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B Cell–Directed Therapy in Autoimmunity

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Abstract

Autoimmune diseases with B cell–directed therapeutics approved by the US Food and Drug Administration are surprisingly diverse in clinical manifestations and pathophysiology. In this review, we focus on recent clinical and mechanistic insights into the efficacy of B cell depletion in these diverse autoimmune disorders, the rapidly expanding armamentarium of approved agents, and future approaches. The pathogenic roles for B cells include direct functions such as production of autoantibodies and proinflammatory cytokines and indirect functions via antigen presentation to T cells. The efficacy of B cell–depleting strategies varies across diseases and likely reflects the complexity of disease pathogenesis and relative contribution of B cell roles. Additionally, B cell–depleting therapies do not equally target all B cell subsets in all patients, and this likely explains some of the variability in responses. Recent reports of B cell depletion with novel chimeric antigen receptor (CAR) T cell approaches in an expanding number of autoimmune diseases highlight the potential role of B cell depletion in resetting immune tolerance. The relative importance of eliminating autoreactive B cells and plasma cells and approaches to doing so will also be discussed.

INTRODUCTION

When B cell depletion therapy (BCDT) was first being considered for autoimmune diseases over two decades ago, it was expected that clinical responses would correlate with autoantibody reduction. However, the variability in autoantibody effects and the utility of BCDT in a diverse spectrum of diseases including rheumatoid arthritis (RA) and multiple sclerosis (MS), which have traditionally been considered strongly T cell mediated, have challenged this notion. In turn, the inconsistent effectiveness of BCDT in diseases like systemic lupus erythematosus (SLE) with a strong B cell contribution has been disappointing. Important factors to consider relevant to efficacy and mechanism of action of BCDT include disease and patient heterogeneity with respect to the role of B cells in pathogenesis, degree of B cell depletion, and the diversity of human B cell subsets and their contribution to disease, including the role of long-lived plasma cells (PCs). In this review we summarize the clinical and mechanistic data supporting B cell–targeted therapy in autoimmune disease, discuss the relevant biological and pathogenic functions of B cells in autoimmunity, and highlight the ever-expanding approaches to BCDT, including the emerging CAR T cell–specific and bispecific antibodies.

B CELL–TARGETING APPROACHES

Treatment approaches targeting the B cell compartment are varied and include direct depletion with monoclonal antibodies (e.g., anti-CD20, anti-CD19), newer depletion strategies with engineered T cells or bispecific antibodies, indirect depletion via survival cytokine blockade (e.g., belimumab), costimulatory blockade (1), approaches to inhibiting B cell activation (e.g., small-molecule inhibitors of Btk) (2, 3), and more direct PC targeting (4). We focus here mostly on cell-depletion approaches, both conventional therapies approved by the US Food and Drug Administration (FDA) and some of the promising developing strategies that evoke more thorough B cell depletion (CAR T cells) (**Table 1**).

The immunological and clinical impacts of various B cell therapies depend on the molecule targeted (**Figure 1**). B cells in the preimmune repertoire become susceptible to depletion with anti-CD19 or anti-CD20 strategies once they express these antigens. Transitional and naive B cells are particularly dependent on BAFF (B cell–activating factor of the tumor necrosis factor family) for survival and are effectively depleted with BAFF-blocking antibodies. Naive B cells can be activated by antigen and other signals to generate memory B cells and PCs in either germinal center (GC) reactions or extrafollicular locations. Human memory B cells are marked by surface expression of CD27 (5), though atypical memory populations lack CD27 expression (6), some of which may arise in extrafollicular reactions. Recent work in human SLE has defined extrafollicular B cell differentiation pathways as a key source for development of autoreactive PCs surprisingly from activated naive B cell subsets (7, 8). This leads to an atypical B cell population, termed age-associated B cells (ABCs) that also expands in autoimmunity (9). These activated B cell populations do express CD20, but whether they may be resistant to BCDT has not been well studied. Once B cells begin to differentiate into PCs they downregulate first CD20 and then CD19. Thus, most mature PCs are not directly susceptible to anti-CD20 treatment (10). Bone marrow PCs are particularly challenging to target, though some fraction of them do express CD19 (11). The relative abundance of autoreactive clones in these various short-lived versus long-lived PC pools in human disease is understudied, especially in the bone marrow. Factors in the bone marrow niche that support long-lived PC survival include the BAFF-related cytokine, APRIL, which binds to BCMA (B cell maturation antigen) and supports memory B cell and PC survival (12). Long-lived PCs also upregulate autophagy pathways and the unfolded protein response, making them susceptible

