher than expected. This may in part reflect the type of antibody (chimeric as opposed human) but may also reflect the method of quantification of ADA. Ublituximab ADA was quantified using an electrochemiluminescent (ECL) assay, which is drug-tolerant, thereby reducing drug interference with the assay. In other studies, for example, ASCLEPIOS, ADA was measured using a qualitative radioimmunoassay, which is not drug tolerant and may potentially underestimate ADA formation.[31]

Drug Approval and Licensing – USFDA and EMA

Ublituximab was approved by the US Food and Drug Administration (USFDA) for relapsing forms of MS in December 2022 and by the European Medicines Agency (EMA) for the treatment of adults with active forms of relapsing MS (defined by clinical or imaging features) in May 2023.

Special Consideration

Pregnancy

Data are not yet available on the use of ublituximab in Pregnancy. It is, however, expected to have similar characteristics to other anti-CD20 mAbs, for which real-world registry data are published.[32,33]

The half-life of ublituximab is 21.8 days, so complete clearance (five half-lives) should occur by point of placental transfer (weeks 17–22 gestation).[32] Fetal exposure should therefore be minimal, even if the last infusion was just prior to conception. Current recommendations from the manufacturer (TG Therapeutics) are for female patients who have received ublituximab to use effective contraception for six months following the last dose. However, it is anticipated that no harm would be caused to the fetus if the last infusion occurred closer to conception date due to the lack of placental transfer of mAbs in earlier stages of pregnancy, as with other anti-CD20 mAbs.[32] As such, expert guidelines regarding family planning and ublituximab are likely to mirror other anti-CD20 mAbs currently used in MS clinical practice.[33]

Breastfeeding

No data are available on the clinical use of ublituximab during Breastfeeding. Current recommendations from the manufacturer state that ublituximab should be used with caution until data become available, particularly while nursing a newborn or preterm infant. Real-world data for rituximab, ocrelizumab and ofatumumab suggest that due to the high molecular weight of mAbs, concentrations in breast milk are low or undetectable and that anti-CD20 mAbs are generally considered safe during breastfeeding.[32] This is reflected in expert guidelines.[33]

Vaccination

Due to the lack of data evaluating safety of live vaccines while on anti-CD20 mAbs, vaccination with live or live-attenuated vaccines is not advised after initiation of ublituximab until complete B cell repletion. Live and live-attenuated vaccinations should be administered at least 4-weeks prior to drug initiation to minimize risk and to optimise vaccination response.

Non-live vaccinations, including mRNA vaccinations against SARS-Cov-2 should be administered at least 2 weeks prior to initial drug initiation to optimise humoral response and formation of SARS-Cov-2-antibody.[16] Similar to what is currently done with other anti-CD20 mAbs, non-live vaccines may be administered while taking ublituximab, but may attenuate the humoral immune response (although T-cell responses appear to be preserved).[34,35] Thus, timing of the vaccine in relation to infusion may be of relevance. A window of approximately 4 weeks between SARS-Cov-2 vaccination and maintenance anti-CD20mAb dosing is generally advised.[36]

Discussion

In the last decade, there has been an evolution both in the number of disease modifying treatments available for use in MS and in the manner in which treatment is approached. Increasing evidence suggests that early initiation of highly effective DMTs improves clinical outcomes.[6,37,38] As a result, highly efficacious DMTs are increasingly being used earlier in the disease course, as first-line treatment, and in "milder" disease.

The majority of highly effective DMTs used in the treatments of MS are monoclonal antibodies. These include the anti-CD20 mAbs (rituximab, ocrelizumab, ofatumumab and now, ublituximab, see Tables 2 and 3), in addition to natalizumab and alemtuzumab.

mAbs Without Anti-CD20 Effect Used in the Treatment of MS: Natalizumab and Alemtuzumab

Natalizumab is a humanized IgG4 mAb that targets α4β1 and α4β7 integrins on lymphocytes and monocytes, thereby reducing transmigration across the blood-brain-barrier (BBB). Alemtuzumab is a humanised IgG1 mAb that targets CD52. CD52 is expressed on a wide variety of B and T lymphocytes, and alemtuzumab therefore acts as non-selective immune reconstitution therapy.

Table 3 Table Summarising Differences Between the Structure, Mechanism of Action, Side Effect Profile and Licensing of Anti-CD20 mAbs

