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REVIEW ARTICLE

The Evolution of Anti-CD20 Treatment for Multiple Sclerosis: Optimization of Antibody Characteristics and Function

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Abstract
B-cell depletion with CD20-targeted agents is commonly used for treatment of multiple sclerosis (MS), other autoimmune diseases, and certain hematologic malignancies. Initial apparent success with rituximab in MS and neuromyelitis optica spurred development of the anti-CD20 monoclonal antibody (mAb) therapies ocrelizumab, ofatumumab, and ublituximab as well as the anti-CD19 mAb inebilizumab. While each are effective at targeting and depleting B cells, structural differences translate into different mechanisms of action affecting maintenance of B-cell depletion and safety and tolerability. Although the anti-CD20 mAbs differ in degree of human versus mouse sequences as well as target CD20 epitope, these properties do not appear to substantially affect activity or tolerability. In contrast, an antibody-dependent cell-mediated cytotoxicity (ADCC) versus a complement-dependent cytotoxicity mechanism of action as well as subcutaneous versus intravenous administration may provide improved tolerability. Glycoengineering of the mAbs ublituximab and inebilizumab enhances ADCC and can overcome the reduced responses to mAb-mediated B-cell depletion associated with certain genetic polymorphisms. Other strategies for therapeutic targeting of CD20, including brain shuttle antibodies (e.g., RO7121932), bispecific antibodies, chimeric antigen receptor T-cell therapies, and antibody–drug conjugates, are in active clinical development and may be future treatment approaches in MS and other B-cell-mediated autoimmune diseases.

1 Introduction

A sea change in multiple sclerosis (MS) therapy occurred with the introduction of anti-CD20 monoclonal antibodies (mAbs). Early work with rituximab suggested that depleting B cells might be highly efficacious in MS and other inflammatory diseases of the central nervous system (CNS) such as neuromyelitis optica (NMO) [1–5]. A phase II trial with rituximab in relapsing–remitting MS (RRMS) showed a surprisingly powerful impact on new lesion formation and relapses and laid the groundwork for the seminal clinical trials with ocrelizumab, a humanized anti-CD20 mAb that showed superiority over thrice-weekly interferon beta-1a on all outcomes [4, 6]. The combination of high efficacy with an excellent safety profile and a well-tolerated, twice-yearly intravenous (IV) infusion regimen [6, 7] propelled the now widespread uptake of this product in relapsing MS (RMS) [8]. With an increasing

Key Points

The anti-CD20 monoclonal antibodies rituximab, ocrelizumab, ofatumumab, and ublituximab are used to treat multiple sclerosis, and the anti-CD19 monoclonal antibody inebilizumab is used to treat neuromyelitis optica spectrum disorder; they work by binding to B cells and causing them to be eliminated.

These therapeutic antibodies were designed to have different characteristics that affect how B cells are depleted and may influence both efficacy and tolerability.

New ways of depleting B cells are being developed as future potential therapies for multiple sclerosis and other diseases where B cells play an important role.

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understanding of mAb structure and function, the engineering of anti-CD20 therapeutics has evolved to achieve more complete and sustained B-cell depletion, tolerability, and facility of administration. The subsequent development of a subcutaneously administered formulation of ofatumumab for RMS provided the option for anti-CD20 treatment for patients who either had poor IV access, were unable to access local infusion centers, or preferred self-administration [9]. The development of the glycoengineered ublituximab, with its 1-h, twice-yearly infusion, offered patients an even greater degree of tolerability compared with either rituximab or ocrelizumab [10, 11]. The objective of this article is to review the differences in chimeric, humanized, and human mAbs; distinctions in antibody class; brain shuttle mechanisms; the impact of glycoengineering on receptor binding and complement activation; and the prospects of further development of B-cell target therapies using bispecific antibodies and chimeric antigen receptor (CAR) T cells. How molecular engineering of these products translates directly into patient care is emphasized. This narrative review with expert opinion was developed following a comprehensive literature search.

2 CD20 Role and Expression in the Immune System

CD20 is a 33–37 kDa non-glycosylated protein that is expressed on the surface of normal and malignant B cells; it is also dimly expressed on a small subset of T cells [12–14]. It is unclear whether CD20-expressing T cells transcribe CD20 or whether these cells acquire CD20 protein by trogocytosis, an exchange of plasma membrane portions between cells, through contact with B cells [15]. The CD20 protein functions as a calcium channel and comprises four hydrophobic transmembrane domains, one intracellular domain, and two extracellular domains (large and small loops); both amino- and carboxy-termini reside within the cytosol (Fig. 1) [14, 16]. On B cells, CD20 is physically coupled to major histocompatibility complex (MHC) class II, CD40, the B-cell receptor (BCR), and the C-terminal-Src-kinase-binding protein. CD20 contributes to B-cell activation and proliferation and may be required for efficient BCR signaling in B cells, optimal T-independent humoral immunity, and immune response to T-dependent antigens [14, 17].

CD20 expression on B cells is more restricted than that of the B-cell-specific marker CD19: CD20 appears later in B-cell development, at the pre-B-cell stage, and is absent on plasmablasts and plasma cells (Fig. 2) [18]. In contrast, CD19 is expressed on the first B-cell lineage cell, at the pro-B-cell stage, and is present on all B-cell types except for long-lived plasma cells. CD20 is highly expressed in the plasma membrane at most B-cell stages, typically remains on the cell surface even when cross-linked with mAb, and is not shed from the surface [17, 19]. These features make CD20 a unique candidate for mAb-mediated targeting of B cells without directly impacting stem cells or plasma cells.

3 Anti-CD20 Mechanisms in MS

Anti-CD20 mAbs are designed to bind to and cause depletion of $CD20^+$ cells [10]. The primary target of anti-CD20 mAbs are $CD19^+$ $CD20^+$ B cells [10, 20]. Depletion of B cells via this mechanism is thought to reduce antigen presentation and activation of pathogenic T cells, arrest inflammatory cytokines produced by B cells, and create a shift away from an activated inflammatory immune environment to one with increased immune downregulation with less activated or less mature T and B cells [21–23].

A subset of T cells, both CD4 and CD8 T cells, also expresses low levels of CD20; these cells are often termed $CD20^{dim}$ T cells and are depleted by anti-CD20 mAbs [10, 22, 24]. While $CD20^{dim}$ T cells make up a small fraction of T cells in the blood, they are implicated in MS pathogenesis [24–29]. $CD20^{dim}$ T cells have a proinflammatory phenotype and produce high levels of interferon-γ (IFN-γ), tumor necrosis factor (TNF)-α, and granulocyte–macrophage colony-stimulating factor [21, 24, 28]. $CD20^{dim}$ T cells express higher levels of adhesion molecules than $CD20^-$ T cells, suggesting an increased potential for migration into the CNS [27, 28]. $CD20^{dim}$ T cells are found at increased frequency in people with MS versus in healthy controls [21, 28]. Lastly, $CD20^{dim}$ T cells are enriched in the cerebrospinal fluid (CSF) of people with MS [28, 29], and in one study, the percentage of $CD20^{dim}$ T cells in the CSF correlated with RMS disease severity [28].

Thus, treatment effects associated with anti-CD20 mAbs may result from the depletion of both B cells and $CD3^+$ $CD20^+$ T cells [10]. In contrast, anti-CD19 mAbs are B-cell specific because T cells do not express CD19 [30, 31]. Both anti-CD20 and anti-CD19 mAbs can be designed to be non-depleting, binding antibodies that interfere with B-cell activation, proliferation, and differentiation [32].

Recent studies demonstrated that treatment with ocrelizumab also impacts $CD20^-$ T cells. More specifically, B-cell depletion results in a decrease in memory $CD8^+$ T cells and alters both phenotype and function of these lymphocytes [33, 34]. A study in treatment-naïve people with MS demonstrated an indirect effect on the frequency of effector memory CD4 and CD8 T-cell populations that preferentially migrate into the CNS following treatment with anti-CD20 therapy [35]. Moreover, in addition to impacts on T-cell populations,

