Unleashing the power of anti-CD20 immunotherapy: Mitigating multiple sclerosis risk in Epstein–Barr virus latent infections

Reem Hamoud Alrashoudi[A–F]

Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2024;33(8):869–880

Address for correspondence
Reem Hamoud Alrashoudi
E-mail: ralrashoudi@ksu.edu.sa

Funding sources
None declared

Conflict of interest
None declared

Acknowledgements
I would like to thank Mrs. Hajera Tabassum for her contribution to this article.

Received on May 21, 2023
Reviewed on August 22, 2023
Accepted on September 13, 2023

Published online on December 12, 2023

Abstract

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, and neurodegenerative connective tissue disease affecting the central nervous system (CNS). Recently, there has been a dramatic improvement in several vital concepts of immune pathophysiology underlying MS. Notably, one of the prerequisites to MS development is Epstein–Barr virus (EBV) infection. Greater attention has been drawn towards promising, innovative immunotherapies in the management and treatment of MS. Whilst there are numerous immunotherapies currently proposed for MS, the B cell depleting therapy that predominantly uses the anti-CD20 monoclonal antibodies (mAbs) such as rituximab, ocrelizumab, and ofatumumab have demonstrated promising clinical benefits by targeting the memory B cells, which are the primary reservoir of EBV latency. Although mAbs have proved beneficial in the treatment of MS, they pose the risk of potential adverse effects. The current systematic review was undertaken to explore the therapeutic role of anti-CD20 therapy and its downsides in the treatment of MS and EBV infection. Clinical trials and prospective and retrospective studies reporting anti-CD20 therapy were carefully reviewed. The initial sections discuss the clinical features of MS, the probable link between EBV and MS, and the role of B cells in MS pathogenesis. Here, we show the potential role of anti-CD20 therapy more of a boon than a bane as the therapy yields more promising results for MS treatment. Nevertheless, the adverse effects could be minimized following a planned therapeutic regimen for treating MS patients.

Key words: Epstein–Barr virus infections, multiple sclerosis, rituximab, ocrelizumab, ofatumumab

Cite as
Alrashoudi MR. Unleashing the power of anti-CD20 immunotherapy: Mitigating multiple sclerosis risk in Epstein–Barr virus latent infections. *Adv Clin Exp Med*. 2024;33(8):869–880. doi:10.17219/acem/172240

DOI
10.17219/acem/172240

Introduction

Multiple sclerosis (MS) is an inflammatory, neurodegenerative, and immune-mediated disorder of the central nervous system (CNS), characterized by the formation of inflammatory lesions of the white matter, axonal damage, loss of oligodendrocyte, gliosis, demyelination, and neurodegeneration.[1] The inter-relationship of various immune, genetic, epigenetic, and environmental factors accounts for the development of this disorder.[2] Before understanding the role of anti-CD20 therapy in mitigating the risk of MS, the epidemiology, together with environmental, genetic, and pathophysiological factors of MS, needs to be reviewed. Multiple sclerosis is one of the most prevalent neurological diseases in the world, affecting mainly women, with about 2.8 million cases worldwide.[3–5] Environmental factors, including exposure to viral and bacterial agents such as Epstein–Barr virus (EBV),[6] human herpes virus, mycoplasma pneumonia,[7] smoking,[8] vitamin deficiency,[9] diet,[10] and exposure to UV radiation are associated with the onset of MS.[11]

Multiple sclerosis has a prevalence gradient dependent on latitude, with a higher incidence in the northern latitudes of Europe and North America.[12] Vitamin D deficiency has been considered as a possible etiology for the noted predisposition of the population in higher latitudes being affected.[13] Genetic susceptibility is not inherited since there is no MS-specific gene,[14] although genetic predisposition may be involved in MS[15–18] as there is a high risk of the disease in patients with affected biological relatives. Moreover, genetic studies have shown a connection between first-, second-, and third-degree relatives.[15,16]

While long considered as a T cell-mediated disease, MS is now known to involve other immune cells like B cells. The role of B cells is now increasingly gaining significance in immunotherapy, and the influence of antibodies on tissue damage is actively investigated. Inflammation of the white and grey matter tissues in the CNS due to focal immune cell infiltration and the subsequent release of cytokines are the primary causes of myelin sheath destruction in MS.[19–22]

Multiple sclerosis is characterized by a wide variety of clinical symptoms. Patients exhibit dysfunction in neural communication as a consequence of demyelination and axonal loss. Approximately 85% of MS patients have alternating episodes of neurological disability and recovery that last for many years, termed relapsing-remitting MS (RRMS). About 90% of RRMS patients progress to steady neurological decline within 25 years, termed secondary progressive MS (SPMS). Nearly 10% of MS patients suffer from steady deterioration of neurological functions without recovery, termed primary progressive MS (PPMS).

In addition to the common motor, sensory, visual, and autonomic deficits, cognitive impairment (CI) is also a common symptom,[23] with approx. 43–65% of MS patients suffering from CI.[24,25] Executive impairment in MS has been related to damage in frontal-subcortical tracts as the prefrontal cortex (PFC) is believed to support executive functions.[26,27] The assessment of PFC function may provide a useful way to assess cognitive changes in executive function in MS patients.

Besides this, behavioral changes with depressive symptoms are among the most common symptoms in MS.[28] Since mood, fatigue, and sleep disorders are widely acknowledged as important contributors to CI in MS, a comprehensive neuropsychological assessment should always include routine monitoring and screening of these factors to assess the patient's psychological state and any arising difficulties.[29] Besides immunological factors, the pathophysiology of MS could also involve oxidative stress that contributes to the disease progression by inducing axonal and neuronal damage.[30] A causal relationship between neurological disorders such as Alzheimer's disease, MS and diabetes is currently researched across the globe due to the role of oxidative stress and redox status on neurological disorders.[31]

Epstein–Barr virus is a human herpesvirus and the causal agent of infectious mononucleosis (IM). Demyelination is understood to be triggered in genetically predisposed individuals by an infectious agent, with EBV being the lead candidate.[6] In the case of post-EBV infection, the virus persists in latent form in B lymphocytes throughout the life of the host, thus posing a major risk in MS development. Epstein–Barr virus is involved in the etiology underlying the pathogenesis of MS and its progressive stages, namely RRMS, PPMS, and SPMS.[32] While EBV involvement in MS pathology has been studied for many years, the rationale underlying the causality remains inconclusive. It is known that patients with a history of IM or with a higher anti-EBV antibody titer are at greater risk of developing MS. Epstein–Barr virus infection is assumed to be a prerequisite in MS owing to the increased prevalence of MS patients with latent EBV infection,[33–38] with EBV-positive individuals being reported to have a 15 times greater risk of MS than EBV-negative individuals.[34] The strongest evidence reporting EBV infection as a critical contributor to MS was reported by Bjornevik et al., who for over 20 years were analyzing a cohort of >10 million people on active duty in the US military. Adults diagnosed with MS were reported positive for EBV serology.[35]

Presently, there is no cure for MS. However, disease-modifying agents (DMA) comprising modulators and cytotoxic compounds are the mainstay of MS treatment. The antiviral drugs or DMA used in the treatment of viral infections are not completely effective in diminishing the viral load and so have limited effect on the progression of MS. The development of therapies that target EBV or B cells that harbor EBV specifically will be instrumental in addressing this question. Monoclonal antibodies (mAbs) are one of the preferred treatments for MS due

to their target specificity and unusually high efficacy. Approximately 18 mAbs have been approved for the treatment of various diseases, such as rheumatoid and psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis, and Crohn's disease.[39] Monoclonal antibodies target the immune system, which plays a key role in the pathophysiology of MS and these diseases.

Depletion of B cells with mAbs targeting CD20 has emerged as one of the most efficacious therapies for MS[6] and is gaining increasing significance in ameliorating the progression of EBV infection to MS.[39–46] For example, an immunosuppressive mAb, ocrelizumab (OCR) is indicated for the treatment of PPMS and ofatumumab (OMB) was recently licensed for the treatment of SPMS.[47,48] In the case of EBV infection, the anti-CD20 therapy could further dampen the cross-reactive immune response by depleting EBV transformed B cells and mitigate relapses in MS.[45] Whilst anti-CD20 therapy has emerged as an efficient therapeutic tool in managing the risk of MS, these antibodies pose the risk of potential adverse effects. Characteristics, drug efficacy, safety, and outlines of the significant findings of a few mAbs used for B cell depletion are listed in Table 1. Whether anti-CD20 therapy is beneficial or harmful to MS patients remains a question, and the efficacy and safety role of these drugs need to be further established. The current review rationalizes the use of anti-CD20 therapy as positive or negative in mitigating the risk of MS in EPV-infected patients.

