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ADIS DRUG Q&A

Ublituximab in relapsing forms of multiple sclerosis: a profile of its use

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Abstract

Ublituximab (BRIUMVI™), an anti-CD20 immunoglobulin G1 monoclonal antibody, is a promising new treatment option for patients with relapsing forms of multiple sclerosis (MS). Ublituximab is approved in the USA and the EU for the treatment of adult patients with relapsing forms of MS. Following a starting dose of 150 mg infused over 4 h, ublituximab is conveniently administered twice-yearly as a short (1 h) intravenous infusion. In phase 3 clinical trials in patients with relapsing MS, ublituximab was more effective than oral teriflunomide at reducing annualized relapse rates and numbers of brain lesions over a period of 96 weeks. However, ublituximab did not result in a significantly lower risk of worsening of disability. Ublituximab had an acceptable tolerability profile in clinical trials. The most commonly reported adverse events were infusion-related reactions (IRRs), which occurred in almost half of ublituximab recipients. However, the majority of IRRs were of mild to moderate severity, occurred after the first dose and decreased in frequency with subsequent dosing.

Plain language summary

Multiple sclerosis (MS) is a chronic illness whereby the body's immune system causes damage to the brain and spinal cord. Most patients with MS have a relapsing-remitting form of the disease, where symptoms flare for a period of time and then ease. Ublituximab (BRIUMVI™) is a monoclonal antibody approved for treating adults with relapsing forms of MS. Of convenience to patients, ublituximab is given intravenously once every 6 months after initial dosing and can be infused rapidly (over 1 h). In clinical trials, ublituximab recipients were half as likely to have a relapse and had fewer areas of inflammation in the brain than patients receiving oral teriflunomide. However, ublituximab did not significantly reduce the risk of worsening disability. Ublituximab had an acceptable safety profile in clinical trials. Nearly half of patients receiving ublituximab had mild to moderate infusion-related reactions that became less frequent with later infusions. Thus, ublituximab is a promising new treatment option for patients with relapsing forms of MS.

What is the rationale for developing ublituximab in relapsing forms of multiple sclerosis (MS)?

Multiple sclerosis (MS) is a chronic immune-mediated disease that causes inflammation, demyelination and neurodegeneration in the central nervous system [1, 2]. The most common form of the disease is relapsing-remitting MS, which ≈85% of the MS population initially presents with [2]. Relapsing-remitting MS is characterized by episodes

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Adis evaluation of ublituximab in the treatment of relapsing forms of multiple sclerosis

Anti-CD20 monoclonal antibody administered by intravenous infusion
Produces near complete B cell depletion
More effective than oral teriflunomide at reducing relapse rates and numbers of lesions
Acceptable tolerability profile, with IRRs being the most common adverse events

of new or worsening neurological symptoms (relapses) followed by periods of relative stability (remission) [3].

Initial research into the pathology of MS concluded that the disease was primarily mediated by T cells [4, 5]. However, due to their function as antigen-presenting cells and their production of autoantibodies and pro- and anti-inflammatory cytokines, B cells are now thought to play a key role in the pathophysiology of MS [1, 3–5]. CD20 is a transmembrane protein expressed on the surface of B cells across different stages of maturation, from pre-B cells in the bone marrow to naïve and memory B cells [1, 4, 5]. Therefore, anti-CD20 monoclonal antibodies have been utilized to deplete B cells in patients with MS, including those with relapsing forms of MS [1, 4, 5].

Ublituximab (BRIUMVI™) is a chimeric immunoglobulin (Ig) G1 monoclonal antibody that selectively targets CD20-expressing cells [2, 5]. It is approved for the treatment of relapsing forms of MS [6, 7]. A summary of the prescribing information for ublituximab in the USA [7] and the EU [6] is provided in Table 1.

How does ublituximab work?