	Rituximab	**Ocrelizumab**	**Ofatumumab**	**Ublituximab**
Antibody structure	Chimeric murine/human IgG1 kappa AB	Recombinant humanised IgG1 AB with humanized AB backbone	Fully humanised IgG1 AB	Chimeric murine/human IgG1 kappa AB
Primary mechanism of B-cell depletion	CDC>ADCC	ADCC>CDC	CDC>ADCC	ADCC≫CDC
B-cell depletion	>95% depletion from week 2–24[39] and week 2–96.[40]	CD19+ undetectable from week 2 to week 96.[25]	By week 2, >95% patients had B cell count below LLN. B-cell depletion (<10 cells/microL) in 82%, 92% and 98% at weeks 2, 4, 12. CD19+ B cells below LLN to week 95.[22]	CD19+ B-cell reduced by 96% 24-hours following initial infusion.[21]
B-cell repopulation	At week 122, 35% had recovered B-cell counts.[40]	B-cell return to LLN or baseline in a median 72 (27–175) weeks.[10]	Median CD19 B cell count returned to LLN 23 weeks following last SC dose.[41]	CD19+ B cells remained consistently depleted to week 96.[21]
Proportion achieving NEDA	Single-centre double-blind, placebo controlled study of RTX vs placebo induction, followed by glatiramer acetate, 44.4% achieved NEDA after an induction with RTX compared with 19.2% who received placebo.[42]	OPERA I/II combined - NEDA - 48%.[25] Subgroup analysis at 9 year follow-up reported NEDA in 48.2%.[43]	Post-hoc analysis ASCLEPIOS I/II - At week 52, 47% achieved NEDA. Month 12–24, 92% achieved NEDA.[44]	RCT III exploratory endpoint - At week 48, 44.6% and 43.0% achieved NEDA.[21]
Regimen	Off-label dosing differs by site. In Sweden, initial dose 500–2000mg, followed by 500mg six monthly.[24]	300mg IV day 1 and 15; then 600mg 6-monthly or EID.[25]	20mg SC days 1, 7 and 14; then 02mg monthly.[22]	IV 6-monthly.[21]
Infusion time	Variable, according to dose (approximately 4 hours).	3.5 hours (conventional dosing) or 2 hours (short-infusion dosing) ENSEMBLE PLUS substudy.[45]	NA	1 hour
Risk of IRR	In 2 RCTs, IRR occurred in 78.3% and 67.1% (without premedication).[23,40]	IRR occurred in 34% in RCT.[25] Further study reported 26.5% (conventional dosing) and 28.8% (short-infusion dosing).[45]	IRR occurred in 20.2% in RCT.[22]	IRR occurred in 47.7% in RCT.[21]

(*Continued*)

https://doi.org/10.2147/DDDT.S388410 DovePress

Table 3 (Continued).

	Rituximab	Ocrelizumab	Ofatumumab	Ublituximab
Risk of infection	In HERMES phase II study, incidence of infection was 70%.[40] In general, treatment is associated with greater risk infection, particularly over long time periods or in PPMS.[46] Estimated risk PML 4.17/1000 treated patients.[47]	In OPERA I/II incidence of infection was 57–60%.[25] 9 year data reported infections in 69.9% and serious infections in 2.7% (across all exposed, N=5848).[43] Two 'carry-over' cases of PML in patients receiving OCZ for MS[48]	In ASCLEPIOS I/II and extension study, incidence of infection was 52–54%.[22] To date, no cases of PML in patients receiving OFT for MS.	In ULTIMATE I/II incidence of infection was 56%.[21] To date, no cases of PML in patients receiving UBT for MS.
Immunoglobulin levels (IgG)	Observational study of N=822 - IgG below LLN at some point in 3%.40 Sustained hypogammaglobulinemia ≥4/12 associated with increased risk serious infections and may relate to baseline levels.[49]	During the phase III RCTs, 1.5% participants receiving OCZ had IgG below LLN.[25] At 5 years, this increased to 5.4%.[50] At 9 years, serious infections were not more common in individuals with IgG<LLN.[43]	Mean IgG levels remained stable after up to five years of treatment and were above LLN in 98%.[51]	During phase III RCT, 6.5% participants receiving UBT had IgG levels below LLN over the 96-week period.[31]
Antidrug antibodies	ADA develop in approximately 1/3 patients. 29% developed ADA at 48 weeks in trials in RRMS.[52] Existing evidence does not support a clinically relevant role for anti-RTX ADA.	A prospective biobank study measured ADA in 72 patients receiving OCZ and found ADA in 4/72 (5.7%), with corresponding low OCZ plasma concentration and partial B-cell repopulation.[31]	Phase IIa extended open label APLIOS study 7/284 + ADA at screening = 6/7 false positives. No neutralising AB.[53]	In ULTIMATE I/II incidence of ADA at least one time point was 81% and incidence of neutralizing AB was 6.4%, with no perceived clinical effect.[31]
Cost per quality-adjusted life year (QALY) gained compared with baseline DMT (DMF), USD	Not assessed. However, cohort study assessing drug survival and rate of sufficient treatment effect found RTX to be cost effective in Sweden compared with other DMTs.[54]	$292,000[5]	$690,000[5]	$451, 000[5]
Regulatory approval	Not approved for use in MS.	Approved for use in adults with relapsing or primary progressive MS in March 2017 (FDA) and January 2018 (EMC).	Approved for use in adults with relapsing forms of MS in August 2020 (FDA) and March 2021 (EMC).	Approved for use in adults with relapsing MS in December 2022 (FDA) and May 2023 (EMC).

Abbreviations: AB, antibody; ADA, antidrug antibodies; ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; DMT, disease modifying treatment; IV, intravenous; LLN, lower limit of normal; MS, multiple sclerosis; NEDA, no evidence of disease activity; PML, progressive multifocal leukoencephalopathy; RCT, randomised controlled trial; SC, subcutaneous; USD, US dollars.

Although both natalizumab and alemtuzumab have demonstrated clear efficacy in relapsing MS as highly effective DMTs,[55,56] their long-term use is cumbersome compared with anti-CD20 agents due to the risk of AEs (including PML and autoimmune AEs) requiring bloodwork and MRI monitoring.[39,57] However, in specific situations, both can be optimal options for pwMS with highly active disease.