Objectives

The current review was undertaken to ascertain the role of anti-CD20 therapy in mitigating the risk of MS in EBV-infected patients and whether the potential benefits of the therapy outweigh the adverse treatment effects.

Methodology

Search strategy and study selection

The current review used the PRISMA protocol. A systematic search was conducted for the published articles across different databases, including PubMed, Scopus, and Google Scholar. Studies on observational, cohort, and case studies evaluating the role of anti-CD20 therapy or B cell depletion in mitigating the risk of EBV and MS were included. All articles included in the review were in English language.

Inclusion and exclusion criteria

Articles were screened based on originality, those falling within the scope of the review question and following the population, intervention, control, and outcome (PICO) guidelines. Furthermore, articles published during the past 5 years were filtered. Articles not adhering to the review question or satisfying the inclusion criteria, and articles with missing information and repeatability were excluded.

Data extraction process

The study selection process is outlined in Fig. 1. A comprehensive search was performed using PubMed (Medline) and MeSH terms: "Epstein Barr virus infection" AND "EBV" AND "multiple sclerosis" AND "MS" AND "B cell" AND "immunotherapy" AND "B cell depletion" AND "memory B cells" AND "anti-CD20 therapy" AND "rituximab", "RTX" AND "ocrelizumab", "OCR" AND "ofatumumab", "OMB", "adverse effects", etc. The method was adopted following guidelines from previously published studies.[49,50] A total of 102 articles were obtained

Table 1. Characteristics, drug efficacy, and safety of mAbs used in anti-CD20 therapy

mAbs	Administration (dose)	Efficacy	Important safety issues
Rituximab	intravenous (500–1000 mg, every 6–12 months	no phase 3 clinical trials	hypogammaglobulinemia, risk of infections, infusion-related reaction, hepatitis reactivation
Ocrelizumab	intravenous (600 mg, every 6 months)	phase 3 clinical trials: OPERA I OPERA II clinical outcomes: ↓ in ARR (annualized relapse rate) by 46–47% ↓ in Gd-enhancing lesions around 94–95%	hypoglobulinemia, infections, malignancies (breast cancer), infusion-related reaction, hepatitis B reactivation
Ublituximab	intravenous (450 mg, every 24 weeks)	phase 3 clinical trials: ULTIMATE I, ULTIMATE II clinical outcomes: • ↓ in ARR (49.1–59.4%) • ↓ in 24-week confirmed; disability progression (34.3%) MRI outcomes: • ↓ in number of Gd-enhancing lesions (96.5–96.7%)	infusion-related reaction, infections, hepatitis B reactivation, hypogammaglobulinemia
Ofatumumab	subcutaneous (20 mg, every 28 days)	phase 3 clinical trials: ASCLEPIOS I, ASCLEPIOS II clinical outcomes: • ↓ in risk of sustained disability progression (32–34%) • ↓ in ARR (50–60%) MRI outcomes • ↓ number of Gd-enhancing lesions (94–97%)	infusion-related reaction, infections, hepatitis B reactivation, hypogammaglobulinemia

mAbs – monoclonal antibodies; ARR – annual relapse rate; Gd – gadolinium; MRI – magnetic resonance imaging.

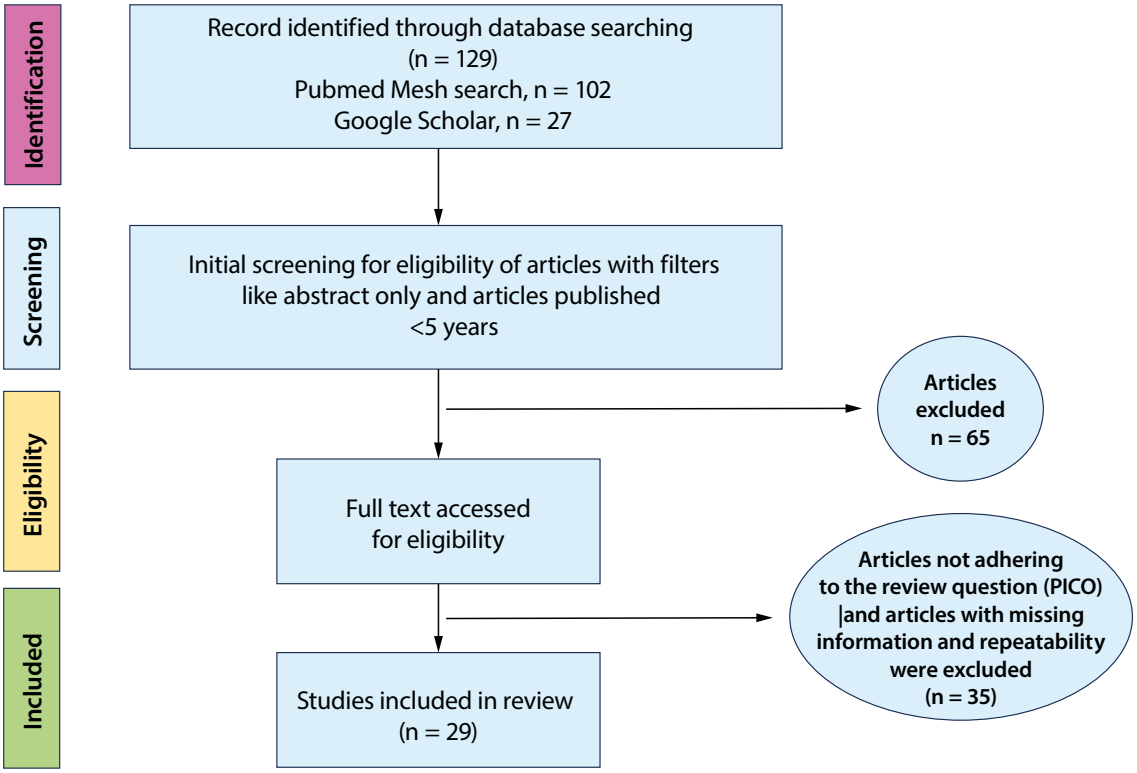

Fig. 1. PRISMA flow diagram showing screening and selection of studies for systematic review

based on the search terms used. An additional 27 articles were also reviewed from a Google search. On applying filters (abstract only and <5 years) and keywords or MeSH used in the review question built on the PICO guidelines, 64 articles were selected. Furthermore, full-text screening of the selected articles resulted in 29 that were reviewed in detail to assess the role of anti-CD20 therapy in treating MS. Articles not adhering to the review question nor meeting the inclusion criteria and articles with missing information and repeatability were excluded. To avoid the risk of bias, 2 reviewers independently evaluated the studies for eligibility and assessed the quality of the included studies. Any conflict between the reviewers was resolved following discussion to reach a common consensus.

Results

The study selection and data extraction process using the PRISMA protocol are depicted in Fig. 1. The initial screening resulted in the extraction of 64 articles, which was reduced to 29 after full-text screening and inclusion/exclusion criteria. To overcome bias, articles with missing information were removed.

Risk of bias and quality assessment

The quality of included studies was assessed for risk of bias using the Cochrane risk of bias tool (RoB 2), a revised version[51] consisting of 5 domains, being the selection of the reported result, randomization, intended interventions, missing outcome data, and outcome measurement (Fig. 2). The risk of bias for a study is determined and categorized as low, high, or some concerns of bias in specific domains. Analysis of domains resulted in raising some concerns that could be due to the following reasons - information on the allocation process used to preserve concealment is not provided in the study, details of intervention in patient information sheet is lacking,and or deviation of the study outcome from intented intervention. Data displayed in Fig. 2 reflect that the study is judged to be at low risk of bias for all domains for this result and ensures the reliability of the included studies.