Ublituximab binds to CD20, a cell surface antigen found on the surface of pre-B and mature B cells [6, 7]. This results in cell lysis through antibody-dependent cellular cytotoxicity (ADCC) and, to a lesser extent, complement-dependent cytotoxicity [6, 7]. The glycoengineered crystallizable fragment (Fc) region of ublituximab has a high affinity for the Fcγ receptor IIIa (FcγRIIIa) [8]. Ublituximab has 16–25 times higher binding affinity to FcγFIIIa 158V (high-affinity receptor) and 10–22 times higher binding affinity to FcγRIIIa 158F (low-affinity receptor) than other anti-CD20 antibodies (e.g. rituximab, ocrelizumab and ofatumumab) [9]. The high binding affinity of ublituximab is associated with increased ADCC activity compared with other anti-CD20 antibodies [8–10]. In vitro, the concentration of ublituximab effective in producing 50% of the maximal ADCC activity (EC_{50}) was 2.42 pg/mL, while rituximab, ocrelizumab and ofatumumab had EC_{50} values of 5457.0 pg/mL, 60.8 pg/mL and 74.1 pg/mL, respectively [9, 10]. This high degree of ADCC activity is potentially related to the shorter infusion times for ublituximab than for other anti-CD20 antibodies [8].

In a phase 2 trial of patients with relapsing MS ($n = 48$), the median extent of B cell depletion following treatment with ublituximab was > 99% [11]. Changes in T cell composition were also reported, including reductions in effector T cells and increases in regulatory T cells [12, 13]. In a pooled analysis of two phase 3 trials (ULTIMATE I and II), ublituximab recipients ($n = 583$) had a 96% reduction in the number of CD19+ B cells starting at day 2 of week 1, which remained consistent through week 96 (98% reduction) [14]. In the phase 2 and ULTIMATE I and II trials, B cell depletion occurred within 24 h of receiving the first dose of ublituximab [11, 15].

In the pooled ULTIMATE I and II trials, treatment-emergent anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) were reported in 81% and 6% of ublituximab recipients at any post-baseline timepoint [16]. The proportion of patients with treatment-emergent ADAs and NAbs declined after 24 weeks, with continued reductions at weeks 48, 72 and 96. Treatment-emergent ADAs were generally transient, and had no effect on B-cell depletion or on the efficacy or tolerability of ublituximab [16].

What are the pharmacokinetic properties of ublituximab?

Following repeated intraveous infusions in patients with relapsing MS, ublituximab pharmacokinetics can be described by a two-compartment model with first-order elimination [14]. Ublituximab exposure increases linearly in a dose-proportional manner across a dose range of 150–600 mg (i.e. 0.33–1.33 times the approved recommeded dose [7]). The median time to reach steady state is 15.5 weeks. Ublituximab has a mean terminal half-life of 22 days and clearance of 11.3 mL/h [14]. The estimated central volume of distribution is 3.18 L [6, 7] and the estimated peripheral volume of distribution is 3.6 L [6]. As a monoclonal antibody, ublituximab is expected to be degraded into small peptides and amino acids by ubiquitous proteolytic enzymes [6, 7].

Age, sex, body weight, presence of ADAs and mild hepatic or renal impairment had no clinically significant impact on ublituximab pharmacokinetics [7]. The effects of moderate to severe hepatic or renal impairment on the pharmacokinetics of ublituximab are unknown [7]. However, hepatic metabolism of monoclonal antibodies is negligible and ublituximab is not excreted in the urine; therefore, no dose adjustment is expected to be required in patients with hepatic or renal impairment (Table 1) [6].

Table 1 Summary of the prescribing information for ublituximab (BRIUMVI™) in relapsing forms of multiple sclerosis in the USA [7] and the EU [6]