Other Anti-CD20 mAbs Used in the Treatment of MS: Rituximab, Ocrelizumab and Ofatumumab

Rituximab (Roche, Basel, Switzerland) is a chimeric murine/human IgG 1 kappa anti-CD20 mAb originally approved for the treatment of B cell lymphoma in 1997.[58] Since then, it has been used extensively in the treatment of rheumatological diseases, where data suggest high tolerability and a generally low risk of serious opportunistic infections or malignancy, although risk of infection may increase with treatment duration.[46,59] Rituximab primarily depletes B cells through CDC.

Beneficial effects of rituximab in MS were demonstrated in a phase II, randomized, placebo-controlled trial in RRMS in 2008 (HERMES)[40] and in a subset of PPMS in 2009 (OLYMPUS).[23] Although these early-phase trials were positive, further clinical development of rituximab in MS was deferred in favour of ocrelizumab.[60] Despite the lack of Phase III clinical trials of rituximab in MS, rituximab remains used in certain countries as an off-label treatment, although significant variability in dosing regimens exists. Recently, a real-world, retrospective, observational study demonstrated that the efficacy of off-label rituximab is comparable with other highly efficacious DMTs in reducing ARR.[59] In addition, a phase III, active-comparator, RCT conducted across Sweden in 2022 randomized participants to rituximab or dimethyl fumarate.[24] The study met its primary endpoint and demonstrated that rituximab is superior to dimethyl fumarate in reducing ARR (3% vs 17%, risk ratio 0.19, $p = 0.006$).

Ocrelizumab (Genentech Roche, San Francisco, USA) is the first anti-CD20 mAb that received regulatory approval for use in both relapsing and primary progressive MS (PPMS). Ocrelizumab is a recombinant humanised IgG1 anti-CD20 mAb licensed for use in RMS after superiority over subcutaneous interferon-beta-1a was demonstrated in two phase III RCTs in RRMS (OPERA I and II, 2017),[25] and superiority over placebo was demonstrated in a phase III RCT in PPMS (ORATORIO, 2017).[26] Ocrelizumab differs from rituximab in that it has a humanized antibody backbone, and it exhibits greater ADCC than CDC, but also directly depletes B cells through apoptosis.[7] Recently, a noninferiority comparative effectiveness observational cohort study conducted between 2015 and 2020 in RMS reported that rituximab was inferior to ocrelizumab in reducing ARR, but no difference in risk of disability accumulation was observed between groups.[60] Whilst these results are of interest, it is difficult to draw definitive conclusions as the efficacy of rituximab and ocrelizumab at uniform doses and standardized intervals is still to be evaluated in randomized non-inferiority clinical trials.

Ofatumumab (Novartis Pharma, Basel, Switzerland) is a fully humanised anti-CD20 mAb that was originally approved for treatment of CLL in 2009. It was approved for use in 2020 after demonstrating superiority over teriflunomide in RMS in two phase III RCTs (ASCLEPIOS I and II).[22] Like rituximab, ofatumumab primarily depletes B-cells through CDC activity. In contrast to rituximab and ocrelizumab, ofatumumab is delivered subcutaneously, on a monthly basis, which has several benefits. Subcutaneous administration of the drug is thought to permit greater access to lymphocytes within lymph nodes (via absorption into the lymphatic system),[61] which may explain why, in post-hoc analyses, even a modest B cell depletion (to levels approximately 25% of baseline) resulted in a significant reduction in the formation of new gadolinium-enhancing lesions in RCTs (relative reduction of 71%).[62] Moreover, monthly dosing at low doses may also reduce fluctuations in plasma drug levels, thereby limiting risk of premature B cell repopulation. Finally, self-administration of the drug allows for greater independence and reduces hospitalisations to receive infusions.

In comparison to natalizumab and alemtuzumab, the overall safety profile of the anti-CD20 mAb class appears relatively favourable (Table 3). However, as each anti-CD20 mAb has unique properties, including different binding sites and different (if overlapping) mechanisms of action, specific nuanced AEs may only become known with real-world data and as greater numbers of patients are treated.

The most common AE of B cell depletion is increased risk of mild infection. Importantly, pre-existing humoral immunity remains intact.[7] Plasma cells are unaffected by anti-CD20 mAbs, and because only 2% of the total pool of lymphocytes circulate in the blood (and depletion of B cells within lymphoid organs is only partial), a large reservoir of

B cells remain.[7,61] In the phase III RCTs of ocrelizumab, ofatumumab and ublituximab, rates of mild infections were increased by approximately 50–60%, similar to active-drug comparator arms (INFβ-1a and teriflunomide).[21,22,25] Rates of serious infections were, however, elevated with rituximab (4.5% versus <1% on placebo) and may increase further with prolonged treatment durations.[23]

PML is a rare complication of John Cunningham virus (JCV) seropositivity. Cases of PML have been described in MS patients receiving rituximab and ocrelizumab, but in the context of a significant risk factor, such as prior treatment with natalizumab, or, in the case of a 78-year old with PPMS, advanced age.[63] To date, there are no reported cases of PML in MS patients treated with ofatumumab or ublituximab. However, the later development and regulatory approval of ofatumumab and ublituximab is likely related to this observation, and it seems unlikely that PML risk is not a class effect. As such, clinicians should be mindful that rare cases of PML may arise with anti-CD20 mAb use if enough patients are exposed for a sufficient duration.