B cell depleting therapy using anti-CD20 mAbs including rituximab (RTX), ocrelizumab (OCR), and ofatumumab (OMB) has been reported to achieve good efficacy. Rituximab depletes B cells through complement-dependent cytotoxicity[52] and is used as an off-label treatment option for MS and its various progressive forms. In a multi-center retrospective study evaluating the efficacy and safety of RTX in RRMS and PPMS, a significant reduction in annual relapse rate (ARR) following RTX administration in RRMS and SPMS in the 1st year of treatment was reported. Three years after RTX treatment, the proportion of patients with the confirmed expanded disability scale (EDSS) progression was 14.6%, 24.7%, and 41.5% in RRMS, SPMS, and PPMS groups, respectively.[53] Infusion-related symptoms were the most prevalent side effects (18.8%), although most were mild. A similar reduction in ARR was observed in a study by Granqvist et al.[54]

Ocrelizumab is the second anti-CD20 humanized mAb and was approved by the US Food and Drug Administration

Fig. 2. Risk of bias and quality assessment

(FDA) in March 2017 with proven therapeutic effects reducing disability progression in PPMS. In a clinical trial study by Montalban et al., 732 PPMS patients (ORATORIO trial) received 600 mg of iv. OCR, resulting in a 3.4% decreased brain lesion volume with OCR vs the placebo group.[55] Intriguingly, lower disability progression was observed in the OCR-treated group compared to the placebo group. Other studies evaluating the efficacy of OCR yielded similar findings in mitigating MS risk.[56–58] By week 120, performance on the timed 25-foot walk worsened by 38.9% in the OCR group vs 55.1% in the placebo.[59] In 2 identical phase 3 trials of OCR, lower rates of disease progression were observed compared to the placebo.[55,60] Infections of the upper respiratory tract, nasopharyngitis, and herpes/respiratory viral infections were reported in the treatment of PPMS with OCR in an RCT, although these were mild-to-moderate in severity.[55,60] Cases of tuberculosis or other opportunistic infections were not documented.[60,61] In the ORATORIO trial, of the 11 patients, 2.3% developed breast cancer compared to the placebo group (0.8%).[62] The reported incidence was within expectations based on other epidemiological studies.[63] Compared to RTX, OMB treatment provides effective B cell depletion within lymphoid tissues. Ocrelizumab depletes B cells by antibody-dependent cellular cytotoxicity (ADCC) activity after binding to a CD20 epitope on circulating B cells.[64,65] Annual relapse rate and the number of new magnetic resonance imaging (MRI) lesions were suppressed following the therapy in RRMS patients.[66] The recently reported phase 3 clinical trials, namely ASCLEPIOS I and II, consisting of 1,882 participants with RRMS (94%) and SPMS (5–6%) administered OMB subcutaneously in loading doses of 20 mg on days 1, 7, and 14, followed by 20 mg every 4 weeks while teriflunomide was given orally at 14 mg daily. By using ARR as the primary endpoint, both studies observed significant decreases (51% in ASCLEPIOS I and 58% in ASCLEPIOS II) with OMB therapy.[67]

The efficacy of OMB in MS treatment demonstrated by other clinical studies also yielded satisfactory results. In a clinical trial by Bar-Or et al., 232 patients were randomized to 3, 30, or 60 mg OMB every 12 weeks, 60 mg every 4 weeks, or placebo for a 24-week treatment period, with a primary endpoint of the cumulative number of new gadolinium-enhancing lesions at week 12. This trial reported a significant reduction in primary endpoint metrics of 65% for all OMB dose groups vs placebo.[68]

Ublituximab (UBX), a newly developed chimeric mAb, is reactive against CD20-positive B lymphocytes, targeting a different epitope on CD20 from that targeted by other CD20 mAbs. Furthermore, it utilizes shorter infusion times and lower doses compared to other anti-CD20 mAbs.[61] In comparison to RTX, UBX has a higher ADCC activity and is 100 times more active on cultured cells from chronic lymphocytic leukemia patients.[69] Following administration, B cell depletion is significant within the first 24 h, reaching approx. 95% within 2 weeks after the 2nd dose is administered.[70] Ublituximab has been evaluated in phase 3 trials to test its safety and efficacy as a potential treatment for relapsing MS.[71–74] Recently, Steinman et al. tested the efficacy and safety of UBX against teriflunomide in RRMS patients.[74] In this trial, UBX was administered iv. on day 1, day 15, weeks 24, 48, and 72. Annual relapse rate was considered the primary endpoint, and several gadolinium-enhancing lesions on MRI were scored as the secondary endpoint. The ARR and gadolinium-enhancing lesions were 0.08 and 0.02, respectively in the ULTIMATE I trial, while during the ULTIMATE II trial, ARR and gadolinium-enhancing lesions were 0.09 and 0.01, respectively. These results demonstrate that UBX treatment results in lower ARR and fewer brain lesions on MRI than teriflunomide over 96 weeks. Regarding its safety, in the treated group, it was well tolerated, and infusion-related reactions were observed in 47.7% of the participants. The trial reported approx. 15–17.2% of patients infected with respiratory tract infections, and 52 patients with serious adverse events, including 2 malignancies and 3 deaths due to encephalitis and salpingitis.[74] No cases of PML were reported after RTX therapy. Similarly, in a phase 2 multi-center study by Fox et al., robust B cell depletion and profound reductions in MRI activity and relapses were demonstrated following

UBX treatment. An absence of T1 gadolinium-enhancing lesions was recorded at weeks 24 and 48 of follow-up, and T2 lesion volume decreased by 10%. The ARR was approx. 0.07 and about 74% of patients had no evidence of disease activity (NEDA).[75]

Clinical findings of some studies are outlined in Table 2.[33,53–59,71–75] Overall, the reviewed articles demonstrated the efficacy of anti-CD20 immunotherapy in mitigating the risk of MS in EBV latent infections. Furthermore, they highlight that anti-CD20 therapy is a net benefit to patients and yields promising results for MS treatment. So far, anti-CD20 antibody treatment has been observed to be superior to other treatments, and will likely continue to be utilized until a more comprehensive understanding of the disease develops.

Discussion

The present review provides evidence from different clinical trials in support of the utility of the therapy in MS management and treatment. B cell depletion via anti-CD20 action is recognized to play a pivotal role in therapeutics for MS. Furthermore, a prophylactic effect may be seen as depletion of infected B cells, which can improve the control of EBV infection and reduce the risk of MS. B cell depleting therapy using anti-CD20 mAbs has been reported to achieve good efficacy. From the articles reviewed in the current study, anti-CD20 therapy was found effective in treating MS and EBV infections, with few downsides or adverse effects in the treatment. As the immune cells are damaged, the patient is at risk of infections from other disease-causing microorganisms, autoimmune diseases, and cancer. Importantly, the observations reported in the present review are in accordance with the previous studies.[76–78]

In this article, the rationale behind the use of anti-CD20 therapy, and whether this is beneficial or risky to the patients, has been discussed. It is of prime importance to understand the involvement of B cells in EBV infection and MS pathophysiology before the action of anti-CD20 therapy is understood. Epstein–Barr virus, as an essential prerequisite in MS development and action of anti-CD20 therapy, is illustrated in Fig. 3.