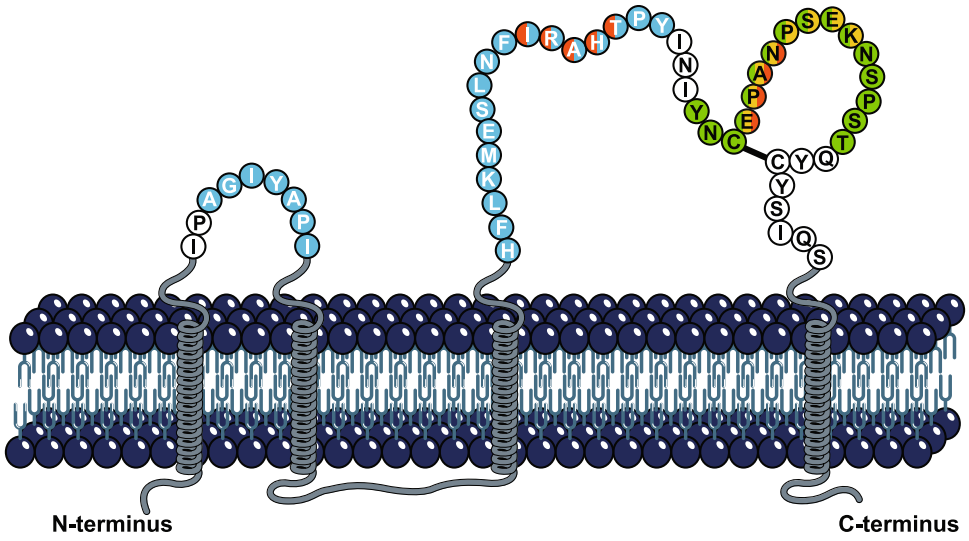


Fig. 1 CD20 is a transmembrane protein on B cells and some T cells. The CD20 protein functions as a calcium channel and comprises four hydrophobic transmembrane domains, one intracellular domain, and two extracellular domains (large and small loops); both amino- and carboxy-termini reside within the cytosol. Rituximab epitope is in yellow, ocrelizumab epitope in green, ofatumumab epitope in blue, and ublituximab epitope in orange. Adapted with permission under Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) license (https://creativecommons.org/licenses/by-nc/4.0/) from Delgado SR, Faissner S, Linker RA, Rammohan K. Key characteristics of anti-CD20 monoclonal antibodies and clinical implications for multiple sclerosis treatment. *J Neurol*. 2024;271(4):1515–1535 [16]. *CD* cluster of differentiation

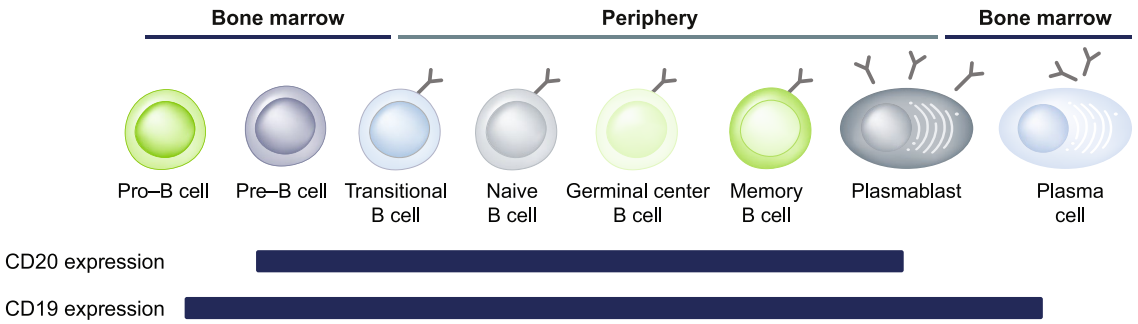


Fig. 2 Expression of CD20 on B-cell lineages. CD20 is first expressed at the pre-B-cell stage and is not expressed on plasma cells. CD19 is expressed on the first B-cell lineage cell, at the pro-B-cell stage, and is present on all B-cell types except for long-lived plasma cells. Adapted from Crickx E, Weill J-C, Reynaud C-A, Mahévas M. Anti-CD20-mediated B-cell depletion in autoimmune diseases: successes, failures and future perspectives. *Kidney International*, volume 97, issue 5. pp. 885–893. Copyright 2020, with permission from International Society of Nephrology [162]. *CD* cluster of differentiation

depletion of B cells in people with primary progressive MS (PPMS) increases the number of monocytes expressing PD-L1 that may promote immune tolerance by suppressing inflammatory T-cell activity [36]. Other studies also implicate a role for B-cell depletion in amelioration of MS disease activity via effects on antigen-specific T-cell populations, including myelin-specific $CD8^+$ T cells and Epstein–Barr virus (EBV)-specific T cells that are postulated to drive progression and play essential roles in pathogenesis [26, 37, 38]. Taken together, these studies highlight the broad immunomodulatory impact of B-cell-depleting therapies.

A perspective that may be important to understanding the impact of anti-CD20 mAbs beyond direct effects on B-cell function is that neither T cells nor B cells evolved separately from each other; rather, they evolved to function together as critical components of adaptive immunity. A more sophisticated understanding of how depletion of B cells perturbs the adaptive immune system could provide further insights into biomarkers relevant to MS pathogenesis and treatment efficacy. Further, given the complexity of immune cascades invoked by anti-CD20 and anti-CD19 mAbs, differences in mAb potency and predominant mechanisms of action (e.g.,

ADCC versus CDC) may have greater relevance beyond just depth of B-cell depletion.

4 Anti-CD20 mAbs for MS

4.1 Initial Anti-CD20 mAb Development and Indications

The first anti-CD20 mAb, rituximab, was approved in 1997 for the treatment of follicular lymphoma [39]. Since then, millions of people have been treated with anti-CD20 mAbs for oncologic and autoimmune indications, with long-term data (published and congress abstracts) demonstrating a favorable benefit/risk profile [7, 39–43].

4.2 History of Anti-CD20 mAb use in MS and Neuromyelitis Optica Spectrum Disorder (NMOSD)

Rituximab was the original anti-CD20 mAb used in MS and NMO. The first case report of rituximab in RRMS and case series in NMO were in 2005 [2, 44]. In 2006, a small study of rituximab showed favorable outcomes in MS patients who experienced suboptimal responses to other disease-modifying therapies [3]. In 2008, a phase I study ($N = 26$) in active RRMS provided initial evidence of an apparent effect of rituximab on gadolinium-enhancing (Gd+) lesions on magnetic resonance imaging (MRI) and clinical relapses along with a reasonable safety profile despite a high rate of infusion-related reactions (IRRs) [1]. In the same year, the randomized, placebo-controlled, phase II HERMES study ($N = 104$) showed that RMS participants who received rituximab 1000 mg experienced reduced inflammatory lesions and relapses compared with placebo [4]. A high rate of IRRs (78%) occurred in this study. Rituximab was evaluated in PPMS in the phase II/III OLYMPUS study ($N = 439$), a 96-week, randomized, controlled trial in which participants received either two 1000 mg doses of rituximab 2 weeks apart every 24 weeks or placebo. Although the overall study failed to meet its primary endpoint (time to confirmed disease progression), it suggested that efficacy might be apparent in younger (< 51 years of age) participants with Gd+ lesions on baseline MRI [45]. Although not approved by the US Food and Drug Administration (FDA) for MS, rituximab is widely used off-label to treat people with MS [42].

The first case series evaluating rituximab to treat NMO found an apparent reduction in attack rate and improvement in neurologic function comparing pretreatment with posttreatment epochs [2]. A subsequent case series of 25 participants refractory to other NMOSD empiric treatments replicated and expanded upon these observations [5]. Subsequently, rituximab became widely used as an off-label NMO treatment. Rituximab was approved for use in Japan in 2022 on the basis of the results of the RIN-1 study ($N = 38$), a 72-week, randomized, controlled trial in anti-aquaporin-4 antibody-positive (AQP4-Ab+) NMOSD participants who received rituximab (375 mg/m^2) every week for 4 weeks followed by 1000 mg every 6 months versus placebo. The study demonstrated a significant reduction in relapses as well as an improvement in quantification of optic nerve and spinal cord impairment scores [46, 47]. Interestingly, both the HERMES and RIN-1 trials showed that rituximab impacts relapsing disease activity in RMS and NMOSD, respectively; in contrast, the OLYMPUS study failed to reduce confirmed disease progression in PPMS despite a larger cohort size, longer study duration, and substantially higher cumulative rituximab dose. These observations suggest that there are fundamental differences in therapeutic efficacy that depend on the underlying disease state rather than simple dosage effects.

4.3 Evolution of Anti-CD20 mAb Use in MS and Anti-CD19 mAb Use in NMOSD

Anti-CD20 therapy evolved through an improved understanding of mAb characteristics and design. Currently, each of the four anti-CD20 therapies used in MS (rituximab, ocrelizumab, ofatumumab, and ublituximab) exhibits unique molecular characteristics (Table 1). The structural differences among the antibodies are responsible for different tolerability profiles and differences in the kinetics of B-cell depletion. Figure 3 illustrates the development timeline of additional anti-CD20 mAbs. How these different aspects contribute to mAb design, structure, function, and clinical applications and effects will be presented next.