Malignancies were reported in 0.5–2% patients treated with mAbs across studies of ocrelizumab and ofatumumab with no evidence of increased risk compared to general population.[64] Similar findings have been demonstrated for rituximab.[65]

Potential Clinical Relevance of Differences Between the Anti-CD20 mAbs

Currently, there are no randomized, direct, head-to-head RCTs of efficacy between the anti-CD20 mAbs, and comparison across trials is difficult due to differences in study populations, active comparators, and outcomes. Nonetheless, based on clinical trial observations and known pharmacokinetic and pharmacodynamic effects, it is possible that there are clinically meaningful differences between the anti-CD20 mAbs used in MS care.

Ublituximab exerts greater ADCC activity than CDC. Greater ADCC activity is thought to enable lower dosing, and therefore allows for more rapid infusions, which may be of benefit for patients from a practical standpoint.[66] Lesser CDC activity was also hypothesised to reduce rates of infusion reactions as complement activation is thought to play an important role in triggering infusion reactions.[66,67] However, ULTIMATE I/II reported infusion reaction rates of 47.4%, compared with rates between 26 and 34% for ocrelizumab and injection reaction rates of 20% for ofatumumab, which may be a greater reflection of the impact of antibody type (chimeric versus humanized versus human) as opposed ADCC versus CDC activity.[21,22,25]

Differences in anti-CD20 mAb structure, binding affinity and mechanisms of action may also alter the rate and duration of B cell depletion. If so, this could be clinically relevant when considering initiation or cessation of an anti-CD20 for an individual patient. However, evaluating the rate and extent of B cell depletion based on peripheral blood sampling is problematic for several reasons.

Mode of administration may impact drug penetration. If subcutaneous administration of ofatumumab does enable penetration of lymph nodes, lymphoid cells within nodes may be altered in response to the drug, but such changes would not be reflected in circulating blood counts.[61,68] Quantification of circulating CD19+ B cell count does not reflect changes within B cell subpopulations. Following treatment with anti-CD20 drugs, B cell repopulation is dominated by naive and transitional B cell subsets, with a comparative depletion of memory B cells.[69] This may partly explain why absolute CD19+ B cell count does not predict achievement of NEDA following B cell depletion, and why peripheral blood CD19+ count cannot be used to guide infusion regimens.[68] Skewing of the B cell repertoire appears to last long beyond drug administration (up to 52 weeks following last rituximab administration).[70] Monitoring CD27+ memory B cell count may be a more relevant measure of post-anti-CD20+ changes in B cell repertoire and has been shown to aid in tailoring B cell depleting therapy regimens in individual patients, resulting in fewer rituximab infusions whilst maintaining a persistent reduction in disease activity.[71]

Although anti-CD20 mAbs primarily target CD20+ B cells, their effect on T-cells may also have a therapeutic effect. CD20 is expressed by a small pool of T cells (primarily CD8+ T cells with an effector memory phenotype). CD20+ T cells have been demonstrated to secrete pro-inflammatory cytokines and to be present in chronic MS lesions.[72] Rituximab, ocrelizumab and ublituximab have been shown to deplete CD20+ T cells in peripheral blood in patients with MS.[64] Therefore, whilst CD20+ T cells make up a minority of CD20+ cells, their depletion may contribute to the therapeutic effect of anti-CD20 mAbs, whilst not being reflected in a CD19+ peripheral cell count.

Rapidity of B cell depletion is of particular clinical significance when considering therapy options for individuals presenting with rapidly evolving, aggressive MS. Ublituximab trial data report a 96% reduction in CD19+ cells 24 hours

following initial infusion.[21] Trial data for the other anti-CD20 mAbs only report on CD19+ cell levels at the 2-week point. Compared with subcutaneous administration of ofatumumab, intravenous administration of ublituximab may offer faster bioavailability and thus more rapid depletion of B cells.[73] However, human-equivalent therapeutic doses of ofatumumab subcutaneously injected into six healthy cynomolgus monkeys resulted in rapid depletion of CD20+ B cells as early as day 2, with B cell counts remaining decreased by approximately 80% on day 30.[61] Although such animal data cannot be extrapolated directly to humans, these data suggest that the rapidity of B-cell depletion described with ublituximab may reflect a class effect, potentially regardless of administration.

Finally, differences in efficacy may also reflect differences in the relative potency of drug dosing. For example, ocrelizumab is considered 3–5 times more potent than rituximab, and so a 600mg dose of ocrelizumab may have greater biological effect than a 1000mg dose of rituximab.[7] Very few trials have been conducted to optimise minimal dosing. One such study demonstrated similar efficacy between rituximab 500mg and 1000mg in achieving six-month CD19+ cell depletion.[59] Further studies such as this have the potential to drive changes in dosing regimens that could minimise the side effect burden of these drugs, whilst also reducing drug costs.