Following EBV infection, the EBV-infected or transformed B cells enter the brain through the blood-brain barrier. Here, the B cells differentiate into plasma cells and produce cross-reactive antibodies against myelin antigens, which attack and damage neurons. Further damage to oligodendrocytes, myelin, and neurons occurs by pro-inflammatory cytokines such as IL-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-β production,

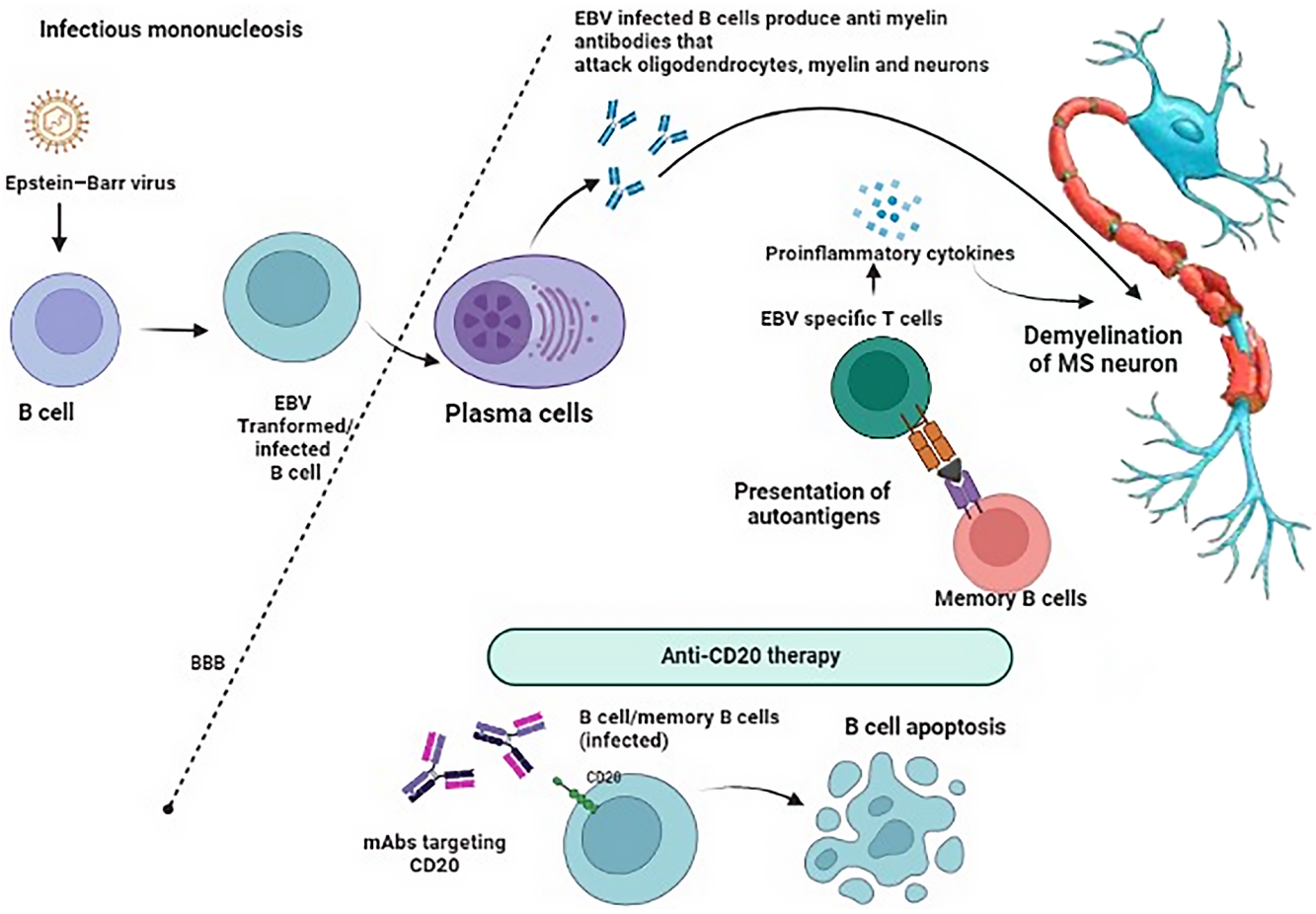

Fig. 3. EBVs association as a prerequisite for MS development and action of anti-CD20 therapy

Table 2. Summary of studies assessing anti-CD20 therapy

Author	Type of anti-CD20 therapy	Study design	Major clinical findings	Adverse events
Bar-Or et al.[33]	OMB	phase 2, double-blind, randomized, placebo-controlled study (MIRROR; 48 weeks); number and type of participants: 232 RRMS	stable EDSS in 79% of patients at week 12 and 24	IARs increased in OFT (52%) vs placebo (15%); equivalent infections with OFT and placebo
Zecca et al.[53]	RTX	retrospective, uncontrolled, observational study; number and type of participants: 355 MS (188 RRMS, 43 PPMS, 124 SPMS)	↓ ARR vs 1 year before (RRMS = 0.86 → 0.09 $p < 0.001$; SPMS = 0.34 → 0.06 $p < 0.001$; PPMS = 0.12→ 0.07 $p = 0.45$	23.7% at least 1 IAR; serious AE (3.1%); death (n = 1) due to mediastinal neoplasm
Granqvist et al.[54]	RTX	retrospective multicenter (follow-up: to 4 years); number and type of participants: 120 RRMS	↓ ARR with RTX vs injectable DMTs ($p < 0.01$)	absence of serious adverse events with RTX; mild adverse events more common for injectable DMTs vs RTX
Montalban et al.[55]	OCR	phase 3, double-blind, randomized, placebo-controlled, parallel study group (ORATORIO; 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%, $p = 0.04$)	IARs increased with OCR (40%) vs placebo (26%); increased rate of infections with OCR (71.4%) vs placebo (69.9%); increase in upper respiratory tract infections with OCR; no increase in SAE; increase neoplasm with OCR (2.3%) vs placebo (0.8%)
Ellwardt et al.[56]	OCR	retrospective, single-center (median follow-up: 200 days); number and type of participants: 210 MS (155 RRMS/ SPMS, 55 PPMS)	relapse rate (13%) and 5% experienced a 12-week CDP	22% AE, 9% IARs: minor infections (8%) and 2 cases of a prolonged herpes labialis; 1 case of toxic drug-induced hepatopathy
Wolinsky et al.[57]	OCR	open-label extension, phase 3 trial (ORATORIO; 144 weeks); number and type of participants: 732 PPMS	↓ proportion of patients with 24 weeks CDP	AE consistent with past reports
Turner et al.[58]	OCR	phase 3, randomized, double-blind, active-controlled, parallel study group (pooled OPERA I and OPERA II; 96 weeks); number and type of participants: 1,656 RRMS	decreased ARR and NEDA-3 re-baselined at week 24 in patients aged < 40 years or with ≥1 Gd^+ lesion at baseline with OCR	–
Hauser et al.[60]	OCR	open-label extension, phase 3 trials (OPERA I and OPERA II); number and type of participants: 702 RRMS	↓ proportion of patients with 6 months CDP (16.1% with OCR/OCR vs 21.3% with IFN-β-1a/OCR at year 5, $p = 0.014$) NEDA-3 = 65.4% with OCR/OCR vs 55.1% with IFN-β-1a/OCR ($p < 0.001$)	no new safety signals emerged with prolonged treatment
Sorensen et al.[66]	OMB	phase 2, double-blind, randomized, placebo-controlled study (48 weeks); number and type of participants: 38 RRMS	lower proportion of patients with relapse(s) with OMB compared to placebo (19% vs 25%)	mostly mild-to-moderate severity AEs; 2 patients discontinued for grade-2 (pruritic rash, bronchospasm, cough) and grade-3 (pharyngeal edema, erythema, pruritus) AEs
Alcala et al.[71]	RTX	retrospective single-center; number and type of participants: 90 MS (31 RRMS, 45 SPMS,14 PPMS)	ARR reduced to 88.4% NEDA-3 at 1 year: all MS = 70% RRMS = 74.2%; PMS = 67%	IAR was 18.8%; 4 SAE (1 agranulocytosis, 3 thrombotic events, 1 death due to pulmonary embolism)
Durozard et al.[72]	RTX	nationwide retrospective multicenter; number and type of participants: 50 RRMS	decrease in ARR	AEs patients = 16; SAEs = 3; discontinuation of treatment due to AE (n = 2)
Honce et al.[73]	RTX	prospective double-blind single center (mean follow-up: 1.5 years); number and type of participants: 55 RRMS	↓ proportion of patients with new T2 lesions (25.9% RTX-GA vs 61.5% placebo-GA, $p = 0.009$)	IARs increased in RTX; 4 serious AEs in RTX, 5 in placebo
Steinman et al.[74]	UBX	phase 3, double-blind, double-dummy trials (ULTIMATE I and II); number and type of participants: RMS, trial I (n = 549); trial II (n = 545)	trial I: ARR and gadolinium-enhancing lesions were 0.08 and 0.02 trial II; ARR and gadolinium-enhancing lesions were 0.09 and 0.01, respectively	IAR: 47.7%; serious infections: 5.0% in UBX compared to teriflunomide
Fox et al.[75]	UBX	phase 2 placebo-controlled study; number and type of participants: 48 RMS	B cell depletion was >99% by week 4	ARR was 0.07; 93% remained relapse free; 74% had NEDA