5 Scaffold: Chimeric Versus Humanized Versus Fully Human mAbs

Therapeutic mAbs can be chimeric, humanized, or fully human. Chimeric antibodies are nonhuman (often murine) mAbs engineered to have their constant regions replaced by human sequences; thus, most of the fragment antigen-binding (Fab) region is mouse-derived, while the fragment crystallizable (Fc) is human [48]. In humanized mAbs, all sequences are human except the complementarity determining regions (CDR) of the variable domains. Murine-sequence-derived CDRs are engrafted onto human-sequence-derived variable regions, while the remaining Fab and Fc components are fully human. Fully human mAbs contain exclusively human sequences and are generated in mice with humanized immune systems [48,

Table 1 Characteristics of MS anti-CD20 mAbs

Therapeutic	Class	Scaffold	Type	MOA	Glycoengineered	Administration route	Approved indication(s)
Rituximab	IgG1	Chimeric	Type I	CDC (CDC > ADCC)	No	IV	NHL, B-cell NHL, B-AL, CLL, RA, GPA, MPA, PV, NMOSD (Japan only)
Ocrelizumab	IgG1	Humanized	Type I	ADCC (ADCC > CDC)	No	IV, SC	RMS, PPMS
Ofatumumab	IgG1	Fully human	Type I	CDC (CDC > ADCC)	No	SC	RMS
Ublituximab	IgG1	Chimeric	Type I	ADCC (ADCC > CDC)	Yes (afucosylated)	IV	RMS

ADCC antibody-dependent cell-mediated cytotoxicity, *B-AL* B-cell acute leukemia, *CD* cluster of differentiation, *CDC* complement-dependent cytotoxicity, *CLL* chronic lymphocytic leukemia, *GPA* granulomatosis with polyangiitis (Wegener's granulomatosis), *IgG1* immunoglobulin G1, *IV* intravenous, *mAb* monoclonal antibody, *MOA* mechanism of action, *MPA* microscopic polyangiitis, *MS* multiple sclerosis, *NHL* non-Hodgkin's lymphoma, *NMOSD* neuromyelitis optica spectrum disorder, *PPMS* primary progressive MS, *PV* pemphigus vulgaris, *RA* rheumatoid arthritis, *RMS* relapsing MS, *SC* subcutaneous.

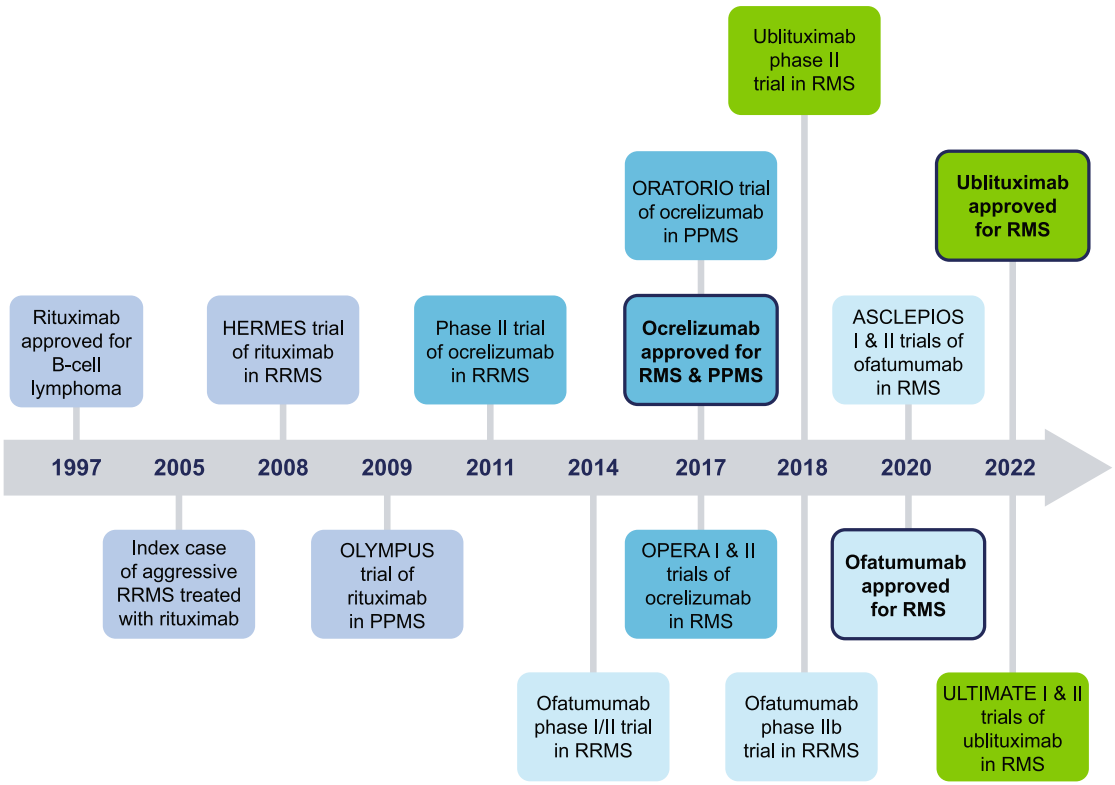


Fig. 3 Anti-CD20 mAb development in MS. Timeline of milestones for anti-CD20 mAb use in MS. Approval dates indicate approval in the USA. *CD* cluster of differentiation, *mAb* monoclonal antibody, *MS* multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *RMS* relapsing multiple sclerosis, *RRMS* relapsing–remitting multiple sclerosis [10, 163]

49]. Ofatumumab is a fully human antibody produced by immunizing HCo7 and KM mice with a murine cell line (NS0) transfected with human CD20 [50, 51]. Rituximab and ublituximab are chimeric mAbs, and ocrelizumab is a humanized mAb [52, 53].

The rationale for increasing the proportion of human sequences in mAbs is to reduce immunogenicity, hypersensitivity reactions, and antidrug antibodies (ADAs) that have the potential to reduce efficacy [48]. ADAs can either be non-neutralizing, binding the drug but do not affect the drug–target interaction, or neutralizing, inhibiting the biological activity of a drug [54]. While humanization of anti-CD20 mAbs reduces immunogenicity, a clear effect on tolerability/IRRs was not observed (discussed further below).

Levels of ADAs are higher with rituximab and ublituximab, both chimeric mAbs, than with other anti-CD20 mAbs,

as noted in published reports and congress abstracts [55, 56]. However, development of ADAs does not impact safety or efficacy outcomes. In a large observational study, there was no difference in efficacy, incidence, or severity of IRRs or adverse events (AEs) with rituximab between ADA groups (positive versus negative) [56]. Furthermore, there was no association between ADA titers and IRRs or AEs. In a congress presentation of data from the ULTIMATE studies, treatment-emergent ADAs with ublituximab were observed in most participants but were generally transient and had no observable impact on B-cell depletion, annualized relapse rate (ARR), the number of new/enlarging T2 lesions, or tolerability [55].

6 Fc Engineering

Anti-CD20 mAb activity is determined by both the specific antigen binding of the Fab region and the effector functions, including antibody-dependent cell-mediated cytotoxicity (ADCC), activated by the Fc region [57]. The Fc region of immunoglobulin G1 (IgG1) antibodies expresses binding sites for Fc receptors, including Fc gamma receptor IIIa (FcγRIIIa) on immune cells, and for the C1q component of complement.

Fc engineering can involve either glycoengineering or amino acid engineering to increase the strength of binding to Fc gamma receptors (FcγRs). Reduced fucosylation with glycoengineering enhances affinity to FcγRIIIa in particular [58] and can enhance natural killer (NK) cell effector functions [57, 59–61]. This is because the core fucose of Fc-linked oligosaccharides inhibits the ADCC of anti-CD20 mAbs by sterically blocking interaction with the FcγRIIIa receptor, thereby reducing affinity [62, 63]. Exclusion of fucose from the Fc region allows for closer interaction and increased affinity with FcγRIIIa receptors without altering antigen binding or complement-dependent cytotoxicity (CDC) [57, 62, 63]. As such, mAbs with low fucose content exhibit significantly higher ADCC activity than those with high fucose content (Fig. 4) [57, 59–61].

Clinical advantages of glycoengineering can only be observed in head-to-head studies, and while no head-to-head studies have been conducted in MS to date, studies in oncology have evaluated obinutuzumab, a glycoengineered anti-CD20, versus rituximab [64, 65]. In a phase III study, obinutuzumab in combination with venetoclax (a blocker of the anti-apoptotic B-cell lymphoma protein) demonstrated improved progression-free survival (PFS) and more robust disease eradication versus rituximab in combination with venetoclax in chronic lymphocytic leukemia [64, 66]. The proportion of participants in the trial achieving undetectable residual disease (the most sensitive measure of residual B cells) was greatly improved with obinutuzumab versus rituximab. Similarly, in a phase III trial in advanced $CD20^+$ follicular lymphoma, first-line obinutuzumab-based chemotherapy with obinutuzumab maintenance therapy provided significantly longer PFS than rituximab-based chemotherapy with rituximab maintenance therapy [67].