Table 1 B cell depletion strategies for autoimmune disease

Drug	Target-based actions	Therapeutic indications	Status
Rituximab	Chimeric anti-CD20 mAb	Rheumatoid arthritis; GPA; MPA; pemphigus vulgaris	FDA approved
		MS	Phase 2/3 active
		Myasthenia gravis	Phase 3 active
		SLE/lupus nephritis	Phase 3 complete. Did not meet primary end point
		Systemic sclerosis	Phase 2/3 complete
Ocrelizumab	Humanized anti-CD20 mAb	Relapsing and primary progressive MS	FDA approved
		SLE	Phase 3 terminated for adverse effects
Ofatumumab	Fully human anti-CD20 mAb	Relapsing MS	FDA approved
		NMOSD	Phase 1/2
		Rheumatoid arthritis	Phase 2 complete; SC phase 1 complete
Ublituximab	Chimeric cytolytic anti-CD20 mAb	Relapsing MS	Phase 3 complete
Obinutuzumab	Humanized anti-CD20 mAb	SLE/SLE nephritis	phase 3 active
		PR-3 ANCA vasculitis	phase 2 active, not yet recruiting
MIL62	Humanized anti-CD20 mAb	SLE	Phase 2/3 active not yet recruiting
		NMOSD	Phase 3 active
Obexelimab	Anti-CD19 and anti-FcRIIb	IgG4-related disease	Phase 3 active
		SLE	Phase 2 complete. Did not meet endpoint
Inebilizumab	Anti-CD19 mAb	NMOSD	FDA approved
		Myasthenia gravis	Phase 3 active
		Systemic sclerosis	Phase 3 active
Belimumab	Anti-BAFF mAb	SLE/lupus nephritis	FDA approved
		Systemic sclerosis with ILD	Phase 2/3 active, not yet recruiting
		Diffuse cutaneous systemic sclerosis	Phase 2 complete
		NMOSD	Phase 1/2 active
		Antiphospholipid syndrome	Phase 2/3 active
		Sjögren syndrome	Phase 2 complete
		GPA/MPA	Phase 3 complete
		Multiple sclerosis	Phase 2 terminated
		Myasthenia gravis	Phase 2 complete
Ianalumab	Anti-BAFF mAb	SLE/lupus nephritis	Phase 3 active
		Rheumatoid arthritis	Phase 1 active, not recruiting
		Sjögren syndrome	Phase 3 active
Telitacicept	TACI-Ig fusion protein	SLE/early SLE/lupus nephritis	Phase 3 active/phase 4 active/phase 2 active
		Antiphospholipid syndrome	Phase 2 active
		Myasthenia gravis	Phase 3 active, not yet recruiting
		Sjögren syndrome	Phase 3 active, not yet recruiting
		Rheumatoid arthritis	Phase 3 active, not recruiting

(*Continued*)

Table 1 (*Continued*)