OMB – ofatumumab; RTX – rituximab; OCR – ocrelizumab; UBX – ublituximab; MS – multiple sclerosis; RMS – relapsing multiple sclerosis; RRMS – relapsing-remitting multiple sclerosis; SPMS – secondary progressive multiple sclerosis; PMS – progressive multiple sclerosis; PPMS – primary progressive multiple sclerosis; EDSS – expanded disability scale; ARR – annual relapse rate; DMT – disease-modifying therapy; CDP – confirmed disability progression; OCR – ocrelizumab; GA – glatiramer acetate; NEDA – no evidence of disease activity; Gd – gadolinium; AE – adverse event; IAR – infusion-associated reaction; SAE – serious adverse event.

which are released in response to cross-reactive T cells and memory B cells.[40–45] A greater proportion of B cells infected with EBV were found in the post-mortem brain tissue of an RRMS patient.[79] The virus in the infected memory B cells escapes the T cell surveillance by expressing transcription factors EBNA-3A and -3C, which blocks the differentiation of EBV-infected B cells into terminal plasma cells, thereby developing long-term latency in these cells.[80–82]

The use of antiviral drugs, immune modulation via B cell depletion, boosting immune responses, and refining immune surveillance are a few of the effective control measures suggestive of preventing or tackling the increasing risk of MS. Due to the effective treatment against HIV, antiviral compounds like famciclovir, stavudine, zidovudine, abacavir, and raltegravir have been assessed as potential tools in the treatment of MS. However, despite their efficacy against viral infections, therapeutic potential in the case of MS remains unresolved with unsatisfactory results.[82] Besides, anti-herpes viral nucleoside analogs have also received attention as antiviral drugs. Yet, their effect in treating MS was discouraging.[59]

Several anti-CD20 mAbs are beneficial in the treatment of MS via the depletion of $CD20^+$ B cells.[59,76,83] Recently, Lovett-Racke et al. investigated the role of B cell depletion that could benefit MS patients. In the phase 2 trial of UBX, immune profiles were monitored in 48 patients at 18 time points over a year. Intriguingly, besides $CD20^+$ B-cells, UBX also depleted CD20 T cellls.[84] It is noteworthy that the depletion of T cell subsets adds to the beneficial effects of B-cell depletion therapy. Yet, whether it is the antigen-presenting or antibody-producing property of B-cells targeted in these therapeutics is unclear. The therapeutic efficiency of anti-CD20 B cell mAbs is thus based on the removal of the antigen-presenting capabilities of the B cells.[85] Memory B cells play a key role in EBV infection and progression to MS. The co-receptor used by EBV to infect and immortalize B cells is also expressed by memory B cells (complement C2),[86,87] thus benefitting the virus to establish latency in these cells. Accordingly, memory B cells are recognized as potential targets in ameliorating the progression from EBV infection to MS.[86–88]

A large number of studies have demonstrated a considerable drop in the risk of RRMS and disability with the introduction of anti-CD20 therapy.[39–45] More recently, in a retrospective study conducted at a university hospital in Saudi Arabia to investigate the efficacy of anti-CD20 antibodies (RTX and OCR) in the treatment of RRMS and PPMS,[89] the number of relapses was significantly reduced after 12 months of treatment. Furthermore, a large cohort study testing the efficacy of RTX in different stages of MS, namely RRMS, PPMS, and SPMS, yielded significant diagnostic findings, supporting the use of this therapy in treating MS and likely preventing its transition to secondary progressive forms. A total of 822 RTX-treated patients with MS consisting of 557 RRMS, 198 SPMS, and 67 PPMS were treated with 500 or 1,000 mg of iv. RTX every 6–12 months, with a mean period of 21.8 months. During treatment, the annualized relapse rates (ARR) were 0.044 (RRMS), 0.038 (SPMS), and 0.015 (PPMS), respectively.[81] Similar findings were reported by Zecca et al. with a significant drop in ARR in different stages of MS in a multi-center study.[53] Having known the role of anti-CD20 therapy in effective management in previous sections, it is imperative to judge whether anti-CD20 therapy has drawbacks or is more advantageous.

Notably, the thought of patients living their lives with vastly reduced numbers of B cells is a rather daunting prospect. CD20 is expressed on all stages of B cell development except for early pro-B cells or plasmablasts and plasma cells. Therefore, anti-CD20 therapy comes with a greater concern towards the impact of B cell depletion on total lifelong immunity. A potential problem may be the long-term effects on immunity to new antigens or decreased responses to vaccines. Over the long run, the failure to mount adequate responses to variants of current pathogens or to new pathogens may put chronically B cell-depleted patients at risk of opportunistic infections[68,70,90–99] and a major threat of tumor and secondary autoimmune diseases. Moreover, immunotherapy using mAbs poses a greater risk of infusion-associated reactions (IAR), especially in its early phases.[66]

Few studies reported yielded no neoplastic risk in MS patients on treatment with RTX, others reported a considerable percentage of MS patients to develop cancer.[62] About 0.7% of MS patients develop cancer compared to 0.2% treated with INF-β-1a.[100] Conversely, no malignancies were reported in trials in OMB-treated patients.[49] During long-term therapy, serum immunoglobulin (mostly IgM and IgG) levels are greatly reduced. The effects of B cell-depleting therapies on Ig levels, infection risk, long-term immunity, and response to vaccines are important considerations in routine MS disease management. Despite the absence of CD20 in plasma cells, IgG levels are known to decrease following anti-CD20-depleting therapy. It has been reported that serum IgM and IgG decreased following RTX treatment, which can result in hypogammaglobulinemia in long-term treatment.[65] However, a differential effect was observed in the case of OCR. In an RCT, OCR reduced IgM more than IgG, although this result was not supported in either the ASCLEPIOS I and II trials.[49]

Patients treated with anti-CD20 therapy are at higher risk of infections and prone to diseases like HIV and tuberculosis owing to reduced Ig count.[91] Decreases in Ig have been reported in patients receiving long-term therapy with RTX and OCR[92,93] and who were infrequently at risk of severe infections as a result of lymphopenia and neutropenia.[94,95] Parallelly, infections in the upper respiratory tract were reported in the treatment of PPMS with OCR in an RCT study.[55] This is together with an increased prevalence of nasopharyngitis and upper respiratory infections being reported in a phase 3 trial following OCR treatment.[60]

In patients with MS and hematological malignancies, a rare but serious viral infection of the brain was reported, termed progressive multifocal leukoencephalopathy (PML), following treatment with OCR and RTX monotherapies, respectively.[96] Moreover, hepatitis B reactivation in patients with prior hepatitis infection and death due to PML on OCR monotherapy is cautioned by the FDA.[97]

Regarding the risk of MS during pregnancy, clinicians have historically discouraged women from conceiving. Yet, this notion changed after the finding by Vukusic et al., who investigated the impact of pregnancy on the clinical course of MS,[101] in which ARR was reported to stay unaltered during pregnancy compared to the pre-pregnancy year. Several studies have assessed the risk of maternal RTX exposure for the fetus. The largest study evaluated 231 pregnancies associated with maternal RTX exposure in lymphoma or autoimmune diseases.[102] Of 153 pregnancies with known outcomes (including 2 patients with MS), nearly 60% resulted in live births, with 24% preterm neonates and only 2.2% of neonates with congenital malformations. However, limited information is available on the use of OCR and OMB during pregnancy. According to the current FDA and European Medicines Agency (EMA) recommendations, OCR should be avoided during pregnancy, and women are recommended to consider pregnancy 6–12 months after the last infusion. This delay could be reduced to 2–3 months for women with active disease as mAbs do not cross the placental barrier during the 1st pregnancy trimester.[103]

The data from the current study provide an overview of the potential applications of anti-CD20 therapy in the management of MS and certainly in mitigating the risk of MS in EBV latent infections. The outcome reported herein broadens our understanding of the pivotal role that various immune components play in the immunopathology of MS, together with the role of EBV as a prerequisite in MS development. This would open doors to the development of advanced therapies underlying the ailment and further assist in the initial choice of pharmacological treatment for MS. We hope that these results will assist in shared decision-making between patients, caretakers, and their clinicians. Immunotherapy using T cells is also under development and clinical trials. ATA188 is an off-the-shelf, allogeneic T cell immunotherapy that specifically targets EBV-infected B cells and plasma cells, developed byATA188 is currently in a phase 2 of randomized, placebo-controlled trial.[104]

The reduction of EBV^+ B cell depletion by anti-CD20 therapy is a promising area of research in MS. While anti-CD20 mAbs have proven efficacy for RRMS treatments, they have failed to prevent long-term disability in SPMS. The most challenging is that the currently available anti-CD20 therapies have little impact on this phase of transitioning MS from RRMS to SPMS. Limited data are available on evidence supporting the efficacy of anti-CD20 therapy in improving the progression of MS by depleting EBV^+ B cells. In the future, extensive translational research investigating the efficacy of this treatment on progressive stages of MS is warranted for the complete treatment of MS in the advanced stages of the disease.