Future Perspectives

The addition of the anti-CD20 mAbs to the MS treatment landscape marks a new era of wide access to high-efficacy treatments in most parts of the world, which will likely be of great benefit for people with MS. Whilst all the anti-CD20+ mAbs are extremely effective in attenuating acute, focal, inflammation (presenting as clinical relapse or new lesions on MRI), their ability to prevent progression independent of relapse (PIRA) outside of their effect on relapse-disease biology is unclear. Recent studies demonstrate that ocrelizumab and ofatumumab may have a modest effect on PIRA, but it is difficult to discern what proportion is related to downstream effects of relapse-disease biology compared with effects on CNS compartmentalized inflammation.[44,74,75] Future studies evaluating the potential effects of ublituximab and other anti-CD20 mAbs on specific components of progressive disease biology will be of high interest for the field.

Despite the success of B cell depleting therapies, the precise mechanisms through which B cells drive MS pathology remain incompletely understood. In addition, details on the timing and differences of B-cell subpopulation depletion and repletion with each of the anti-CD20 mAbs remain unclear, but may have clinical implications.

Future studies that evaluate both circulating and tissue lymphocytes will be helpful to fully understand lymphocyte depletion dynamics with all anti-CD20 mAbs, and whether there are clinical efficacy and safety implications to the depth and breadth of tissue lymphocyte depletion in both the short and long term. Future discontinuation studies of anti-CD20 mAbs will be helpful to better understand B-cell repletion following treatment cessation and what the clinical implications of differential B-cell repopulation portend.[76]

There is also interest in targeting CD19 (as opposed CD20) in neuroinflammatory disorders, including MS, as this would encompass a greater range of cells and may therefore have greater immunomodulatory effects.[9] Combining glyco-engineering and protein engineering technologies can enhance ADCC and CDC antibody functions simultaneously and have gained interest in oncology for the treatment of cancer.[13] Whether double-engineering might augment treatment response in MS, and whether, in turn, this would have a clinically meaningful impact over and above current anti-CD20 mAbs, is not known and is an area that may be of interest for the field.

Finally, it is likely that there will be therapies that induce neuroprotection and repair in the coming years. As most people with MS are on DMTs for decades, how to best sequence appropriate therapies depending on disease characteristics, personal circumstances, and life stage is of high interest. In the future, B-cell depleting therapies may be considered part of a specific sequencing strategy, for example, an initial "induction" with a B cell therapy, followed by a DMT with remyelinating and/or neuroprotective effects.

Conclusion

B cells are critical to the pathogenesis of MS. B cell depletion has been shown to be a successful treatment strategy, with profound suppression of both clinical and radiological evidence of focal inflammatory disease. Ublituximab is the latest anti-CD20 mAb that has received regulatory approval for use in relapsing MS.

Trial and real-world data on the use of anti-CD20 mAbs in MS suggest that their efficacy represents a class-effect. However, differences in structural and functional characteristics may be of clinical relevance, and longer-term studies will be essential to understand if there are key differences in efficacy and safety amongst anti-CD20 agents. Ublituximab's shorter infusion time is of practical benefit, and likely to appeal to patients and health-care systems. Moreover, given the rapidity of B-cell depletion with ublituximab, it is possible that it has a faster onset of action than other anti-CD20 mAbs, and thus may prove favourable for individuals with rapidly evolving, severe MS.

In the immediate future, ublituximab is likely to be used by clinicians in a similar manner to existing anti-CD20 mAbs. Ultimately, choice of specific anti-CD20 mAbs will also likely to reflect legislative and economic barriers to prescription, and vary regionally according to availability and access to alternative B cell depleting therapies.

In summary, ublituximab is a highly efficacious disease modifying treatment for use in individuals with relapsing forms of multiple sclerosis. Long-term, real-world data will be required to fully answer the question of the place of ublituximab in the therapy of multiple sclerosis.

Funding

Dr. Sarah-Jane Martin is funded by a postdoctoral fellowship from MS Canada. Dr. Jiwon Oh holds the Waugh Family Chair in MS Research from the University of Toronto.

Disclosure

Dr. Jiwon Oh has received grant funding from Biogen-Idec, Roche, and EMD-Serono and has received personal compensation for consulting or speaking from: Biogen-Idec, EMD-Serono, Eli-Lilly, Horizon Therapeutics, Novartis, Roche, and Sanofi-Genzyme. The authors report no other conflicts of interest in this work.