What is the approved indication for ublituximab?	
USA	Treatment of relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease, in adults
EU	Treatment of adult pts with relapsing forms of multiple sclerosis with active disease defined by clinical or imaging features
How is ublituximab available?	
150 mg/6 mL (25 mg/mL) clear to opalescent, colourless to slightly yellow solution in a single-dose glass vial, for IV infusion	
How should ublituximab be stored before dilution?	
Refrigerate vial at 2–8 °C (36–46 °F) in the outer carton to protect from light; do not freeze or shake	
How should ublituximab be administered?	
First infusion	150 mg administered as an IV infusion over 4 h
Second infusion	450 mg administered as an IV infusion over 1 h, 2 weeks after the first infusion
Subsequent infusions	450 mg administered as an IV infusion over 1 h, 24 weeks after the first infusion and every 24 weeks thereafter
How is the dose prepared?	
Visually inspect single-dose vial (USA); do not use if foreign particles are present or the solution is discoloured	
Dilute product into an infusion bag containing 0.9% sodium chloride; gently invert (do not shake) to mix diluted solution (USA)	
For the first infusion, dilute one vial (6 mL) into the infusion bag (150 mg/250 mL); for the second and subsequent infusions, dilute three vials (18 mL) into the infusion bag (450 mg/250 mL)	
Use prepared infusion solution immediately; if not administered immediately, refrigerate (do not freeze) at 2–8 °C (36–46 °F) for up to 24 h; store at room temperature for an additional 8 h	
Ensure contents of infusion bag are at room temperature prior to starting IV infusion	
Administer diluted infusion solution through a dedicated IV line; do not administer as an IV push or bolus (EU)	
How should delayed or missed doses be handled?	
If a planned infusion is missed, administer ublituximab as soon as possible; maintain treatment interval of 24 weeks (with a minimum of 5 months) between doses	
What are the contraindications to the use of ublituximab?	
USA	Active hepatitis B infection; history of life-threatening infusion reaction to ublituximab
EU	Hypersensitivity to active substance or any excipients; severe active infection; severely immunocompromised state; known active malignancies
How should ublituximab be used in special populations?	
Pts with renal or hepatic impairment	No dosage adjustment is expected to be required (EU)
Paediatric pts	Safety and effectiveness not established
Elderly pts	Unknown whether response in pts aged ≥ 65 years differs from that in younger adult pts (USA)
	No dose adjustment necessary in pts aged > 55 years (EU)
Breastfeeding pts	Unknown whether ublituximab is excreted in human milk; risk to breastfed infant cannot be excluded (EU)
	Consider breastfeeding benefits alongside clinical need for ublituximab and any potential adverse effects of ublituximab exposure or the maternal condition on the breastfed infant (USA)
What clinically relevant drug interactions may potentially occur with ublituximab?	
Consider risk of potential additive immunosuppressive effects (e.g. increased risk of infection) when coadministered with other immune-modulating or immunosuppressant drugs (USA); coadministration with other immunosuppressive drugs (except corticosteroids for symptomatic treatment of relapses) is not recommended (EU)	

Unless otherwise indicated, information applies to both the USA and the EU. Consult local prescribing information for further details

IV intravenous, *pts* patients

What is the efficacy of ublituximab in relapsing forms of MS?

Ublituximab was more effective than teriflunomide at reducing relapse rates and numbers of lesions in patients with relapsing MS [15]. The efficacy of ublituximab was demonstrated in two identical, multicentre, randomized, double-blind, phase 3 trials: ULTIMATE I and ULTIMATE II [15]. A multicentre, randomized, placebo-controlled, phase 2 trial also supported the clinical efficacy of ublituximab, in which ublituximab eradicated all

new and persisting T1-weighted gadolinium-enhancing lesions and reduced T2-weighted lesion volume [11].

The phase 3 ULTIMATE trials enrolled patients aged 18–55 years with a diagnosis of relapsing MS according to the 2010 revised McDonald criteria [15]. Eligibility criteria included ≥ 2 relapses in the previous 2 years, or 1 relapse or ≥ 1 gadolinium-enhancing lesion or both in the year prior to screening; brain MRI with abnormalities consistent with MS; an Expanded Disability Status Scale (EDSS) score of ≤ 5.5 (scores range from 0 to 10, with higher scores indicating greater disability); and neurological stability for ≥ 30 days prior to screening and baseline. In both trials, patients were randomized to receive intravenous infusions of ublituximab (150 mg for 4 h on day 1, followed by 450 mg for 1 h on day 15 and at weeks 24, 48 and 72) or oral doses of teriflunomide (14 mg once daily); both treatment groups received matched placebos (i.e. oral placebo for the ublituximab group and intravenous placebo for the teriflunomide group). All patients were premedicated with an antihistamine (oral diphenhydramine 50 mg or equivalent) and oral dexamethasone 10–20 mg or equivalent glucocorticoid 30–60 min before each infusion. Antipyretics were excluded from the first dose of 150 mg but could be used at physician discretion thereafter. The primary endpoint was the adjusted annualized relapse rate (ARR), defined as the number of centrally confirmed relapses of MS per participant-year [15].