Drug	Target-based actions	Therapeutic indications	Status
RTX/Beli combo	Chimeric anti-CD20 mAb and anti-BAFF mAb	SLE/lupus nephritis	Phase 3 completed/Phase 3 active
		PR3 ANCA vasculitis	Phase 2 active, not recruiting
		Sjögren syndrome	Phase 2 complete
		Diffuse cutaneous systemic sclerosis	Phase 2 active
Rozibafusp alfa	Bispecific anti-BAFF and anti-ICOSL mAb	SLE	Phase 2 active, not recruiting
		Rheumatoid arthritis	Phase 1 complete
Mosunetuzumab	Bispecific anti-CD20 and anti-CD3 mAb	SLE	Phase 1 active
Epratuzumab	CD22	SLE	Phase 3 complete. Did not meet primary end point
4SCAR T cells	CD19, BCMA, CD138, and BAFF-R	Autoimmune diseases	Phase 1/2 active
CAR T cells	CD19/BCMA	POEMS syndrome, amyloidosis, autoimmune hemolytic anemia, vasculitis	Early phase 1 active
		Immune nephritis, lupus nephritis, autoimmune disease	Early phase 1 active
		Refractory scleroderma	Early phase 1 active
		Refractory Sjögren syndrome	Early phase 1 active
		Refractory SLE	Early phase 1 active
		Refractory SLE	Phase 1 active
CAR T cells	CD19	Refractory SLE	Phase 1, not yet recruiting
		SLE	Phase 1 active
		SLE/lupus nephritis	Phase 1/2 active
		Myasthenia gravis	Phase 1 active
CAR T	BCMA	Autoimmune diseases, autoimmune diseases of the nervous system, NMOSD, myasthenia gravis, CIDP, immune-mediated necrotizing myopathy	Early phase 1 active
		Myasthenia gravis	Phase 2 active
DSG3-CAART cells	Anti-DSG3 BCR	Mucosal dominant pemphigus vulgaris	Phase 1 active
MuSK-CAART cells	Anti-MuSK BCR	MuSK myasthenia gravis	Phase 1 active

Abbreviations: 4SCAR, fourth-generation-specific chimeric antigen receptor; ANCA, antineutrophil cytoplasmic antibody; BAFF, B cell–activating factor of the tumor necrosis factor family; BCMA, B cell maturation antigen; BCR, B cell receptor; CAART, chimeric autoantibody receptor T; CIDP, chronic inflammatory demyelinating polyneuropathy; DSG3, desmoglein 3; FDA, US Food and Drug Administration; GPA, granulomatous polyangiitis; mAb, monoclonal antibody; ILD, interstitial lung disease; MPA, microscopic polyangitis; MS, multiple sclerosis; MuSK, muscle-specific tyrosine kinase; NMOSD, neuromyelitis optica spectrum disorder; SC, subcutaneous form; SLE, systemic lupus erythematosus.

to alternative targeting approaches such as proteasome inhibition (13, 14). Proteasome inhibition alone does not effectively target B cell precursors (15) (**Figure 1**).

CONVENTIONAL B CELL THERAPIES IN RHEUMATOLOGIC DISEASE

Systemic Lupus Erythematosus

Given the strong rationale for B cell roles in SLE via both antibody-mediated and antibody-independent functions (16, 17), SLE was among the first autoimmune diseases to be studied with