References

1. Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. *Mult Scler J*. 2020;26(14):1816–1821. doi:10.1177/1352458520970841
2. Kingwell E, Zhu F, Marrie RA, et al. High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991–2010). *J Neurol*. 2015;262(10):2352–2363. doi:10.1007/s00415-015-7842-0
3. Koch-Henriksen N, Sørensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol*. 2010;9(5):520–532. doi:10.1016/S1474-4422(10)70064-8
4. Hartung DM. Economics and Cost-Effectiveness of Multiple Sclerosis Therapies in the USA. *Neurotherapeutics*. 2017;14(4):1018–1026. doi:10.1007/s13311-017-0566-3
5. McKenna A, Lin GA, Whittington MD, et al. Oral and monoclonal antibody treatments for relapsing forms of multiple sclerosis: effectiveness and value: a summary from the institute for clinical and economic review's New England comparative effectiveness public advisory council. *J Manag Care Spec Pharm*. 2023;29(7):857–860. doi:10.18553/jmcp.2023.29.7.857
6. Simonsen CS, Flemmen HØ, Broch L, et al. Early high efficacy treatment in multiple sclerosis is the best predictor of future disease activity over 1 and 2 years in a Norwegian population-based registry. *Front Neurol*. 2021;12. doi:10.3389/fneur.2021.693017
7. Greenfield AL, Hauser SL. B-cell therapy for multiple sclerosis: entering an era. *Ann Neurol*. 2018;83(1):13–26. doi:10.1002/ana.25119
8. Martin R, Sospedra M, Rosito M, et al. Current multiple sclerosis treatments have improved our understanding of MS autoimmune pathogenesis. *Eur J Immunol*. 2016;46(9):2078–2090. doi:10.1002/eji.201646485
9. Lee DSW, Rojas OL, Gommerman JL. B cell depletion therapies in autoimmune disease: advances and mechanistic insights. *Nat Rev Drug Discov*. 2021;20(3):179–199. doi:10.1038/s41573-020-00092-2
10. Arneth BM. Impact of B cells to the pathophysiology of multiple sclerosis. *J Neuroinflammation*. 2019;16(1):1–9. doi:10.1186/s12974-019-1517-1
11. Payandeh Z, Bahrami AA, Hoseinpoor R, et al. The applications of anti-CD20 antibodies to treat various B cells disorders. *Biomed Pharmacother*. 2019;109:2415–2426. doi:10.1016/j.biopha.2018.11.121
12. Margoni M, Preziosa P, Filippi M, et al. Anti - CD20 therapies for multiple sclerosis: current status and future perspectives. *J Neurol*. 2022;269(3):1316–1334. doi:10.1007/s00415-021-10744-x
13. Wirt T, Rosskopf S, Rösner T, et al. An Fc double-engineered CD20 antibody with enhanced ability to trigger complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. *Transfus Med Hemother*. 2017;44(5):292–300. doi:10.1159/000479978
14. Persky DO, Dornan D, Goldman BH, et al. Fc gamma receptor 3a genotype predicts overall survival in follicular lymphoma patients treated on SWOG trials with combined monoclonal antibody plus chemotherapy but not chemotherapy alone. *Haematologica*. 2012;97(6):937–942. doi:10.3324/haematol.2011.050419
15. Sawas A, Farber CM, Schreeder MT, et al. A Phase 1/2 trial of ublituximab, a novel anti-CD 20 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma or chronic lymphocytic leukaemia previously exposed to rituximab. *Br J Haematol*. 2017;177(2):243–253. doi:10.1111/bjh.14534
16. FDA. FDA prescribing information: briumvi; 2022.
17. Klein C, Lammens A, Schäfer W, et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. *MAbs*. 2013;5(1):22–33. doi:10.4161/mabs.22771