In both trials, ublituximab was associated with significantly lower adjusted ARRs and significantly fewer brain lesions than teriflunomide over a period of 96 weeks (Table 2) [15]. Ublituximab significantly reduced the time to first confirmed relapse versus teriflunomide in both ULTIMATE I [hazard ratio (HR) 0.50; 95% CI 0.33–0.75; $p = 0.0099$] and ULTIMATE II (HR 0.43; 95% CI 0.28–0.65; $p < 0.0001$) [17]. The proportion of patients with worsening of disability confirmed at 12 weeks (pooled across both trials) was not significantly different between ublituximab and teriflunomide (5% vs 6%; HR 0.84; 95% CI 0.36–1.21) [15]. Therefore, all subsequent secondary endpoints in the hierarchical analysis (i.e. percent change in brain volume, the proportion of patients with no evidence of disease activity and the proportion of patients with worsening on Symbol Digit Modalities Test) were not considered to be significantly different between treatment groups (Table 2) [15].

In prespecified pooled tertiary analyses, 12% of ublituximab recipients and 6% of teriflunomide recipients had lessening of disability confirmed at 12 weeks (HR 2.16; 95% CI 1.41–3.31); similar results were seen at 24 weeks (10% vs 5%; HR 2.03; 95% CI 1.27–3.25) [15]. Relative to teriflunomide, ublituximab significantly ($p < 0.05$) improved the Multiple Sclerosis Functional Composite score (tertiary endpoint) from baseline to 96 weeks [18]. These improvements were driven by improvements in disability, as measured by the 9-Hole Peg Test and the Timed 25-Foot Walk [18].

Post hoc pooled analyses of ULTIMATE I and II also indicated potential benefits of ublituximab versus teriflunomide, including improvements in volume and number of brain lesions [19], disability [10, 20–22], disease activity [23, 24], fatigue [25], cognitive processing speed [26] and quality of life [27]. Potential improvements in clinical outcomes (including ARR) were reported across multiple demographic and disease characteristic patient subgroups [28], including subgroups of treatment-naïve patients [29] and patients with highly active disease [30].

What is the tolerability profile of ublituximab?

Ublituximab had an acceptable tolerability profile in patients with relapsing MS [15]. In a pooled analysis of ULTIMATE I and II, the incidence of adverse events (AEs) was 89% with ublituximab and 91% with teriflunomide [15]. The most commonly reported AEs (occurring in ≥ 5% of ublituximab recipients and with greater incidence than with teriflunomide) were infusion-related reactions (IRRs; 48% with ublituximab vs 12% with teriflunomide), upper respiratory tract infections (45% vs 41%), lower respiratory tract infections (9% vs 7%), herpes virus-associated infections (6% vs 5%), pain in extremity (6% vs 4%), insomnia (6% vs 3%) and fatigue (5% vs 4%) [7]. Serious AEs occurred in 11% of ublituximab recipients and 7% of teriflunomide recipients [15].

A number of warnings and precautions pertain to the use of ublituximab, including IRRs, infections and reduced Ig levels (Table 3). Where specified, monitoring is recommended, with subsequent treatment delay or discontinuation required in some cases (Table 3) [6, 7]. In a pooled analysis of ULTIMATE I and II, most IRRs were of mild to moderate severity, occurred after the first dose and decreased in frequency with subsequent dosing [31]. The most common IRRs of any grade with ublituximab were pyrexia (10% vs 1% with teriflunomide), chills (8% vs 1%), headache (8% vs 2%) and influenza-like illness (6% vs 1%). Six patients discontinued ublituximab due to an IRR. The route of administration of pre-medications (oral, intravenous, intramuscular or mixed) did not impact the frequency of IRRs [31].

In a pooled analysis of ULTIMATE I and II, infections occurred in 56% of ublituximab recipients and 54% of teriflunomide recipients [15]. Most infections were respiratory-related and were grade 1 or 2 in severity. Serious infections occurred in 5% of ublituximab recipients and 3% of teriflunomide recipients [15]. Infection was the most common reason for discontinuing ublituximab (1%) [7]. There were three infection-related deaths among ublituximab recipients, which occurred as a result of pneumonia, post-measles

Table 2 Efficacy of ublituximab in relapsing forms of multiple sclerosis in the phase 3 ULTIMATE trials