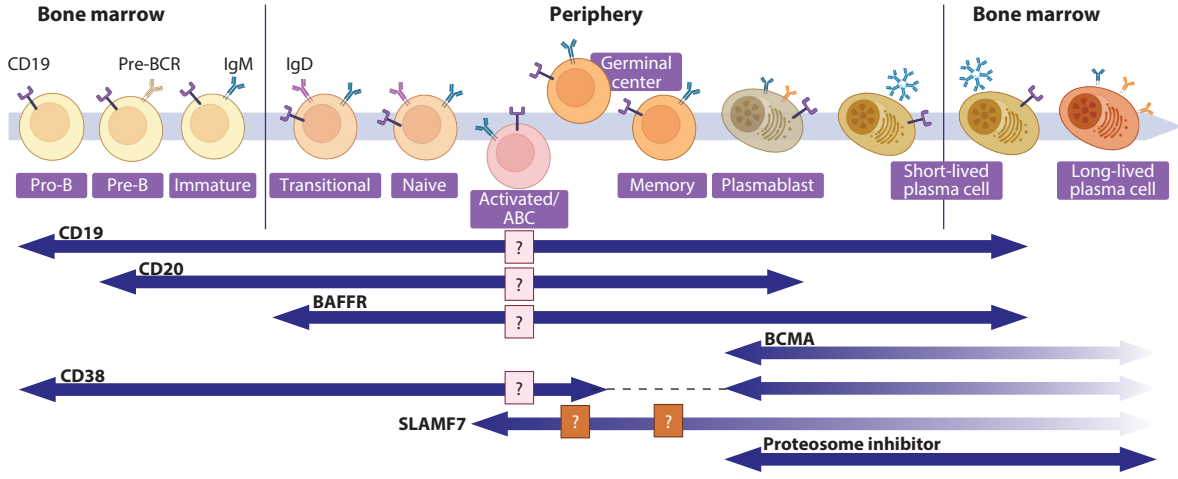


Figure 1

B cell developmental pathways and therapeutic targets. B cells progress through defined developmental stages and activation pathways, with changes in surface marker expression that dictate susceptibility to various targeting strategies. The earliest B lineage cells developing in the bone marrow express first CD19 (pro-B cell) and later CD20 (pre-B cell). Successful light chain recombination characterizes progression to the immature stage, followed by the transitional and mature naive B cell stage. B cells in this preimmune repertoire are theoretically susceptible to depletion with anti-CD20 and anti-CD19 monoclonal antibodies. Transitional and naive B cells are particularly dependent on BAFF for survival and are effectively depleted with BAFF-blocking antibodies. The human mature B cell compartment consists of diverse cell populations including naive and memory cell subsets. Naive follicular B cells that are successfully activated by antigen and T cell–derived signals in spleen or lymph node can give rise to germinal centers, crucial for class switch recombination and somatic hypermutation, which in turn are responsible for the acquisition of different immunoglobulin isotypes, increased antigen affinity, and long-lived memory B cell and PC generation. Atypical memory populations may arise in extrafollicular reactions as age-associated B cells that also expand in autoimmunity. Activated memory, germinal center, and age-associated B cells may have some resistance to BCDT (indicated with a *question mark*). Once B cells begin to differentiate to PCs they downregulate first CD20 and then CD19. Thus, most mature PCs are not directly susceptible to anti-CD20 treatment, although if B cell precursors are effectively depleted, short-lived PCs should eventually die. Some PCs do express CD19, including a likely short-lived subset in the bone marrow. B cell precursors, germinal center cells, and PCs also express high levels of CD38. Thus, antibodies against CD38 would target these populations, though CD38 is not specific to the B cell compartment. Factors in the bone marrow niche that support long-lived PC survival include the BAFF-related cytokine, APRIL, which binds to BCMA and supports memory and PC survival. Long-lived PCs also upregulate autophagy pathways and the unfolded protein response, making them susceptible to alternative targeting approaches such as proteasome inhibition. Proteasome inhibition alone does not effectively target B cell precursors. SLAMF7 is another interesting molecule that is upregulated upon PC differentiation and has been targeted in multiple myeloma. Abbreviations: ABC, age-associated B cell; BAFFR, B cell–activating factor of the tumor necrosis factor family receptor; BCMA, B cell maturation antigen; BCR, B cell receptor; BCDT, B cell depletion therapy; PC, plasma cell; SLAMF7, signaling lymphocytic activation molecule family 7. Figure adapted from images created with BioRender.com.

B cell–depletion approaches. The largest clinical experience has been with anti-CD20 B cell depletion with rituximab. CD20 is specifically expressed on immature, naive, memory, and GC cells and the more recently elucidated, alternatively activated ABCs (7), but not on early pre-B cells or plasma cells (18, 19). Initial evidence for the potential benefit of B cell depletion in SLE was supported by the original dose-escalation trials of rituximab performed by our own group at the University of Rochester as well as from several open-label series (20–24). Despite considerable enthusiasm for rituximab in SLE based on this open-label experience, two placebo-controlled trials in nonrenal lupus (EXPLORER) and renal lupus (LUNAR) failed to meet primary end points (25, 26). The reasons for this failure are complex and include early challenges with clinical trial design and outcome assessment in SLE (27).