Glycoengineering of anti-CD19 mAbs showed similar improvements in effector function. MDX-1342, an afucosylated anti-CD19 mAb, was compared with its fucosylated parental mAb and showed higher ADCC and more potent B-cell depletion in preclinical studies [68]. Inebilizumab is an afucosylated anti-CD19 IgG1 mAb approved for the treatment of AQP4-Ab+ NMOSD [69]. Similar to MDX-1342, when compared with its fucosylated parental mAb, inebilizumab had higher affinity to FcγRIIIa and stronger ADCC. When compared with rituximab, in vitro and in vivo B-cell depletion was higher with inebilizumab [70, 71]. Inebilizumab was evaluated in a phase I study in people with RMS and showed rapid and robust B-cell depletion and a trend toward a reduction in MRI lesions [30]. Inebilizumab is indicated for treatment of AQP4-Ab+ NMOSD and IgG4-mediated disease and is under investigation in generalized myasthenia gravis [69, 72]. Neither obinutuzumab nor inebilizumab are in development for MS.

In MS, ublituximab was glycoengineered to have a low fucose content in the Fc region [52, 73], resulting in greater in vitro ADCC activity compared with rituximab, ocrelizumab, and ofatumumab, as reported in a congress presentation [74]. Ocrelizumab was amino-acid-engineered to increase its ADCC, which is two to five times higher relative to rituximab [75].

7 Pharmacogenetics: FcγRIIIa Polymorphisms

Humans have six different FcγRs that vary in their affinities for IgG Fc as well as their signaling activities. The expression of different FcγRs by immune cells, in addition to the genomic complexity of the FcγR family, allows for fine tuning of immune responses [76]. Genetic diversity in FcγRs is in part due to single-nucleotide polymorphisms that can have pharmacogenetic effects influencing clinical outcomes.

Polymorphisms of FcγRIIIa on NK cells modulate the strength of interaction with the lower hinge region of IgG1 and therefore determine the strength of IgG1 binding (Fig. 5A) [77–79]. The FcγRIIIa 158F polymorphism, expressed in approximately 40% of healthy individuals, has weaker IgG binding than the FcγRIIIa 158V polymorphism [80]. NK cells with 158F have less effective ADCC compared with NK cells with the 158V variant [77].

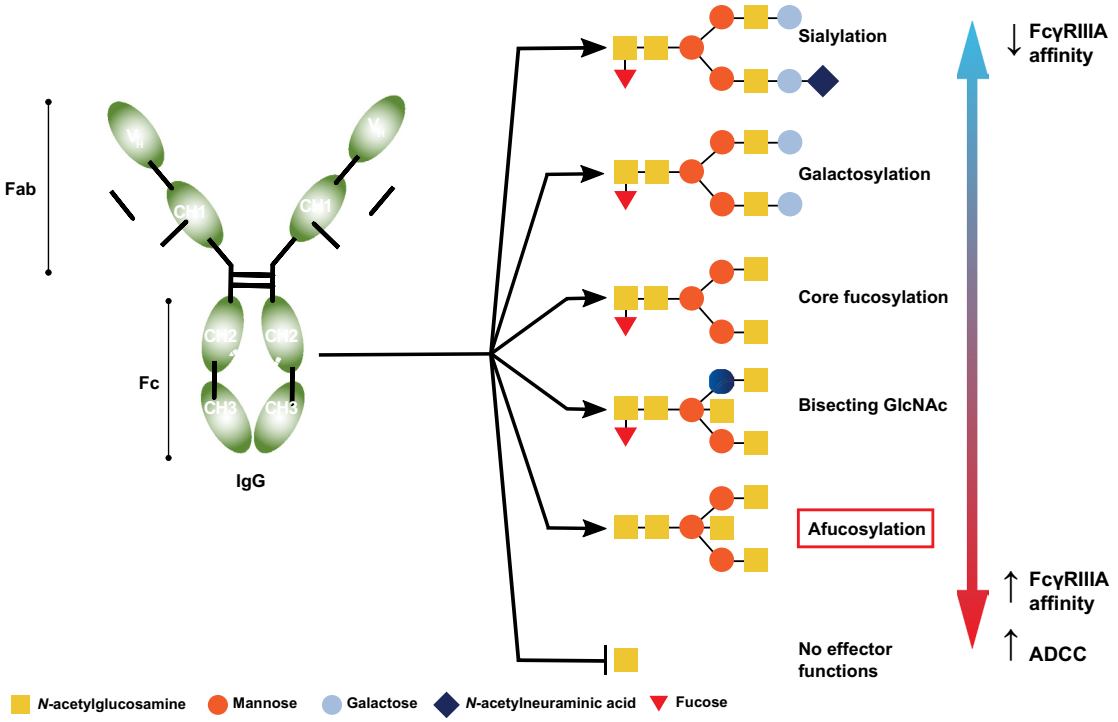


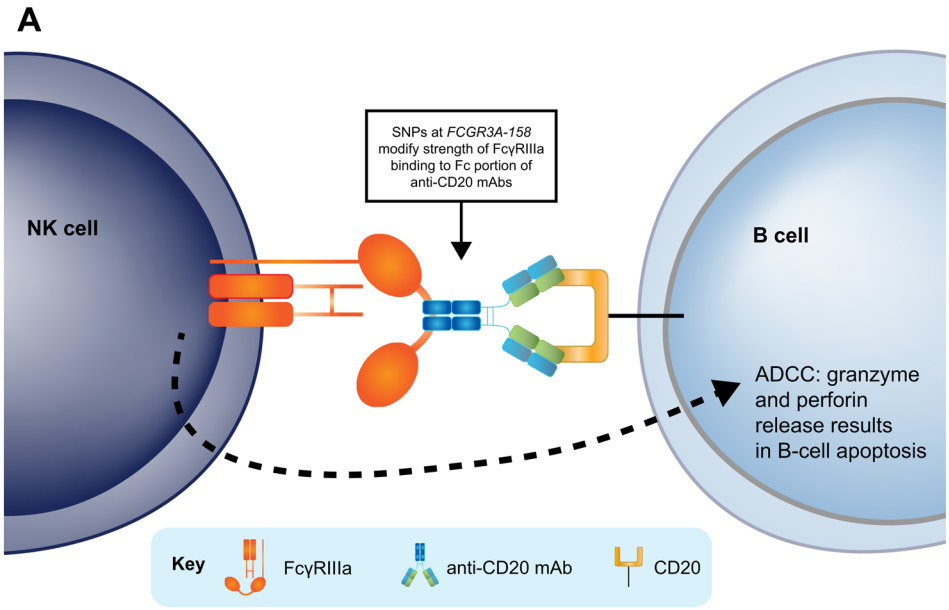
Fig. 4 Fc engineering enhances cell-effector functions. Fc-linked oligosaccharides inhibit the ADCC of anti-CD20 mAbs by sterically blocking interaction with the FcγRIIIa receptor. Removal of the *N*-glycans by glycoengineering (afucosylation) allows for closer interaction and increased affinity with FcγRIIIa and enhanced ADCC and ADCP. Adapted from Štambuk T, Klasić M, Zoldoš V, Lauc G. *N*-glycans as functional effectors of genetic and epigenetic disease risk. *Molecular Aspects of Medicine*, volume 79. p. 100891. Copyright 2021, with permission from Elsevier [61]. *ADCC* antibody-dependent cell-mediated cytotoxicity, *ADCP* antibody-dependent cell phagocytosis, *GlcNAc N*-acetylglucosamine, *Ig* immunoglobulin, *Fab* fragment antigen-binding, *Fc* fragment crystallizable, *FcγR* Fc gamma receptor