Endpoints at week 96[a]	ULTIMATE 1 [15]		ULTIMATE II [15]	
	UBL ($n = 271$)	TER ($n = 274$)	UBL ($n = 272$)	TER ($n = 272$)
Adjusted annualized relapse rate[b]	0.08	0.19	0.09	0.18
RR (95% CI)	0.41 (0.27–0.62)**		0.51 (0.33–0.78)*	
Mean no. of gadolinium-enhancing lesions per T1-weighted MRI scan	0.02	0.49	0.01	0.25
RR (95% CI)	0.03 (0.02–0.06)**		0.04 (0.02–0.06)**	
Mean no. of new/enlarging hyperintense lesions per T2-weighted MRI scan	0.21	2.79	0.28	2.83
RR (95% CI)	0.08 (0.06–0.10)**		0.10 (0.07–0.14)**	
No evidence of disease activity from week 24 (% of pts)	45	15	43	11
OR (95% CI)	5.44 (3.54–8.38)		7.95 (4.92–12.84)	
Worsening from BL on SMDT (% of pts)	20	32	29	32
OR (95% CI)	0.87 (0.60–1.26)		0.86 (0.60–1.25)	
LSM percent Δ from BL in brain volume	− 0.20	− 0.13	− 0.19	− 0.18

BL baseline, *LSM* least-squares mean, *OR* odds ratio, *pts* patients, *RR* rate ratio, *SMDT* Symbol Digit Modalities Test, *TER* teriflunomide, *UBL* ublituximab, Δ change

*$p = 0.002$, **$p < 0.001$ vs TER

[a]Secondary endpoints were tested hierarchically in the order presented in the table

[b]Primary endpoint, defined as the number of centrally confirmed relapses of multiple sclerosis per participant-year

encephalitis and salpingitis following an ectopic pregnancy [15].

In clinical trials, the proportion of ublituximab recipients with IgG, IgA and IgM levels below the lower limit of normal increased from 6%, 1% and 1%, respectively, at baseline to 7%, 2% and 21%, respectively, at 96 weeks [6, 7].

What is the current clinical position of ublituximab in relapsing forms of MS?

Ublituximab is a promising new treatment option for patients with MS. It is one of three anti-CD20 monoclonal antibodies approved for the treatment of relapsing forms of MS, with ocrelizumab and ofatumumab the first two drugs in this class to have gained approval. However, ublituximab has been designed to induce higher ADCC than other anti-CD20 monoclonal antibodies [4] and targets a unique epitope on CD20-expressing B cells that is distinct from the epitopes targeted by other anti-CD20 monoclonal antibodies [15]. In clinical trials, intravenous ublituximab was more effective than oral teriflunomide at reducing relapse rates and numbers of lesions in patients with relapsing MS. However, the proportion of patients with worsening disability was similar in both treatment groups. The lack of effect of ublituximab on disability progression may have been due to the low ARRs and the small number of patients with confirmed disease progression [32].

European Committee of Treatment and Research in Multiple Sclerosis and European Academy of Neurology [33] and American Academy of Neurology [34] guidelines published prior to the approval of ublituximab recommend a wide range of available modestly effective to highly effective disease-modifying drugs for relapsing forms of MS, with the choice of treatment dependent on factors such as patient preferences and lifestyle, comorbidities, disease severity/activity, efficacy, safety/tolerability, route of administration, accessibility and cost. Treatment guidelines for MS are likely to be revised in the near future to include the full range of approved treatments, including ublituximab.

Ublituximab may represent a more affordable and convenient treatment option for patients with relapsing MS [35]. Maintenance doses of ublituximab are infrequently administered (once every 6 months) and have a shorter infusion time (1 h) [6, 7] than other MS infusion treatments such as ocrelizumab (2–3.5 h) [36]. Furthermore, some patients may prefer a twice-yearly infusion to daily oral pills or frequent self-administered subcutaneous injections. Although ublituximab has an acceptable tolerability profile, the most commonly reported AEs in clinical trials were IRRs, occurring in almost 50% of ublituximab recipients [15]. However, IRRs associated with ublituximab were of mild to moderate severity and decreased in frequency with subsequent doses [15], possibly due to the shorter infusion times [35].