Limitations

The current study has some limitations. First, studies reporting data to minimize adverse effects following anti-CD20 therapy are limited, as is the data on the impact of anti-CD20 therapy on the phase transitioning of MS to its progressive stages. The inclusion of such studies and further meta-analysis with statistical evaluation of the main diagnostic findings of the included study would add more information to the outcome of the study and affect the data and future perspectives.

Conclusions

Data from included studies provides strong evidence in support of anti-CD20 therapy in the management and treatment of EBV infection and MS. Based on the current knowledge of anti-CD20 antibodies, mAbs remain a mainstay in the treatment of MS. Although this therapy has some adverse effects, these can be minimized or managed by timely monitoring of the risk assessment. Thus, it can be justified that anti-CD20 therapy is a net positive in mitigating the risk of MS and EBV infection. Of major concern, the various clinical trials studying the efficacy of different anti-CD20 therapies yielded promising results in treating MS in its early stages. Robust research on the progressive stages of MS is thus needed. Moreover, valuable clues stem from translational research, animal experimentation and other interventional studies on neurodegenerative and neuropsychiatric disorders like those observed in MS. This would further assist in the search for useful biomarkers and exploring novel targets for the treatment of diseases. Several extensive preclinical, clinical, and computational studies are underway for their potential translatability and synthesizability in the search for novel therapeutics for reducing the risk of MS.

ORCID iDs

Reem Alrashoudi https://orcid.org/0000-0002-6842-8893

References

1. Ikram MA, Vernooij MW, Roshchupkin GV, et al. Genetic susceptibility to multiple sclerosis: Brain structure and cognitive function in the general population. *Mult Scler.* 2017;23(13):1697–1706. doi:10.1177/1352458516682104
2. Walton C, King R, Rechtman L, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult Scler.* 2020;26(14):1816–1821. doi:10.1177/1352458520970841
3. Orton SM, Herrera BM, Yee IM, et al. Sex ratio of multiple sclerosis in Canada: A longitudinal study. *Lancet Neurol.* 2006;5(11):932–936. doi:10.1016/S1474-4422(06)70581-6

4. Didonna A, Oksenberg JR. The genetics of multiple sclerosis. In: Zagon IS, McLaughlin PJ, eds. *Multiple Sclerosis: Perspectives in Treatment and Pathogenesis*. Brisbane, Australia: Codon Publications; 2017: 3–16. doi:10.15586/codon.multiplesclerosis.2017.ch1
5. Wallin MT, Culpepper WJ, Coffman P, et al. The Gulf War era multiple sclerosis cohort: Age and incidence rates by race, sex and service. *Brain*. 2012;135(6):1778–1785. doi:10.1093/brain/aws099
6. Guan Y, Jakimovski D, Ramanathan M, Weinstock-Guttman B, Zivadinov R. The role of Epstein–Barr virus in multiple sclerosis: from molecular pathophysiology to in vivo imaging. *Neural Regen Res*. 2019;14(3):373. doi:10.4103/1673-5374.245462
7. Fujinami RS, Von Herrath MG, Christen U, Whitton JL. Molecular mimicry, bystander activation, or viral persistence: Infections and autoimmune disease. *Clin Microbiol Rev*. 2006;19(1):80–94. doi:10.1128/CMR.19.1.80-94.2006
8. Palacios N, Alonso A, Brønnum-Hansen H, Ascherio A. Smoking and increased risk of multiple sclerosis: Parallel trends in the sex ratio reinforce the evidence. *Ann Epidemiol*. 2011;21(7):536–542. doi:10.1016/j.annepidem.2011.03.001
9. Speer G. Impact of vitamin D in neurological diseases and neurorehabilitation: From dementia to multiple sclerosis. Part I: the role of vitamin D in the prevention and treatment of multiple sclerosis [in Hungarian]. *Ideggyogy Sz*. 2013;66(9–10):293–303. PMID:24358684.
10. Swank RL, Lerstad O, Strøm A, Backer J. Multiple sclerosis in rural Norway: Its geographic and occupational incidence in relation to nutrition. *N Engl J Med*. 1952;246(19):721–728. doi:10.1056/NEJM195205082461901
11. Sloka S, Silva C, Pryse-Phillips W, Patten S, Metz L, Yong VW. A quantitative analysis of suspected environmental causes of MS. *Can J Neurol Sci*. 2011;38(1):98–105. doi:10.1017/S0317167100011124
12. Simpson S, Blizzard L, Otahal P, Van Der Mei I, Taylor B. Latitude is significantly associated with the prevalence of multiple sclerosis: A meta-analysis. *J Neurol Neurosurg Psychiatry*. 2011;82(10):1132–1141. doi:10.1136/jnnp.2011.240432
13. Sintzel MB, Rametta M, Reder AT. Vitamin D and multiple sclerosis: A comprehensive review. *Neurol Ther*. 2018;7(1):59–85. doi:10.1007/s40120-017-0086-4
14. Miller DH, Leary SM. Primary-progressive multiple sclerosis. *Lancet Neurol*. 2007;6(10):903–912. doi:10.1016/S1474-4422(07)70243-0
15. Ebers GC, Yee IM, Sadovnick AD, Duquette P; Canadian Collaborative Study Group. Conjugal multiple sclerosis: Population-based prevalence and recurrence risks in offspring. *Ann Neurol*. 2000;48(6):927–931. PMID:11117550.
16. Oksenberg JR, Baranzini SE, Sawcer S, Hauser SL. The genetics of multiple sclerosis: SNPs to pathways to pathogenesis. *Nat Rev Genet*. 2008;9(7):516–526. doi:10.1038/nrg2395
17. Quelvennec E, Bera O, Cabre P, et al. Genetic and functional studies in multiple sclerosis patients from Martinique attest for a specific and direct role of the HLA-DR locus in the syndrome. *Tissue Antigens*. 2003;61(2):166–171. doi:10.1046/j.0001-2815.2002.00008.x
18. Alcina A, Abad-Grau MDM, Fedetz M, et al. Multiple sclerosis risk variant HLA-DRB1*1501 associates with high expression of *DRB1* gene in different human populations. *PLoS One*. 2012;7(1):e29819. doi:10.1371/journal.pone.0029819
19. Lubetzki C, Stankoff B. Demyelination in multiple sclerosis. *Handb Clin Neurol*. 2014;122:89–99. doi:10.1016/B978-0-444-52001-2.00004-2
20. Weiner HL. A shift from adaptive to innate immunity: A potential mechanism of disease progression in multiple sclerosis. *J Neurol*. 2008;255(Suppl 1):3–11. doi:10.1007/s00415-008-1002-8
21. Chunder R, Schropp V, Kuerten S. B cells in multiple sclerosis and virus-induced neuroinflammation. *Front Neurol*. 2020;11:591894. doi:10.3389/fneur.2020.591894
22. Duddy M, Niino M, Adatia F, et al. Distinct effector cytokine profiles of memory and naive human B cell subsets and implication in multiple sclerosis. *J Immunol*. 2007;178(10):6092–6099. doi:10.4049/jimmunol.178.10.6092
23. Läderach F, Münz C. Epstein–Barr virus exploits genetic susceptibility to increase multiple sclerosis risk. *Microorganisms*. 2021;9(11):2191. doi:10.3390/microorganisms9112191
24. Goitia B, Bruno D, Abrevaya S, et al. The relationship between executive functions and fluid intelligence in multiple sclerosis. *PLoS One*. 2020;15(4):e0231868. doi:10.1371/journal.pone.0231868
25. Clough M, Foletta P, Frohman A, et al. Multiple sclerosis: Executive dysfunction, task switching and the role of attention. *Mult Scler J Exp Transl Clin*. 2018;4(2):205521731877178. doi:10.1177/2055217318771781
26. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*. 2001;24(1):167–202. doi:10.1146/annurev.neuro.24.1.167
27. Audoin B, Reuter F, Duong M, et al. Efficiency of cognitive control recruitment in the very early stage of multiple sclerosis: A one-year fMRI follow-up study. *Mult Scler*. 2008;14(6):786–792. doi:10.1177/1352458508089360
28. Heldner MR, Kaufmann-Ezra S, Gutbrod K, et al. Behavioral changes in patients with multiple sclerosis. *Front Neurol*. 2017;8:437. doi:10.3389/fneur.2017.00437
29. Portaccio E, Amato MP. Cognitive impairment in multiple sclerosis: An update on assessment and management. *NeuroSci*. 2022;3(4):667–676. doi:10.3390/neurosci3040048
30. Shiri E, Pasbakhsh P, Borhani-Haghighi M, et al. Mesenchymal stem cells ameliorate cuprizone-induced demyelination by targeting oxidative stress and mitochondrial dysfunction. *Cell Mol Neurobiol*. 2021;41(7):1467–1481. doi:10.1007/s10571-020-00910-6
31. Xue H, Zeng L, Liu S. Unraveling the link: Exploring the causal relationship between diabetes, multiple sclerosis, migraine, and Alzheimer's disease through Mendelian randomization. *Front Neurosci*. 2023;17:1233601. doi:10.3389/fnins.2023.1233601
32. Confavreux C, Vukusic S. The clinical course of multiple sclerosis. *Handb Clin Neurol*. 2014;122:343–369. doi:10.1016/B978-0-444-52001-2.00014-5
33. Bar-Or A, Pender MP, Khanna R, et al. Epstein–Barr virus in multiple sclerosis: Theory and emerging immunotherapies. *Trends Mol Med*. 2020;26(3):296–310. doi:10.1016/j.molmed.2019.11.003
34. Ahmed SI, Aziz K, Gul A, Samar SS, Bareeqa SB. Risk of multiple sclerosis in Epstein–Barr virus infection. *Cureus*. 2019;11(9):e5699. doi:10.7759/cureus.5699
35. Bjornevik K, Cortese M, Healy BC, et al. Longitudinal analysis reveals high prevalence of Epstein–Barr virus associated with multiple sclerosis. *Science*. 2022;375(6578):296–301. doi:10.1126/science.abj8222
36. Moreno MA, Or-Geva N, Aftab BT, et al. Molecular signature of Epstein–Barr virus infection in MS brain lesions. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(4):e466. doi:10.1212/NXI.0000000000000466
37. Serafini B, Rosicarelli B, Veroni C, Mazzola GA, Aloisi F. Epstein–Barr virus-specific CD8 T cells selectively infiltrate the brain in multiple sclerosis and interact locally with virus-infected cells: Clue for a virus-driven immunopathological mechanism. *J Virol*. 2019;93(24):e00980-19. doi:10.1128/JVI.00980-19
38. 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
39. Margoni M, Preziosa P, Filippi M, Rocca MA. 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
40. Bar-Or A, O'Brien SM, Sweeney ML, Fox EJ, Cohen JA. 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
41. Miyazaki Y, Niino M. B-cell depletion therapy for multiple sclerosis. *Immunol Med*. 2022;45(2):54–62. doi:10.1080/25785826.2021.1952543
42. Elsbernd PM, Carter JL. Using monoclonal antibody therapies for multiple sclerosis: A review. *Biol Targets Ther*. 2021;15:255–263. doi:10.2147/BTT.S267273
43. Krajnc N, Bsteh G, Berger T, Mares J, Hartung HP. Monoclonal antibodies in the treatment of relapsing multiple sclerosis: An overview with emphasis on pregnancy, vaccination, and risk management. *Neurotherapeutics*. 2022;19(3):753–773. doi:10.1007/s13311-022-01224-9
44. Läderach F, Münz C. Altered immune response to the Epstein–Barr virus as a prerequisite for multiple sclerosis. *Cells*. 2022;11(17):2757. doi:10.3390/cells11172757
45. Sabatino JJ, Wilson MR, Calabresi PA, Hauser SL, Schneck JP, Zamvil SS. Anti-CD20 therapy depletes activated myelin-specific $CD8^+$ T cells in multiple sclerosis. *Proc Natl Acad Sci U S A*. 2019;116(51):25800–25807. doi:10.1073/pnas.1915309116
46. Von Essen MR, Ammitzbøll C, Hansen RH, et al. Pro-inflammatory $CD20^+$ T cells in the pathogenesis of multiple sclerosis. *Brain*. 2019;142(1):120–132. doi:10.1093/brain/awy301