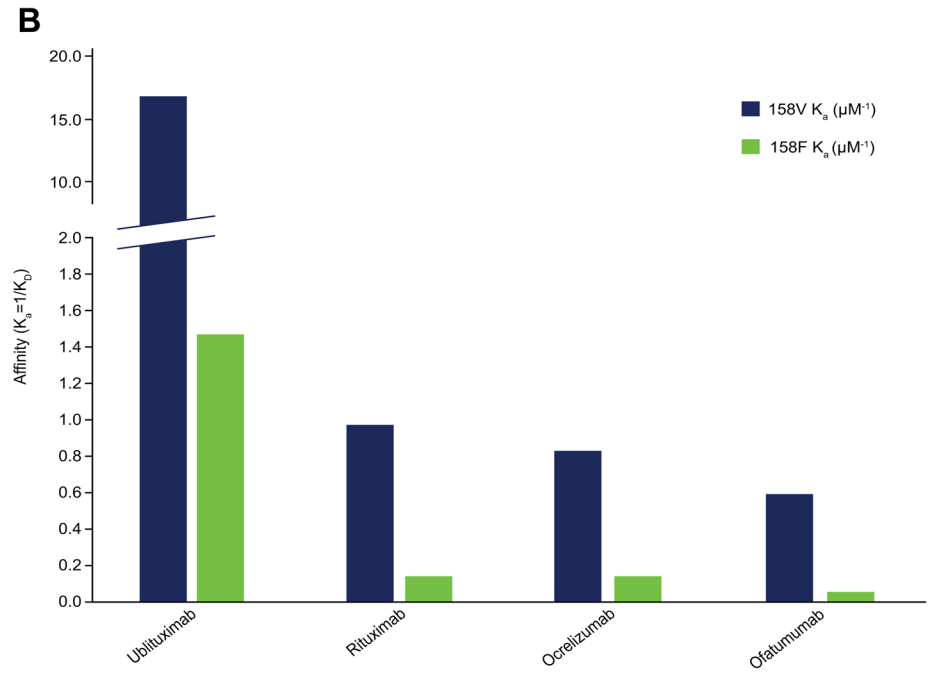
FcγRIIIa polymorphisms are associated with variable clinical response to rituximab. In a study of people with NMOSD ($N = 100$), the 158F variant was associated with a greater risk of insufficient memory B-cell depletion and relapse during rituximab treatment [81]. In a retrospective study of people with rheumatoid arthritis ($N = 212$), there was a significantly higher rate of clinical response to rituximab in participants with the 158V polymorphism (89%) compared with the 158F polymorphism (64%) [82]. In a systemic lupus erythematosus (SLE) study ($N = 262$), participants homozygous for 158V had a statistically significant 2.5-fold improvement in odds of a clinical response with rituximab compared with those with 158F [83]. In the oncology setting, the 158V polymorphism was associated with higher response rates to rituximab in people with lymphoma across multiple trials [84]. In people with MS, a presentation at a recent congress showed that, among 45 people treated with ocrelizumab, there was no significant correlation between FcγRIIIa polymorphisms and disease activity over 18 months. However, all nine participants who experienced early B-cell repopulation carried at least one F allele at position 158, further supporting a link between this genetic polymorphism and ADCC activity [85].

Glycoengineering may overcome the differential effects of FcγRIIIa polymorphisms. In contrast to what was observed in studies with rituximab, the activity of the glycoengineered anti-CD19 mAb inebilizumab was not impacted by FcγRIIIa polymorphisms in a study of people with NMOSD. B-cell depletion was similar in participants with either FcγRIIIa 158F or 158V variants, and there was no significant difference in the risk of relapse, ARR, or worsening Expanded Disability Status Scale score between the groups [86]. Ublituximab, which is similarly glycoengineered, has enhanced affinity for all variants of the FcγRIIIa receptor, with the highest binding and relative affinity for FcγRIIIa 158V and FcγRIIIa 158F variant receptors compared with other, non-glycoengineered anti-CD20 mAbs (reported in congress presentation) (Fig. 5B) [52, 73, 74].

8 Type I versus Type II Antibodies

The difference between type I and type II antibodies pertains to their relative abilities to translocate antibody-bound CD20 into lipid rafts [53]. Lipid rafts are lipid–protein microdomains that are important for





	158V		158F	
	K_D (nM)	K_a (μM^{-1})	K_D (nM)	K_a (μM^{-1})
Ublituximab	64	15.63	680	1.47
Rituximab	1025	0.98	6762	0.15
Ocrelizumab	1199	0.83	6960	0.14
Ofatumumab	1641	0.61	14,815	0.07

Fig. 5 Polymorphisms of FcγIIIa-receptor and anti-CD20 mAb Fc-binding affinity. **A** FcγRIIIa polymorphisms on NK cells modulate the strength of interaction with the Fc region and determine the strength of anti-CD20 IgG1 binding. The FcγRIIIa 158F polymorphism has weaker IgG binding than the FcγRIIIa 158V polymorphism. Adapted from Zhong M, van der Walt A, Campagna MP, Stankovich J, Butzkueven H, Jokubaitis V. The pharmacogenetics of rituximab: potential implications for anti-CD20 therapies in multiple sclerosis. *Neurotherapeutics*, volume 17. pp. 1768–1784. Copyright 2020, the American Society for Experimental NeuroTherapeutics, Inc. [79]. **B** Ublituximab, due to its glycoengineering, has enhanced affinity for all variants of the FcγRIIIa receptor, with the highest binding and relative affinity for FcγRIIIa 158V and FcγRIIIa 158F variant receptors compared with other, non-glycoengineered anti-CD20 mAbs [74]. *ADCC* antibody-dependent cell-mediated cytotoxicity, *CD* cluster of differentiation, *Fc* fragment crystallizable, *FCGR* Fc gamma receptor gene, *FcγR* Fc gamma receptor, *IgG* immunoglobulin G, K_a association constant, K_D equilibrium dissociation constant, *mAb* monoclonal antibody, *NK* natural killer, *SNP* single-nucleotide polymorphism

signal transduction via colocalization of receptors and effector molecules [87]. Type I antibodies promote CD20 translocation to lipid rafts [53]. Rituximab, ocrelizumab, ofatumumab, and ublituximab are all type I antibodies [52, 53]. In contrast, type II antibodies do not aggregate CD20 in lipid rafts and include obinutuzumab and tositumomab, both used to treat hematologic malignancies [53].

Clustering of CD20 with type I antibodies stabilizes CD20 on lipid rafts, leading to stronger C1q binding and higher CDC, with limited induction of programmed cell death (PCD) [53, 88]. Conversely, because type II antibodies do not stabilize CD20 in lipid rafts, their ability to activate complement is reduced. However, type II antibodies can induce PCD independent of complement activation.

Both type I and type II antibodies induce ADCC (Fig. 6) [87, 88]. Type I antibodies are capable of binding substantially more CD20 receptors than type II antibodies, which may increase CD20 internalization and cause CD20 degradation and downregulation of CD20 expression [87]. All therapeutic anti-CD20 mAbs thus far used in MS are type I [52, 53].

9 CD20-Antigen Binding

Anti-CD20 mAbs also bind different CD20 epitopes and differ in CD20-binding affinity [53]. Rituximab and ocrelizumab bind the same epitope on the large loop of CD20, ublituximab binds a different epitope (with some overlap with rituximab/ocrelizumab) on the large loop, and ofatumumab binds portions of the small loop and a distinct epitope on the large loop (Fig. 1) [20]. mAb epitope-binding location and angle influences cell depletion [19]. Binding of the small loop (ofatumumab only) is associated with higher CDC due to oblique positioning of the antibody, which encourages IgG–IgG interaction (facilitating C1q recruitment), increases Fc proximity to cell membrane, and promotes CD20 translocation into lipid rafts.