More mechanistic explanations are important to consider as we try to optimize B cell–targeted therapy in lupus. Recent single-cell analysis of the kidney in 24 lupus nephritis patients from

the Accelerating Medicines Partnership (AMP) phase 1 study revealed heterogeneity in B cell infiltration (28), leading to the speculation that some subsets of lupus may be more B cell dependent. Marcus Clark's group examined lupus nephritis biopsies by highly multiplexed confocal microscopy and defined two patient subsets, a T cell– and a B cell–enriched subset. Interestingly, high B cell densities were associated with better outcomes in SLE, though response to BCDT was not specifically assessed (29). Even with largely B cell–dependent disease, response to B cell–targeted therapy may vary with the depth of depletion achieved. Elegant studies in murine models have demonstrated that different B cell subsets may be more dependent on certain mechanisms of depletion than others because of tissue microenvironment effects (30, 31). These considerations translate to human studies in that the kinetics of B cell depletion in tissues is slower than that in peripheral blood, and certain tissue-bound subsets in spleen, lymph nodes, and tertiary lymphoid tissues may be incompletely and variably depleted (32–35). This is particularly relevant for human autoimmune diseases where complete depletion of autoreactive B cell clones is likely critical for full therapeutic potential. Failure to deplete in these tissue sites may lead to nonresponse or early relapse (34) and could be particularly problematic in SLE where B cell survival factors are high (36) and antidrug antibodies develop with greater frequency (37). In support of the importance of thorough B cell depletion, we have reported that long-term clinical responses in SLE are associated with a paucity of memory B cells at reconstitution and a normalization of autoantibodies (38). Additionally, a post hoc analysis of the LUNAR study reported substantial variability even in peripheral blood B cell depletion in patients with lupus nephritis. Notably, more rapid, complete, and durable depletion was associated with complete renal responses (39). In sum, these observations raise the possibility that more thorough B cell depletion, possibly with alternative dosing strategies, other B cell–depleting agents (such as CAR T cells or bispecifics), or combinations of rituximab and belimumab, could improve outcomes.

Obinutuzumab is a humanized type II monoclonal anti-CD20 antibody that exhibits more effective B cell depletion than rituximab (40, 41). In a randomized, placebo-controlled, phase 2 trial in lupus nephritis (NOBILITY), it was superior to placebo for the achievement of complete and overall renal responses at week 52 when added to mycophenolate and corticosteroids (42). It also may have a role in nonrenal SLE and in patients with secondary nonresponse to rituximab (43). Phase 3 trials in renal (REGENCY) and nonrenal (ALLEGORY) SLE are underway (**Table 1**).

Another approach to enhance B cell depletion is to combine anti-CD20 with BAFF blockade. This theoretically may promote a more favorable B cell reconstitution and resetting of the immune system. BAFF is an important B cell activation and survival cytokine. BAFF overexpression promotes lupus-like disease in murine models, and a subset of human lupus patients have elevated serum BAFF (reviewed in 44). Indeed, anti-BAFF (belimumab) therapy alone has had success in the treatment of SLE in large clinical trials (45, 46) and was approved for nonrenal lupus in 2011 and recently in 2020 for renal disease by the FDA. Three separate trials have examined the impact of rituximab followed by belimumab therapy and had mixed results. The BEAT-Lupus (Belimumab After B Cell Depletion Therapy in Patients with Systemic LUPUS Erythematosus) study asked whether combination therapy might improve proper censoring of newly emerging autoreactive B cells and did find lower anti-DNA levels and fewer flares (47).

Rheumatoid Arthritis

RA is a systemic autoimmune disease characterized by joint inflammation, bone and cartilage damage, and the variable presence of autoantibodies [rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs)]. Because of the role of autoantibodies, RA was one of the early

autoimmune diseases treated with rituximab. Since the FDA approved it in 1997, rituximab has become a mainstay of therapy, typically after failure of traditional disease-modifying agents and TNF antagonists. However, not all patients respond. An outstanding question in the field is which subsets of patients benefit from rituximab. Seropositivity has clearly been associated with better responses to rituximab (48), though interestingly, clinical responses do not clearly relate to decreases in autoantibody titers (49). The latter supports autoantibody-independent roles for B cells in the disease. As with SLE, a multitude of studies highlight the relationship between depth of depletion and clinical response (50). For example, our group has observed residual memory B cells after rituximab therapy with remaining cells undergoing homeostatic proliferation (51). There are also reports of residual B cells in the synovium after rituximab despite complete peripheral blood B cell depletion (52), which may contribute to nonresponse or early relapse.