18. Bar A, Susan O, Michael MOB, et al. Clinical perspectives on the molecular and pharmacological attributes of anti - CD20 therapies for multiple sclerosis. *CNS Drugs*. 2021;35(9):985–997. doi:10.1007/s40263-021-00843-8
19. Cartron G, Cazin B, Coiffier B, et al. A phase I study of LFB-R603, a novel anti-CD20 antibody, in patients with relapsed Chronic Lymphocytic Leukemia (CLL). *Blood*. 2010;116(21):2447. doi:10.1182/blood.V116.21.2447.2447
20. Fox E, Lovett-Racke AE, Gormley M, et al. A Phase 2 multicenter study of ublituximab, a novel glycoengineered anti-CD20 monoclonal antibody, in patients with relapsing forms of multiple sclerosis. *Mult Scler J*. 2021;27(3):420–429. doi:10.1177/1352458520918375
21. Steinman L, Fox E, Hartung H-P, et al. Ublituximab versus teriflunomide in relapsing multiple sclerosis. *N Engl J Med*. 2022;387(8):704–714. doi:10.1056/NEJMoa2201904
22. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. *N Engl J Med*. 2020;383(6):546–557. doi:10.1056/NEJMoa1917246
23. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. 2009;66(4):460–471. doi:10.1002/ana.21867
24. Svenningsson A, Frisell T, Burman J, et al. Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial. *Lancet Neurol*. 2022;21(8):693–703. doi:10.1016/S1474-4422(22)00209-5
25. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2016;376(3):221–234. doi:10.1056/NEJMoa1601277
26. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2016;376(3):209–220. doi:10.1056/NEJMoa1606468
27. Fox EJ Pharmacodynamics of B-cell depletion and pharmacokinetics of the novel anti-CD20 monoclonal antibody ublituximab in patients with relapsing multiple sclerosis - ACTRIMS2022_Fox_ULTIMATE-I-and-II_2.24.22; 2022.
28. Lovett-Racke AE, Gormley M, Liu Y, et al. B cell depletion with ublituximab reshapes the T cell profile in multiple sclerosis patients. *J Neuroimmunol*. 2019;332:187–197. doi:10.1016/j.jneuroim.2019.04.017
29. Schuh E, Berer K, Mulazzani M, et al. Features of Human CD3+CD20+ T Cells. *J Immunol*. 2016;197(4):1111–1117. doi:10.4049/jimmunol.1600089
30. Alvarez E, Steinman L, Fox EJ, et al. Neutralizing antibodies and antidrug antibodies in the ublituximab phase 3 ultimate i and ii studies in relapsing multiple sclerosis. In: *ACTRIMS*. Florida; 2022.
31. Toorop AA, Hogenboom L, Bloem K, et al. Ocrelizumab concentration and antidrug antibodies are associated with B- - cell count in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2023;94(6):487–493. doi:10.1136/jnnp-2022-330793
32. Gklinos P, Dobson R. Monoclonal antibodies in pregnancy and breastfeeding in patients with multiple sclerosis: a review and an updated clinical guide. *Pharmaceuticals*. 2023;16(5):770. doi:10.3390/ph16050770
33. Krysko KM, Dobson R, Alroughani R, et al. Family planning considerations in people with multiple sclerosis. *Lancet Neurol*. 2023;22(4):350–366. doi:10.1016/S1474-4422(22)00426-4
34. Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. *Neurology*. 2020;95(14):E1999–E2008. doi:10.1212/WNL.0000000000010380
35. Räuber S, Korsen M, Huntemann N, et al. Immune response to SARS-CoV-2 vaccination in relation to peripheral immune cell profiles among patients with multiple sclerosis receiving ocrelizumab. *J Neurol Neurosurg Psychiatry*. 2022;93(9):978LP–985. doi:10.1136/jnnp-2021-328197
36. National MS Society: multiple sclerosis and COVID-19. Available from: https://www.nationalmssociety.org/managing-ms/living-with-ms/diet-exercise-and-healthy-behaviors/vaccination/covid. Accessed July 10, 2024.
37. Spelman T, Magyari M, Piehl F, et al. Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis: data from 2 different national strategies. *JAMA Neurol*. 2021;78(10):1197–1204. doi:10.1001/jamaneurol.2021.2738
38. Filippi M, Amato MP, Centonze D, et al. Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: an expert opinion. *J Neurol*. 2022;269(10):5382–5394. doi:10.1007/s00415-022-11193-w
39. Riera R, Torloni MR, Martimbianco ALCPR. Alemtuzumab for multiple sclerosis. Cochrane database of systematic reviews. *Cochrane Database Syst Rev*. 2023. doi:10.1002/14651858.CD011203.pub3
40. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing–remitting multiple sclerosis. *N Engl J Med*. 2008;358(7):676–688. doi:10.1056/NEJMoa0706383
41. Graham G, Yu H, David OJ, et al. Rapid and sustained B-cell depletion with ofatumumab: population pharmacokinetic B-cell modeling in relapsing multiple sclerosis patients. ACTRIMS-ECTRIMS; 2020:1–10.
42. Honce J, Nair K, Sillau S, et al. Rituximab vs placebo induction prior to glatiramer acetate monotherapy in multiple sclerosis. *Neurology*. 2019;92(7):e723–e732. doi:10.1212/WNL.0000000000006916
43. Cerqueira J, Berthele A, Cree B, et al. Long-term treatment with first-line ocrelizumab in patients with early RMS: 9-year follow-up data from the OPERA trial. In: *American Academy of Neurology*. Boston; 2023.
44. Gärtner J, Hauser SL, Bar-Or A, et al. Efficacy and safety of ofatumumab in recently diagnosed, treatment-naive patients with multiple sclerosis: results from ASCLEPIOS I and II. *Mult Scler*. 2022;28(10):1562–1575. doi:10.1177/13524585221078825
45. Hartung H, Berger T, Bermel RA, et al. Shorter infusion time of ocrelizumab: results from the randomized, double-blind ENSEMBLE PLUS substudy in patients with relapsing-remitting multiple sclerosis. *Mult Scler Relat Disord*. 2020;46:102492. doi:10.1016/j.msard.2020.102492
46. Chisari CG, Sgarlata E, Arena S, et al. Rituximab for the treatment of multiple sclerosis: a review. *J Neurol*. 2022;269(1):159–183. doi:10.1007/s00415-020-10362-z
47. Kartau M, Sipilä JO, Auvinen E, Palomäki MV-A-A, Verkkoniemi-Ahola A. Progressive Multifocal Leukoencephalopathy: current Insights. *Degener Neurol Neuromuscul Dis*. 2019;9:109–121. doi:10.2147/DNND.S203405
48. Toorop AA, van Lierop ZYG, Strijbis EEM, et al. Mild progressive multifocal leukoencephalopathy after switching from natalizumab to ocrelizumab. *Neurol Neuroimmunol Neuroinflammation*. 2020;8(1):e904. doi:10.1212/NXI.0000000000000904
49. Barmettler S, Ong M-S, Farmer JR, Choi H, Walter J. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. *JAMA Network Open*. 2018;1(7):e184169–e184169. doi:10.1001/jamanetworkopen.2018.4169
50. Hauser SL, Kappos L, Arnold DL, et al. Five years of ocrelizumab in relapsing multiple sclerosis: OPERA studies open-label extension. *Neurology*. 2020;95(13):e1854–e1867. doi:10.1212/WNL.0000000000010376