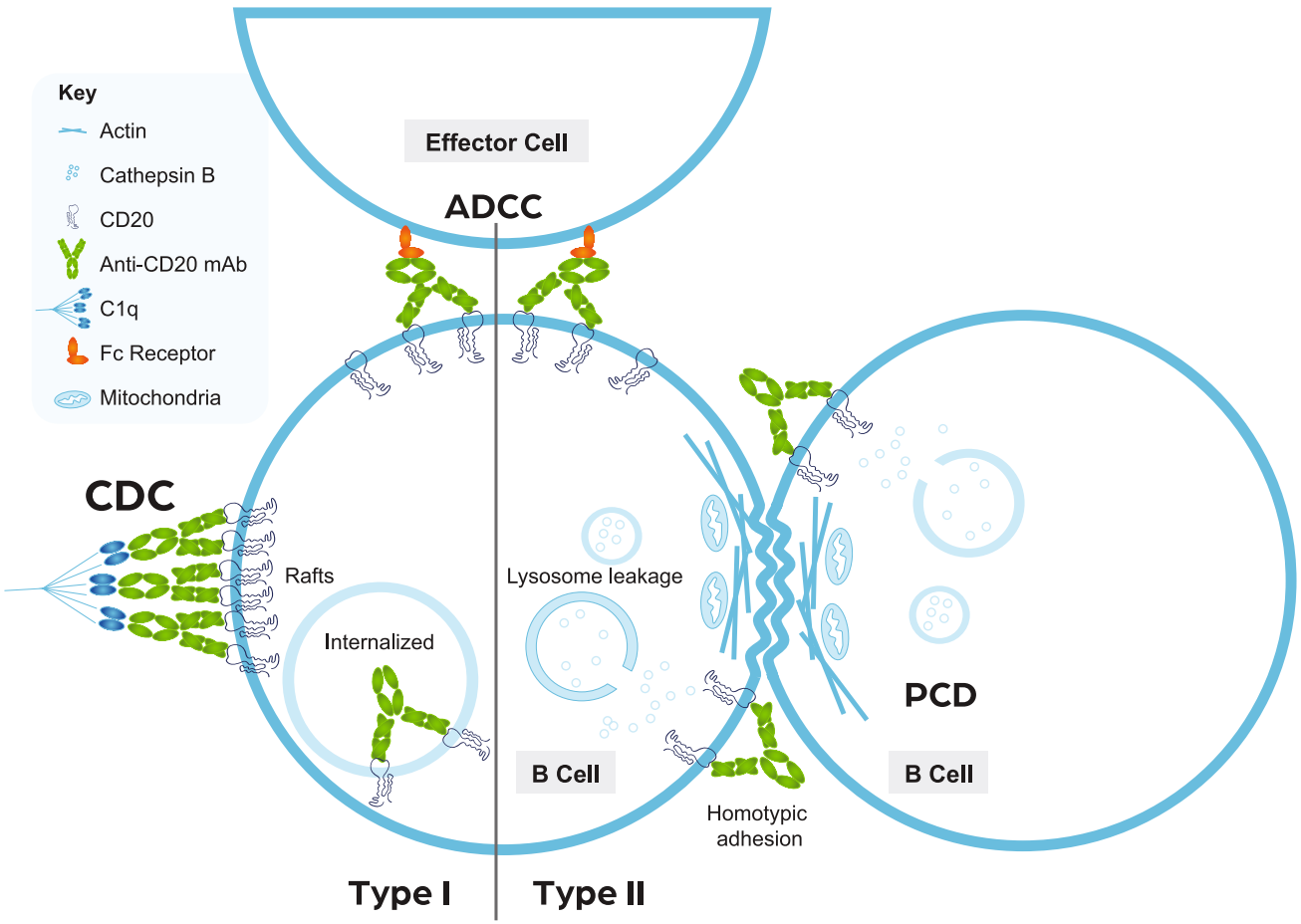


Fig. 6 Type I and type II mAb-mediated cell lysis. Type I mAbs are able to engage CDC and ADCC but do not elicit efficient direct cell death, whereas type II mAbs can mediate direct cell death through a lysosomal pathway and can engage ADCC but not CDC. Reprinted from Beers SA, Chan CHT, French RR, Cragg MS, Glennie MJ. CD20 as a target for therapeutic type I and II monoclonal antibodies. *Seminars in Hematology*, volume 47, issue 2. pp. 107–114. Copyright 2010, with permission from Elsevier [164]. *ADCC* antibody-dependent cell-mediated cytotoxicity, *C1q* complement component 1q, *CD* cluster of differentiation, *CDC* complement-dependent cytotoxicity, *Fc* fragment crystallizable, *mAb* monoclonal antibody, *PCD* programmed cell death

10 Mechanisms of Cell Death

Anti-CD20 mAbs induce target cell lysis through different mechanisms: CDC, ADCC, antibody-dependent cell phagocytosis (ADCP), and PCD/direct apoptosis [88]. CDC and ADCC are thought to be the most common mechanisms for anti-CD20 mAb-mediated cell lysis [20, 89]. CDC involves antibody-mediated activation of the complement pathway and occurs when IgG antibodies coat a target cell [20]. The Fc region of the anti-CD20 mAb is bound by C1q of the complement system, resulting in the formation of the membrane attack complex and subsequent lysis of the target cell [20, 88]. ADCC is independent of the complement system and is largely mediated by interactions between the Fc region of the anti-CD20 mAb and FcγRIIIa, an IgG-binding FcγR, on NK cells [59, 90]. This interaction initiates a series of signaling pathways in NK cells, including release of cytolytic compounds such as granzyme B and perforin, leading to B-cell lysis [53, 87, 88, 91]. In ADCP, FcγRs on macrophages bind to anti-CD20 mAbs that are attached to target B cells, leading to antibody-dependent cellular phagocytosis of the B cells by the macrophages; FcγRIIa is thought to be the main FcR involved in ADCP by macrophages [88]. Lastly, type II antibodies can induce direct cell death (i.e., PCD) upon binding to CD20 in an Fc-independent manner [53, 88].

Of interest, the relative contribution of CDC and ADCC to mediating B-cell lysis varies depending on the specific anti-CD20 mAb [10]. For rituximab and ofatumumab, CDC predominates over ADCC, whereas for ocrelizumab and ublituximab, ADCC is the primary mechanism, although CDC also occurs [10, 20]. Inebilizumab does not fix complement and depletes B cells exclusively by ADCC and ADCP. In preclinical studies, ublituximab had the strongest ADCC of all four anti-CD20 mAbs, resulting from its glycoengineered Fc region, as discussed above [10, 74].

11 Antibody Structure and Infusion-Related Reactions

The mechanistic cause of infusion reactions explains why differences in antibody scaffold (i.e., level of "humanness") do not appear to have a clinically meaningful effect on IRRs with anti-CD20 mAbs. Infusion reactions are most correlated with cytokine release events and/or complement activation. Cytokine release is the most common cause of IRRs with mAbs, including with anti-CD20 mAbs, and this is distinct from allergic reactions mediated by IgE (hypersensitivity reactions) [92]. During mAb-mediated cell lysis, both the target cells and the immune effector cells release cytokines into the circulation [92, 93]. Symptoms of anti-CD20 mAb cytokine release syndrome (CRS) are generally mild to moderate in severity, usually occur within the first several hours postinfusion (most often with the first infusion) [92], and tend to decrease with subsequent doses due to the reduced number of target cells, which is the pattern of IRRs observed with anti-CD20 mAbs in MS [6, 94]. Cytokine release reactions may be managed by infusion interruptions, use of histamine blockers with or without corticosteroids, and slowed infusion rate [92].

In oncology, an increase in inflammatory cytokines, including interleukin (IL)-6, TNF-α, IL-8, and IFN-γ, follows anti-CD20 mAb infusion [95–98]. Levels of inflammatory cytokines positively correlate with the amount of circulating malignant B cells [97, 98] as well as with the prevalence and severity of IRR symptoms [96].

Some mAbs, however, can directly activate complement, releasing complement 3a (C3a), 5a (C5a), and 5b-9 (C5b-9), leading to production of vasoactive mediators by mast cells, basophils, and other immune cell types, a phenomenon termed "complement activation-related pseudoallergy" (CARPA) [93]. Rituximab causes both CARPA and CRS [93, 99]. Similar to cytokine-release-mediated IRRs, CARPA occurs most frequently at the first infusion and can be reduced with pre-medications and slower infusion rates [93]. IV-infused anti-C20 mAbs used in MS have recommended pre-medications to reduce IRRs [10, 11, 20, 100]. In contrast, pre-medications are not needed for subcutaneous ofatumumab, presumably related to the route of administration and lower dose, because IRR rates with IV ofatumumab were higher than those seen with other IV anti-CD20 mAbs [101–103].

Due to the predominant mechanism of cytokine-release-mediated IRRs, the mAb scaffold (chimeric, humanized, or fully human) appears to not have a substantial effect on infusion/injection reactions in clinical practice.

In contrast, the predominance of an ADCC- versus CDC-mediated mechanism may have clinical relevance because CDC has a potential role in IRRs [20, 104, 105]. Activation of complement generates C3a and C5a, which are potent inflammatory mediators and anaphylatoxins that can affect vasodilation; stimulate macrophages, neutrophils, and eosinophils; cause histamine release; and activate antigen-presenting cells to produce IL-12 and IL-13 [106]. Clinical data from people with lymphoma treated with rituximab support an association between CDC and IRRs: following the first rituximab dose, there was a correlation between the amount of CDC activation (C3b/c levels) and IRR severity [105]. Supporting the notion that IRR frequency may be complement-mediated is the observation that the afucosylated anti-CD19 mAb, inebilizumab, which does not activate complement, is not associated with a higher rate of

IRRs compared with placebo—although, as with MS, premedications are used with inebilizumab infusions [31].

12 Rationale for Improving Anti-CD20 mAbs for MS

Anti-CD20 mAb therapy revolutionized the treatment of MS; however, opportunities to improve treatment outcomes with anti-CD20 mAbs remain.

12.1 B-Cell Depletion/Repletion

In some people treated with anti-CD20 mAbs, B-cell depletion is incomplete, and repletion between infusions occurs. Nearly all data are from blood tests, representing levels of circulating B cells. In an observational study, 26% of people with MS treated with ocrelizumab ($N = 155$) had B-cell repletion at 6 months, and fast repopulation (B-cell repletion at 6 months) was associated with significantly higher MRI activity at 12 months [107]. In the OPERA I and II and ORATORIO studies, population pharmacokinetic analyses found that body weight impacted ocrelizumab exposure and B-cell depletion, and that > 30% of participants in the lowest exposure quartile had incomplete B-cell depletion at week 96 [108]. Additionally, higher B-cell counts pretreatment and greater body mass index (BMI) appear to contribute to early reconstitution of B cells [107, 109]. These data are in accordance with results from the OPERA and ORATORIO studies. Beyond clinical factors influencing early repopulation, the kinetics of B-cell repletion in different immune compartments is not well understood. A study using the experimental autoimmune encephalomyelitis (EAE) model investigated B-cell repopulation following ocrelizumab treatment and demonstrated reconstitution of B cells in the spleen and bone marrow prior to their appearance in the blood. The data suggest that certain subpopulations of B cells might differ in their response to ocrelizumab treatment and contribute to the early repopulation reported in some patients [110].