47. Robertson D, Moreo N. Disease-modifying therapies in multiple sclerosis: Overview and treatment considerations. *Fed Pract*. 2016; 33(6):28–34. PMID:30766181. PMCID:PMC6366576.
48. 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
49. Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing–remitting multiple sclerosis: A systematic review and network meta-analysis. *J Neurol*. 2020;267(12):3489–3498. doi:10.1007/s00415-019-09395-w
50. Eriksen MB, Frandsen TF. The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: A systematic review. *J Med Libr Assoc*. 2018;106(4):420–431. doi:10.5195/jmla.2018.345
51. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomized trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
52. Ganne V, Siddiqi N, Kamaplath B, et al. Humanized anti-CD20 monoclonal antibody (rituximab) treatment for post-transplant lymphoproliferative disorder. *Clin Transplant*. 2003;17(5):417–422. doi:10.1034/j.1399-0012.2003.00054.x
53. Zecca C, Bovis F, Novi G, et al. Treatment of multiple sclerosis with rituximab: A multicentric Italian–Swiss experience. *Mult Scler*. 2020; 26(12):1519–1531. doi:10.1177/1352458519872889
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. doi:10.1001/jamaneurol.2017.4011
55. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017; 376(3):209–220. doi:10.1056/NEJMoa1606468
56. Ellwardt E, Rolfes L, Klein J, et al. Ocrelizumab initiation in patients with MS: A multicenter observational study. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(4):e719. doi:10.1212/NXI.0000000000000719
57. Wolinsky JS, Arnold DL, Brochet B, et al. Long-term follow-up from the ORATORIO trial of ocrelizumab for primary progressive multiple sclerosis: A post-hoc analysis from the ongoing open-label extension of the randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2020;19(12):998–1009. doi:10.1016/S1474-4422(20)30342-2
58. Turner B, Cree BAC, Kappos L, et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. *J Neurol*. 2019; 266(5):1182–1193. doi:10.1007/s00415-019-09248-6
59. Drosu NC, Edelman ER, Housman DE. Could antiretrovirals be treating EBV in MS? A case report. *Mult Scler Relat Dis*. 2018;22:19–21. doi:10.1016/j.msard.2018.02.029
60. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376(3): 221–234. doi:10.1056/NEJMoa1601277
61. Babiker HM, Glode AE, Cooke LS, Mahadevan D. Ublituximab for the treatment of CD20 positive B-cell malignancies. *Exp Opin Investig Dugs*. 2018;27(4):407–412. doi:10.1080/13543784.2018.1459560
62. 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
63. Gelfand JM, Cree BAC, Hauser SL. Ocrelizumab and other CD20$^+$ B-cell-depleting therapies in multiple sclerosis. *Neurotherapeutics*. 2017;14(4):835–841. doi:10.1007/s13311-017-0557-4
64. Masoud S, McAdoo SP, Bedi R, Cairns TD, Lightstone L. Ofatumumab for B cell depletion in patients with systemic lupus erythematosus who are allergic to rituximab. *Rheumatology (Oxford)*. 2018; 57(7):1156–1161. doi:10.1093/rheumatology/key042
65. Florou D, Katsara M, Feehan J, Dardiotis E, Apostolopoulos V. Anti-CD20 agents for multiple sclerosis: Spotlight on ocrelizumab and ofatumumab. *Brain Sci*. 2020;10(10):758. doi:10.3390/brainsci10100758
66. Sorensen PS, Lisby S, Grove R, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: A phase 2 study. *Neurology*. 2014;82(7):573–581. doi:10.1212/WNL.0000000000000125
67. Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. *Neurology*. 2016;87(20):2074–2081. doi:10.1212/WNL.0000000000003331
68. 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–e1814. doi:10.1212/WNL.0000000000005516
69. Sharman JP, Farber CM, Mahadevan D, et al. Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed and/or refractory chronic lymphocytic leukaemia: Results of a phase 2 trial. *Br J Haematol*. 2017;176(3):412–420. doi:10.1111/bjh.14447
70. Fox EJ, Buckle GJ, Singer B, Singh V, Boster A. Lymphopenia and DMTs for relapsing forms of MS: Considerations for the treating neurologist. *Neurol Clin Pract*. 2019;9(1):53–63. doi:10.1212/CPJ.0000000000000567
71. Alcalá C, Gascón F, Pérez-Miralles F, et al. Efficacy and safety of rituximab in relapsing and progressive multiple sclerosis: A hospital-based study. *J Neurol*. 2018;265(7):1690–1697. doi:10.1007/s00415-018-8899-3
72. Durozard P, Maarouf A, Boutiere C, et al. Efficacy of rituximab in refractory RRMS. *Mult Scler*. 2019;25(6):828–836. doi:10.1177/1352458518772748
73. Honce JM, Nair KV, 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
74. Steinman L, Fox E, Hartung HP, et al. Ublituximab versus teriflunomide in relapsing multiple sclerosis. *N Engl J Med*. 2022;387(8):704–714. doi:10.1056/NEJMoa2201904
75. 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*. 2021;27(3):420–429. doi:10.1177/1352458520918375
76. 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
77. De Sèze J, Maillart E, Gueguen A, et al. Anti-CD20 therapies in multiple sclerosis: From pathology to the clinic. *Front Immunol*. 2023;14: 1004795. doi:10.3389/fimmu.2023.1004795
78. Serafini B, Scorsi E, Rosicarelli B, Rigau V, Thouvenot E, Aloisi F. Massive intracerebral Epstein–Barr virus reactivation in lethal multiple sclerosis relapse after natalizumab withdrawal. *J Neuroimmunol*. 2017; 307:14–17. doi:10.1016/j.jneuroim.2017.03.013
79. Geginat J, Paroni M, Pagani M, et al. The enigmatic role of viruses in multiple sclerosis: Molecular mimicry or disturbed immune surveillance? *Trends Immunol*. 2017;38(7):498–512. doi:10.1016/j.it.2017.04.006
80. Tracy SI, Kakalacheva K, Lünemann JD, Luzuriaga K, Middeldorp J, Thorley-Lawson DA. Persistence of Epstein–Barr virus in self-reactive memory B cells. *J Virol*. 2012;86(22):12330–12340. doi:10.1128/JVI.01699-12
81. Styles CT, Bazot Q, Parker GA, White RE, Paschos K, Allday MJ. EBV epigenetically suppresses the B cell-to-plasma cell differentiation pathway while establishing long-term latency. *PLoS Biol*. 2017;15(8): e2001992. doi:10.1371/journal.pbio.2001992
82. Küry P, Nath A, Créange A, et al. Human endogenous retroviruses in neurological diseases. *Trends Mol Med*. 2018;24(4):379–394. doi:10.1016/j.molmed.2018.02.007
83. 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
84. Lovett-Racke AE, Yang Y, Liu Y, et al. B cell depletion changes the immune cell profile in multiple sclerosis patients: One-year report. *J Neuroimmunol*. 2021;359:577676. doi:10.1016/j.jneuroim.2021.577676
85. Naismith RT, Piccio L, Lyons JA, et al. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: A 52-week phase II trial. *Neurology*. 2010;74(23):1860–1867. doi:10.1212/WNL.0b013e3181e24373
86. Fernández-Menéndez S, Fernández-Morán M, Fernández-Vega I, Pérez-Álvarez A, Villafani-Echazú J. Epstein–Barr virus and multiple sclerosis: From evidence to therapeutic strategies. *J Neurol Sci*. 2016;361:213–219. doi:10.1016/j.jns.2016.01.013
87. Ascherio A, Munger KL. EBV and autoimmunity. In: Münz C, ed. *Epstein Barr Virus Volume 1*. Vol. 390. Current Topics in Microbiology and Immunology. Cham, Switzerland: Springer International Publishing; 2015:365–385. doi:10.1007/978-3-319-22822-8_15
88. Serafini B, Severa M, Columba-Cabezas S, et al. Epstein–Barr virus latent infection and BAFF expression in B cells in the multiple sclerosis brain: Implications for viral persistence and intrathecal B-cell activation. *J Neuropathol Exp Neurol*. 2010;69(7):677–693. doi:10.1097/NEN.0b013e3181e332ec