51. Cohen JA, Hauser SL, Cross AH, et al. Five-year safety of ofatumumab in people living with relapsing multiple sclerosis. In: *American Academy of Neurology*; 2023.
52. Bar-Or A, Calabresi PA, Arnold D, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. *Ann Neurol*. 2008;63(3):395–400. doi:10.1002/ana.21363
53. Bar-Or A, Wiendl H, Montalban X, et al. Rapid and sustained B-cell depletion with subcutaneous ofatumumab in relapsing multiple sclerosis: APLIOS, a randomized phase-2 study. *Mult Scler*. 2022;28(6):910–924. doi:10.1177/13524585211044479
54. Granqvist M, Boremalm M, Poorghobad A, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. *JAMA Neurol*. 2018;75(3):320–327. doi:10.1001/jamaneurol.2017.4011
55. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):899–910. doi:10.1056/NEJMoa044397
56. Cohen JA, Coles A, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet*. 2012;380(9856):1819–1828. doi:10.1016/S0140-6736(12)61769-3
57. Bloomgren G, Richman S, Hotermans C, et al. Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy. *N Engl J Med*. 2012;366(20):1870–1880. doi:10.1056/NEJMoa1107829
58. National Cancer Institute. Available from: https://www.cancer.gov/research/progress/discovery/blood-cancer#:~:text=Key%20Takeaway,improve%20patient%20outcomes%20every%20day. Accessed 1 June, 2024.
59. Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis. *Neurology*. 2016;87(20):2074–2081. doi:10.1212/WNL.0000000000003331
60. Roos I, Hughes S, McDonnell G, et al. Rituximab vs ocrelizumab in relapsing-remitting multiple sclerosis. *JAMA Neurol*. 2023;80(8):789–797. doi:10.1001/jamaneurol.2023.1625
61. Theil D, Smith P, Huck C, et al. Imaging mass cytometry and single-cell genomics reveal differential depletion and repletion of B-cell populations following ofatumumab treatment in cynomolgus monkeys. *Front Immunol*. 2019;10:1–11. doi:10.3389/fimmu.2019.01340
62. Bar-Or A, Grove RA, Austin DJ, et al. Subcutaneous ofatumumab in patients with relapsing-remitting multiple sclerosis: the MIRROR study. *Neurology*. 2018;90(20):e1805–14. doi:10.1212/WNL.0000000000005516
63. Patel A, Sul J, Gordon ML, et al. Progressive multifocal leukoencephalopathy in a patient with progressive multiple sclerosis treated with ocrelizumab monotherapy. *JAMA Neurol*. 2021;78(6):736–740. doi:10.1001/jamaneurol.2021.0627
64. Mariottini A, Muraro PA, Lünemann JD. Antibody-mediated cell depletion therapies in multiple sclerosis. *Front Immunol*. 2022;13:1–23. doi:10.3389/fimmu.2022.953649
65. Alping P, Askling J, Burman J, et al. Cancer risk for fingolimod, natalizumab, and rituximab in multiple sclerosis patients. *Ann Neurol*. 2020;87(5):688–699. doi:10.1002/ana.25701
66. de Sèze J, Maillart E, Gueguen A, et al. Anti-CD20 therapies in multiple sclerosis: from pathology to the clinic. *Front Immunol*. 2023;14. doi:10.3389/fimmu.2023.1004795
67. Van Der Kolk LE, Grillo-López AJ, Baars JW, et al. Complement activation plays a key role in the side-effects of rituximab treatment. *Br J Haematol*. 2001;115(4):807–811. doi:10.1046/j.1365-2141.2001.03166.x
68. Freeman SA, Lemarchant B, Alberto T, et al. Assessing sustained B-cell depletion and disease activity in a French multiple sclerosis cohort treated by long-term IV anti-CD20 antibody therapy. *Neurotherapeutics*. 2023;20(6):1707–1722. doi:10.1007/s13311-023-01446-5
69. Dorcet G, Migné H, Biotti D, et al. Early B cells repopulation in multiple sclerosis patients treated with rituximab is not predictive of a risk of relapse or clinical progression. *J Neurol*. 2022;269(10):5443–5453. doi:10.1007/s00415-022-11197-6
70. Palanichamy A, Jahn S, Nickles D, et al. Rituximab efficiently depletes increased CD20-expressing T cells in multiple sclerosis patients. *J Immunol*. 2014;193(2):580–586. doi:10.4049/jimmunol.1400118
71. Novi G, Bovis F, Fabbri S, et al. Tailoring B cell depletion therapy in MS according to memory B cell monitoring. *Neurol Neuroimmunol Neuroinflammation*. 2020;7(5):1–6. doi:10.1212/NXI.0000000000000845
72. Holley JE, Bremer E, Kendall AC, et al. CD20+inflammatory T-cells are present in blood and brain of multiple sclerosis patients and can be selectively targeted for apoptotic elimination. *Mult Scler Relat Disord*. 2014;3(5):650–658. doi:10.1016/j.msard.2014.06.001
73. Sánchez-Félix M, Burke M, Chen HH, Patterson CMS, Mittal S. Predicting bioavailability of monoclonal antibodies after subcutaneous administration: open innovation challenge. *Adv Drug Deliv Rev*. 2020;167:66–77. doi:10.1016/j.addr.2020.05.009
74. Bajrami A, Tamanti A, Peloso A, et al. Ocrelizumab reduces cortical and deep grey matter loss compared to the S1P-receptor modulator in multiple sclerosis. *J Neurol*. 2024;271(5):2149–2158. doi:10.1007/s00415-023-12179-y
75. Kappos L, Wolinsky JS, Giovannoni G, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol*. 2020;77(9):1132–1140. doi:10.1001/jamaneurol.2020.1568
76. Bar-Or A ClinicaTrials.gov Ocrelizumab Discontinuation in Relapsing Multiple Sclerosis (AMS05); 2022. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05285891. Accessed March 25, 2024.