The extent of B-cell depletion may affect clinical efficacy. A post hoc analysis of OPERA I and II and ORATORIO revealed a nonsignificant trend toward an association of higher median B-cell levels with higher rates of 24-week confirmed disability progression during the 96-week double-blind period and open-label extension [111]. An observational study of 108 ocrelizumab-treated people with MS corroborated data from the clinical trials [109]. Fast B-cell repopulation was associated with higher BMI, and people with fast B-cell repopulation had numerically lower rates of no evidence of disease activity-3 and no evidence of progression or active disease and experienced worsening disability. However, these observations do not exclude the possibility that higher BMI might be associated with higher disease activity independently from reduced B-cell depletion. Clinical trials investigating the pharmacodynamics, efficacy, and safety of higher doses of ocrelizumab are underway in RMS (NCT04544436) and PPMS (NCT04548999).

Studies extending dosing intervals with rituximab or ocrelizumab did not find an association between B-cell levels and clinical activity [112–115]. In one study that evaluated B-cell repopulation following extended interval dosing, no associations with inflammatory activity were found, and higher percentages of naïve, transitional, and regulatory B cells were associated with extended interval dosing versus standard interval dosing [116]. The WINDOCRE trial (NCT05999604) will investigate noninferiority of yearly dosing of ocrelizumab versus standard 6-month dosing in people with MS who have been stable on therapy for 2 years. This study will provide insight into whether extended dosing intervals for anti-CD20 therapies can result in increased safety profiles without compromising efficacy. Whether extended dosing and corresponding repopulation of B cells translates into decreased efficacy long term is not known.

The extent of B-cell depletion in peripheral blood does not necessarily reflect the extent of B-cell depletion in lymphoid tissues. Only 2% of lymphocytes circulate in peripheral blood, whereas lymphoid tissues house the remainder of the population [117]. In people with MS, B cells are also found in tertiary lymphoid structures (TLS) within the meninges and perivascular spaces of the CNS [118]. It is presumed that TLS are the intrathecal source of antibodies detected as oligoclonal bands and IgG index elevation in CSF. Further, it is hypothesized that these CNS-resident B cells are directly involved in MS pathogenesis because cortical demyelination is topographically associated with meningeal TLS [119].

The extent of B-cell depletion in tissues by anti-CD20 mAb treatment was studied in people treated with rituximab across different disease states [120–122]. These studies found that B cells are depleted to a variable extent in spleen, lymph nodes, and bone marrow, with a greater depletion in spleen and bone marrow than in lymph nodes.

Studies of B-cell depletion in the CSF of people with MS treated with anti-CD20 mAbs are limited but generally show that CSF B cells are substantially reduced following anti-CD20 mAb treatment [3, 123]. A more recent study evaluated the effects of ocrelizumab on CSF lymphocytes in people with PPMS and reported a significant reduction of total B cells as well as $CD4^+$ $CD20^{dim}$ $CD45RA^-$ memory T cells. Interestingly, $CD8^+$ $CD20^{dim}$ T cells were not substantially depleted in the CSF [124].

In a small observational study of people with progressive MS and leptomeningeal-enhancing (LME) lesions,

intrathecal rituximab resulted in a reduction of CSF B-cell counts at 2 weeks after the first dose, with recovery at 8 weeks despite a second dose at week 2 [125]. There were no changes in the number or appearance of LME lesions or development of new LME lesions. A small study of people with MS and LME lesions initiating ocrelizumab reported that there was no significant reduction in the number or volume of LME lesions after approximately 1 year of treatment [126].

Evidence for B-cell depletion in the CNS with anti-CD20 mAb treatment also comes from preclinical studies. One study using a transgenic human CD20 EAE model showed no effect on B-cell depletion in the spinal cord with rituximab treatment [127]. Another study using a transgenic human CD20 EAE model found that rituximab depleted only dense perivascular B-cell infiltrates but not parenchymal B-cell infiltrates [128]. In contrast, obinutuzumab, a glycoengineered type II mAb, depleted both perivascular and intraparenchymal B-cell infiltrates [128, 129]. Compared with rituximab, obinutuzumab has stronger in vitro ADCC activity and can also trigger PCD; therefore, these preclinical data suggest that anti-CD20 mAbs with non-CDC mechanisms of B-cell lysis might have higher CNS activity. However, findings about depletion in CNS appear to be model dependent; results using a different, humanized CD20 mouse model of secondary progressive MS showed similar reductions in CNS B cells when administering either rituximab or obinutuzumab [130].

Data on whether anti-CD20 mAb route of administration (IV versus subcutaneous) affects B-cell depletion in secondary lymphoid organs come from animal studies. In cynomolgus monkeys, there was slightly higher depletion of B cells in distant (non-draining) lymph nodes with subcutaneous versus IV rituximab treatment (57% versus 42% depletion of B cells, respectively), although numbers were small [131]. In a larger imaging study of mice expressing human CD20, improved lymph node targeting was observed with subcutaneous administration of ofatumumab or ocrelizumab versus IV administration; however, similar depletion of B cells in spleen and lymph nodes occurred regardless of antibody or route of administration [132].

12.2 Administration Experience

Administration of the different anti-CD20 mAbs can affect people's treatment experiences, and the anti-CD20 mAbs used in MS have different administration protocols. Ofatumumab is self-administered monthly by subcutaneous injection [9]. A formulation of ocrelizumab administered every 6 months by subcutaneous infiltration over 10 min by a healthcare professional recently became available [133, 134].

IV administration of ocrelizumab and ublituximab is every 6 months and every 24 weeks, respectively, following the initial dose(s) [11, 100], with a similar cadence typically used for rituximab in MS [56]. In clinical trials of rituximab, the minimum infusion time was 4.5 h for the first dose and 3 h for subsequent doses [4, 41]. The ocrelizumab IV infusion rate is ≥ 2.5 h for the initial dose and ≥ 2 h for subsequent doses [100]. The ublituximab IV infusion rate is 4 h for the initial dose on day 1 and 1 h for subsequent doses [11]. Postinfusion, an observation period of ≥ 1 h is required for ocrelizumab [100], whereas for ublituximab, a 1-h postinfusion observation period is only required for people who experienced an IRR during the first two infusions [11]. Therefore, modifications in anti-CD20 mAb structure and formulation may impact patient experience and convenience.

The route and dose of administration might also impact hypogammaglobulinemia. Initial data from the ASCLEPIOS (and open-label extension) studies demonstrated immunoglobulin levels above the lower limit of normal [135]. The decreased rates of hypogammaglobulinemia in people treated with ofatumumab was attributed to the idea that subcutaneous administration of a lower, more frequent dose of antibody would result in a more specific (i.e., targeted to the lymph node) and readily reversible mechanism of B-cell depletion. However, a subsequent study presented at a recent conference showed equal rates of hypogammaglobulinemia in people treated with ocrelizumab versus ofatumumab (9.9% and 8.9%, respectively) [136]. Further comparative studies are needed to determine whether ofatumumab reduces the risk of hypogammaglobulinemia compared with other anti-CD20 mAbs.

13 Continuing Evolution of Strategies to Target CD20

Brain shuttle antibodies, bispecific antibodies, CAR T-cell (CAR T) therapies, and antibody–drug conjugates are also being designed and evaluated for therapeutic targeting of B cells.

13.1 Brain Shuttle Antibodies

Transferrin is transported across the blood–brain barrier using transferrin receptors [137]. This receptor system can be leveraged to move mAbs across the blood–brain barrier by coupling mAbs to transferrin. A newer anti-CD20 mAb,

RO7121932, uses brain shuttle technology to increase brain and CNS penetrance and is in development for MS (NCT05704361) [138].

Although the specific characteristics of the mAb are not yet detailed, it is presumed that this molecule is based on the type II antibody obinutuzumab, which uses PCD rather than requiring complement activation to affect B-cell lysis.

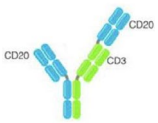
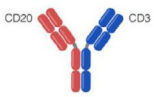
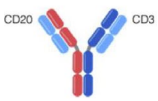
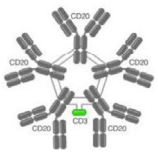
13.2 Bispecific Antibodies

Bispecific antibodies co-targeting CD3 and B-cell antigens activate and engage T cells against CD19- or CD20-expressing cells; cytotoxicity occurs in an MHC-independent fashion [139]. As an example, a CD20 × CD3 bispecific antibody binds to CD20 expressed on the surface of B cells and to the CD3 receptor expressed on the surface of T cells, causing T-cell activation and proliferation, secretion of cytokines, and B-cell lysis [140]. Bispecific antibodies can be engineered in multiple ways: CD20 × CD3 bispecific antibodies can have one or more CD20-binding Fab arms, varying arrangement of CD20- and CD3-binding sites, or bind different CD20 epitopes (Table 2) [139].