There has been growing interest in synovial histology to guide precision medicine approaches. Indeed, RA patients display substantial heterogeneity in synovial histology with variable infiltration of inflammatory cells and B cells, suggesting there are subsets of disease. A recent study reported the cellular and molecular analysis of synovial biopsies in 144 treatment-naive RA patients. Remarkably, a lymphoid/B cell–rich synovial pathotype was associated with autoantibody positivity, elevation of osteoclast-targeting genes, and predicted radiographic joint damage progression at 12 months (53). This suggests that B cells in the synovium may propagate tertiary lymphoid tissue formation that can support local production of antibody-secreting B cells and potentially play an antibody-independent role such as production of proinflammatory and osteoclastogenic cytokines (54, 55). It is tempting to speculate that a B cell–rich synovial pathotype may be predictive of response to B cell–depletion therapy (56). A recent landmark study from Pitzalis and colleagues employed a biopsy-based, precision medicine, randomized clinical trial of rituximab versus tocilizumab in RA to address this very question (57, 58). Notably, patients with low synovial B cell molecular signatures had a lower response to rituximab.

ANCA-Associated Vasculitis

BCDT has transformed the treatment of ANCA (antineutrophil cytoplasmic antibody)-associated vasculitis (AAV). Approved by the FDA in 2011 for treating this condition, rituximab is remarkably efficacious. The majority of patients achieve remission by 6 months and over 95% achieve complete responses during maintenance therapy (59). It has even recently been reported to be effective in severe renal disease and diffuse alveolar hemorrhage (60). It is thus the preferred agent for remission induction and often a key therapy for remission maintenance (61). An interesting question is what distinguishes AAV immunologically from other autoimmune diseases such as SLE and RA with more variable responses to BCDT. One potential explanation is the differential contribution of long-lived and short-lived PCs to disease pathogenesis. In this model AAV and pemphigus are put forth as models for disease driven by short-lived PCs, whereas SLE and RA may have a mixed contribution, and Sjögren syndrome is a model for disease driven by long-lived PCs (62). In AAV, as well as RA and SLE, B cells may also effectively mediate indirect antibody-independent effects on the T cell compartment (63).

Relapses are common in AAV even after effective induction of remission with rituximab, suggesting that full tolerance has not been restored. Multiple high-quality studies (MAINRITSAN, RITAZAREM) have demonstrated the superiority of repeat-dose rituximab compared to disease-modifying antirheumatic drugs for maintenance of remission (64–66). Proteinase-3 antibody positivity at diagnosis, persistent ANCA positivity despite clinical remission, and early B cell repopulation have been identified as risk factors for relapse in individual studies (reviewed in 61 and 67). However, surprisingly, treatment individually tailored based on CD19 and ANCA biomarkers

was not superior to a fixed-schedule rituximab regimen in MAINRITSAN2 (68). Moreover, the optimal duration of maintenance treatment remains uncertain.

PEMPHIGUS VULGARIS

BCDT with rituximab and prednisone was approved by the FDA in 2018 for the treatment of moderate to severe pemphigus vulgaris, an autoimmune blistering disease caused by autoantibodies to desmoglein adhesion proteins. The pathogenicity of autoantibodies in pemphigus has been established through multiple lines of evidence indicating the necessity and sufficiency of antidesmoglein antibodies for induction of typical pemphigus blisters in various animal and human skin models, as well as the occurrence of neonatal pemphigus due to passive transfer of IgG autoantibodies from a serologically positive mother to her fetus (reviewed in 69 and 70).

Data from the pivotal Ritux 3 study (71, 72) indicate that BCDT with first-line rituximab plus maintenance rituximab infusions and short-term prednisone therapy is superior to high-dose prednisone alone, resulting in a 90% rate of complete remission off steroids compared to 28% in the high-dose prednisone group, along with fewer relapses and corticosteroid-related serious adverse events. The PEMPHIX study (73) demonstrated the superiority of BCDT with rituximab (1,000 mg on days 1, 15, 168, and 182) and prednisone to mycophenolate mofetil and prednisone in achieving complete remission off steroids at week 52 (40% versus 10%), although more serious adverse events occurred in the rituximab-treated group (22% versus 15%), with 9% of rituximab-treated subjects experiencing serious infectious adverse events during the 52-week follow-up period.