89. Bauthman MS. Effectiveness of anti-cluster of differentiation 20 as a disease-modifying therapy in multiple sclerosis across its different phenotypes at the University Hospital of Caen. *Cureus*. 2022; 14(2):e22120. doi:10.7759/cureus.22120
90. Schwab N, Schneider-Hohendorf T, Melzer N, Cutter G, Wiendl H. Natalizumab-associated PML: Challenges with incidence, resulting risk, and risk stratification. *Neurology*. 2017;88(12):1197–1205. doi:10.1212/WNL.0000000000003739
91. Vollmer BL, Wallach AI, Corboy JR, Dubovskaya K, Alvarez E, Kister I. Serious safety events in rituximab-treated multiple sclerosis and related disorders. *Ann Clin Transl Neurol*. 2020;7(9):1477–1487. doi:10.1002/acn3.51136
92. Roberts DM, Jones RB, Smith RM, et al. Immunoglobulin G replacement for the treatment of infective complications of rituximab-associated hypogammaglobulinemia in autoimmune disease: A case series. *J Autoimmun*. 2015;57:24–29. doi:10.1016/j.jaut.2014.11.004
93. Cohen BA. Late-onset neutropenia following ocrelizumab therapy for multiple sclerosis. *Neurology*. 2019;92(9):435–436. doi:10.1212/WNL.0000000000006924
94. Auer M, Bsteh G, Hegen H, et al. Late-onset neutropenia in a multiple sclerosis patient after first dose of ocrelizumab switched from rituximab. *Mult Scler Relat Dis*. 2020;43:102155. doi:10.1016/j.msard.2020.102155
95. Genetech. RITUXAN® (rituximab) [package insert]. South San Francisco, USA; Genetech; 2020. https://www.gene.com/download/pdf/rituxan_prescribing.pdf. Accessed June 3, 2021.
96. 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. doi:10.1001/jamaneurol.2021.0627
97. GlaxoSmithKline plc. ARZERRA® (ofatumumab) [package insert]. London, UK; GlaxoSmithKline plc; 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125326s062lb. Accessed June 3, 2021.
98. Sormani MP, De Rossi N, Schiavetti I, et al. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. *Ann Neurol*. 2021;89(4):780–789. doi:10.1002/ana.26028
99. Reder AT, Centonze D, Naylor ML, et al. COVID-19 in patients with multiple sclerosis: Associations with disease-modifying therapies. *CNS Drugs*. 2021;35(3):317–330. doi:10.1007/s40263-021-00804-1
100. Mathias A, Perriard G, Canales M, et al. Increased ex vivo antigen presentation profile of B cells in multiple sclerosis. *Mult Scler*. 2017; 23(6):802–809. doi:10.1177/1352458516664210
101. Vukusic S, Hutchinson M, Hours M, et al. Pregnancy and multiple sclerosis (the PRIMS study): Clinical predictors of post-partum relapse. *Brain*. 2004;127(6):1353–1360. doi:10.1093/brain/awh152
102. Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. *Blood*. 2011;117(5):1499–1506. doi:10.1182/blood-2010-07-295444
103. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol*. 2012;2012:985646. doi:10.1155/2012/985646
104. U.S. Food and Drug Administration (FDA). FDA Drug Safety Communication: Boxed Warning and new recommendations to decrease the risk of hepatitis B reactivation with the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab). Silver Spring, USA: U.S. Food and Drug Administration (FDA): September 25, 2013. http://www.fda.gov/Drugs/DrugSafety/ucm366406.htm. Accessed November 19, 2018.