Bispecific antibodies are divided into two major classes [139, 141]: (1) antibodies containing an Fc region, conferring an Ig-like structure, and (2) antibodies that lack an Fc region, an example of which are the bispecific T-cell engagers (BiTEs), which contain only the variable regions of antibodies in the form of antigen-binding fragments connected by linker peptides.

The first bispecific antibody to be approved by the FDA was blinatumomab, a CD19 × CD3 BiTE comprising two single-chain antibody fragments, one targeting CD19 and one targeting CD3, connected by a linker [139, 142]. Blinatumomab is approved for $CD19^+$ acute lymphoblastic leukemia [142] and was used off-label in autoimmune diseases with some success. Compassionate use of blinatumomab in people with refractory rheumatoid arthritis reduced disease activity, improved synovitis, reduced

Table 2 Characteristics of CD20 × CD3 bispecific antibodies

Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc-silencing mutations*
Mosunetuzumab		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Glofitamab		IgG1	Head-to-tail fusion	2:1	SP34-der. (CD3ε)	By-L1 (type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (no FcγR binding)
Epcoritamab		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.) (CD3ε)	7D8 (type 1 epitope, shared by ofatumumab)	L234F, L235E, D265A (no FcγR, C1q binding)
Odronextamab		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumumab)	Modified IgG4 (no FcγRIII binding)
Plamotamab		IgG1	Fab-Fc × scFv-Fc	1:1	α-CD3_H1.30 (SP34-der.) (CD3ε)	C2B8_H1_L1 (type 1 epitope, shared by rituximab)	G236R, L328R (no FcγR binding)
IgM-2323		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

Reprinted from Falchi L, Vardhana SA, Salles GA. Bispecific antibodies for the treatment of B-cell lymphoma: promises, unknowns, and opportunities. *Blood*, volume 141, issue 5. pp. 467–480. Copyright 2023, with permission from the American Society of Hematology [139]

C1q complement component 1q, *CD* cluster of differentiation, *Fab* fragment antigen-binding, *Fc* fragment crystallizable, *FcγR* Fc gamma receptor, *FcR* Fc receptor, *Ig* immunoglobulin, *scFv* single-chain variable fragment

*These Fc-silencing mutations do not abolish the binding of bispecific antibodies to neonatal FcR

autoantibodies, and depleted activated memory B cells [143].

Currently, there are three CD3 × CD20 bispecific antibodies that received accelerated approval in the USA: glofitamab and epcoritamab for relapsed or refractory diffuse large B-cell lymphoma and mosunetuzumab for relapsed or refractory follicular lymphoma [140, 144, 145]. These target the same or overlapping CD20 epitopes as approved anti-CD20 mAbs [139] (Table 2). There are also bispecific antibodies targeted against B-cell activating factor or inflammatory cytokines in clinical development for autoimmune and/or inflammatory conditions [146, 147].

13.3 CAR T-Cell Therapies

CD19-directed CAR T therapies showed impressive success in treating B-cell malignancies [148, 149] and offer the potential for a single-dose treatment with long-term efficacy [150]. Sustained beneficial effects of CD19 CAR T cells were observed in people with SLE, idiopathic inflammatory myositis, and systemic sclerosis [151]. KYV-101 is a CD19 CAR T therapy designed to improve tolerability over earlier CD19 CAR Ts that is being evaluated in people with MS and myasthenia gravis (studies NCT06451159, NCT06384976, NCT06138132, and NCT06193889). In an initial study, an acceptable safety profile was observed in two participants with progressive MS who received KYV-101 [152].

CD20 is also a target of CAR T therapies [149] and is being evaluated in clinical trials of hematologic malignancies, including combinations of CD20 with other B-cell antigens, such as dual CD20/CD19 and CD20/CD22, or trivalent CAR T therapies, including CD19/CD20/CD22 [153].

Currently, all approved CAR T therapies use autologous cells; however, "off the shelf" allogeneic CAR T therapies are in clinical development. CAR Ts targeting CD19 (azercabtagene zapreleucel; ALLO-501A; CTX110) and CD20 (PBCAR20A) have phase II trials completed or ongoing [154].

Because anti-CD19 CAR T therapies result in the depletion of all B cells, excluding long-lived plasma cells, efforts are ongoing to develop chimeric autoantibody receptor (CAAR) T cells, in which T cells are genetically modified with a chimeric receptor containing a target autoantigen with the aim of targeting specific B-cell populations that express autoantibodies to the target autoantigens [148]. Therapeutic efficacy using CAAR T cells was demonstrated in preclinical models of pemphigus vulgaris [155] and muscle-specific tyrosine kinase (MuSK) myasthenia gravis [156]. A clinical trial of MuSK-CAART is underway (NCT05451212). A preclinical EAE study evaluated a novel CAAR T cell containing part of the myelin basic protein autoantigen. The CAAR T cells induced higher B-cell lysis than controls and increased proliferation and production of inflammatory cytokines when co-cultured with autoreactive B cells, providing initial proof of concept that CAAR T cells might have activity in MS [157].

13.4 Antibody–Drug Conjugates

Antibody–drug conjugates utilize the capacity of mAbs to target specific cells with an attached cytotoxic agent, typically microtubule inhibitors or DNA-damaging agents [158, 159]. Upon binding of the mAb to the cell surface antigen followed by internalization of the mAb–drug complex, the cytotoxic payload is delivered selectively to the target cell and causes cell death or apoptosis [159]. The Fc-mediated immune effector functions may also play a pivotal role by inducing ADCC, CDC, and ADCP [159, 160]. The first antibody–drug conjugates were developed for use in the treatment of various cancers such as loncastuximab tesirine (ADCT-402), a CD19-targeted antibody–drug conjugate used to treat diffuse large B-cell lymphoma [161].

14 Conclusion

Since the initial experience of rituximab in MS and NMOSD, engineering of anti-CD20 mAbs has evolved. These changes in antibody structure and function were made to improve clinical efficacy and safety. The adaptation of antibody scaffolds from chimeric to humanized or fully human altered the immunogenicity of anti-CD20 mAbs but did not translate into meaningful differences in tolerability or efficacy, as supported by data from studies with rituximab and ublituximab, two chimeric antibodies with good tolerability profiles. Rather, tolerability with anti-CD20 therapy, which is an important consideration for patients and healthcare providers when choosing a medication, may be a consequence of the predominant pathway of B-cell depletion: either ADCC or CDC. Ublituximab and ocrelizumab mediate B-cell depletion predominately via ADCC, whereas rituximab and ofatumumab rely on complement activation for efficient lysis of target cells. These different mechanisms of cell lysis can translate into differences in tolerability and IRRs for patients. Deeper and sustained peripheral B-cell depletion could be an important predictor of disease activity suppression and may be influenced by mAb-binding epitope and mechanism and strength of cell lysis, as well as individual characteristics such as body weight and FcγR polymorphisms. Glycoengineered antibodies, such as ublituximab and inebilizumab, correlate with stronger binding affinities and more efficient cell lysis, even when polymorphisms in the FcRs of effector cells are present. Whether this translates to improved long-term

efficacy or impacts safety is still being evaluated. The role of genetic polymorphisms and pharmacogenetics is a new concept in MS and could open the door to potentially more personalized approaches as novel treatment options become available. Further elucidation of the characteristics that drive therapeutic success for anti-CD20 mAbs could pave the way for the development of new treatments, including bispecific antibodies and CAR T-cell therapies, and improve the overall quality of life for people living with MS.

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Conflicts of Interest B.A.A.C. has received personal compensation for consulting from Alexion, Autobahn, Avotres, Biogen, Boston Pharma, EMD Serono, Hexal/Sandoz, Horizon, Immunic AG, Kyverna, Neuron23, Novartis, Sanofi, Siemens, and TG Therapeutics and received research support from Genentech and Kyverna. J.R.B. has served as a consultant for Celgene/BMS, Cellevolve, EMD Serono/Merck, Genentech/Roche, Genzyme, Gilead, Janssen/J&J, Morphic, NeuVIR, Novartis, Population Bio, Sanofi, Takeda, and TG Therapeutics. He has served on the scientific advisory or data safety monitoring board for MAPI and Excision BioTherapeutics. He has served for *Neurology Reviews* and WebMD. B.G. has received consulting fees from Alexion, Novartis, EMD Serono, Horizon Therapeutics/Amgen, Genentech/Roche, Signant, IQVIA, Sandoz, Sanofi/Genzyme, TG Therapeutics, Cycle Pharma, Arialys, Clene, Syneos, and PRIME Education. He has received grant funding from NIH, Anokion, and Regeneron. He serves as an unpaid member of the board of the Siegel Rare Neuroimmune Association. He has equity in Clene and GenrAb. He receives royalties from UpToDate.

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