Randomized controlled trials directly comparing ublituximab with other treatments for relapsing MS (other than

Table 3 Summary of warnings and precautions pertaining to the use of ublituximab (BRIUMVI™) in relapsing forms of multiple sclerosis in the USA [7] and the EU [6]

IRRs	May cause IRRs; reactions may occur up to 24 h after infusion
	Observe pts for IRRs during and for ≥ 1 h after completion of first two infusions
	Administer pre-medications, i.e. methylprednisolone 100 mg (or dexamethasone 10–20 mg in the EU) or an equivalent corticosteroid and an antihistamine (e.g. diphenhydramine) to reduce frequency and severity of IRRs; consider the addition of an antipyretic (e.g. paracetamol)
	In the case of a life-threatening or disabling IRR, stop ublituximab administration immediately and provide appropriate supportive treatment; manage less serious IRRs by temporarily stopping the infusion, reducing infusion rate and/or administering symptomatic treatment
Infections	Serious (including life-threatening or fatal) infections have been reported; delay ublituximab administration in pts with an active infection until infection is resolved
	May cause HBV reactivation; perform HBV screening in all pts before initiating ublituximab; do not start treatment in pts with active HBV; for pts who are HBsAg– and HBcAb+ or who are HBV carriers (HBsAg+), consult a liver disease expert before starting and during treatment with ublituximab
	Monitor pts for clinical signs or symptoms of PML; withhold ublituximab at first sign or symptom suggestive of PML and perform appropriate diagnostic evaluation; discontinue ublituximab if PML is confirmed
Reduced Ig levels (USA)	Decreased Ig levels have been observed; monitor serum Ig levels during treatment with ublituximab, especially in pts with opportunistic or recurrent infections, and after treatment until B-cell repletion
	Consider discontinuing ublituximab if a pt with low Ig levels develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires IVIG treatment
Vaccinations	Use of live-attenuated (EU) or live vaccines is not recommended during treatment with ublituximab or until B-cell repletion; ublituximab may interfere with effectiveness of non-live vaccines (USA)
	Administer any required immunizations ≥ 2 weeks (for non-live vaccines) or ≥ 4 weeks (for live or live-attenuated vaccines) prior to initiating treatment with ublituximab
Foetal risk	May cause foetal harm (e.g. immunosuppression) when administered to pregnant pts (USA)
	Avoid use during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus (EU)
	Advise females of reproductive potential to use effective contraception during treatment and for 4 months (EU) or 6 months (USA) after the last infusion; administer pregnancy test prior to each infusion (USA)

Unless otherwise indicated, information applies to both the USA and the EU. Consult local prescribing information for further details

HBcAb hepatitis B core antibody, *HBsAg* hepatitis B surface antigen, *HBV* hepatitis B virus, *Ig* immunoglobulin, *IRR* infusion-related reaction, *IVIG* intravenous immunoglobulin, *PML* progressive multifocal leukoencephalopathy, *pt(s)* patient(s)

teriflunomide) are not available. Results from a systematic review and network meta-analysis comparing the relative efficacy of various disease-modifying therapies for relapsing MS found that the monoclonal antibody therapies (e.g. ublituximab, ocrelizumab, ofatumumab, alemtuzumab and natalizumab) were the most effective in terms of ARR and/or disability progression [37]. Of the newer treatment options (e.g. ublituximab, ozanimod and ponesimod), only ublituximab ranked among the three most effective treatments in terms of ARR [37]. However, results from such indirect comparisons should be interpreted with caution. Direct comparisons with other monoclonal antibodies in clinical trials would be of use in elucidating the relative position of ublituximab in the management of relapsing forms of MS.

Additional clinical trials evaluating ublituximab in patients with relapsing MS are currently underway, including the phase 3b ENHANCE trial, which plans to assess the maintenance of efficacy after transition from current anti-CD20 therapy to ublituximab [38]. Also underway is the phase 4 DELIVER-MS trial, which plans to determine the effectiveness of early intensive therapy (e.g. ublituximab, ofatumumab, ocrelizumab, alemtuzumab or natalizumab) versus escalation therapy (e.g. β-interferon, glatiramer acetate, teriflunomide, cladribine, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, fingolimod, siponimod, ozanimod or ponesimod) for the treatment of relapsing-remitting MS [39]. Results of these trials, along with results from ongoing long-term (up to 312 weeks) open-label extensions of ULTIMATE I and II, are awaited with interest. Additional studies investigating the use of ublituximab in the real-world setting would also be useful, particularly those with larger and more diverse cohorts of patients [32]. Real-world experience will also show if ublituximab has an effect on disability progression similar to other anti-CD20 monoclonal antibodies [32].

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