Disease relapse in pemphigus is attributed to incomplete B cell depletion, based on longitudinal B cell repertoire and CDR3 spectratype profiling data indicating the recurrence of identical clones or clonal families found in active disease (74, 75). These findings have led to the rationale for seeking strategies for deeper B cell depletion for pemphigus treatment (76). Retrospective analysis indicates that patients receiving the lymphoma dose regimen (375 mg/m^2 weekly $\times$ 4) were 2.7 times more likely than those receiving the pemphigus vulgaris regimen (1,000 mg on days 1 and 15) to achieve complete remission off steroids. Similarly, other studies examining low-dose or comparing multiple infusion regimens indicate that time to remission and/or incidence of relapse may be more favorable with higher-dose regimens (76, 77).

EVOLUTION OF ANTI–B CELL THERAPY IN AUTOIMMUNE NEUROLOGICAL DISEASES

The greatest diversity of B cell–depletion approaches has emerged in research on MS and a wide array of other predominantly autoantibody-mediated neurological diseases. In MS, the largest clinical experience has been with anti-CD20 B cell depletion with rituximab, though there are now several FDA-approved, second-generation anti-CD20 monoclonal antibodies that are humanized in an effort to reduce immunogenicity, including ocrelizumab, ofatumumab, and ublituximab. Some of these have increased binding affinity to the Fc receptor on B cells and increased complement-dependent cytotoxicity and/or antibody-dependent cellular cytotoxicity and have been shown to be more potent than rituximab in vitro (78), though not necessarily confirmed to be more potent in vivo (79) (**Table 1**). As recently reviewed, BCDT appears to be particularly effective for relapsing-remitting MS where peripheral proinflammatory leukocytes may breach the blood-brain barrier in waves and promote central nervous system demyelination (80). However, the efficacy of B cell depletion in MS does not appear to be related to a reduction in cerebrospinal fluid (CSF) antibody levels, again suggesting the importance of antibody-independent B cell functions. These functions include antigen presentation and

cytokine production. A recent study of MS patients demonstrated that memory B cells drive proliferation of self-reactive $CD4^+$ T cells. These T cells recognize antigen presented by B cells expressed in brain lesions after homing to the central nervous system (81). Another study in experimental autoimmune encephalomyelitis (EAE) found that antigen-experienced B cells persist in secondary lymphoid tissue after B cell depletion and are efficient antigen-presenting cells for myelin-specific T cells, in contrast to transitional and naive B cells (82). Granulocyte-macrophage colony-stimulating factor (GM-CSF)-producing memory B cells are more frequent in MS patients than healthy controls and promote proinflammatory myeloid responses (83). After BCDT, GM-CSF-producing memory B cells decrease, whereas IL-10-producing regulatory B cells are predominant upon B cell repopulation, which has led to a mechanistic model in which the relative proportion of pro- and anti-inflammatory B cell subsets determines disease activity in MS.

In addition to MS, B cell–targeted therapy has a role in other autoimmune central and peripheral neurologic diseases, including neuromyelitis optica (NMO), autoimmune encephalitis, chronic autoimmune polyneuropathies, stiff-person syndrome, myasthenia gravis, and inflammatory myopathies (reviewed in 84). The role of B cells and in turn BCDT in many of these diseases is more easily understood than in MS because of the presence of clearly pathogenic autoantibodies, e.g., aquaporin 4 in NMO, NMDA receptors in some autoimmune encephalitides, and acetylcholine receptor or muscle-specific tyrosine kinase (MuSK) in myasthenia gravis. The beneficial effects of BCDT in these diseases are predicated on thorough elimination of autoreactive cells, including memory B cells and presumably short-lived PCs. A recent study in myasthenia gravis utilized single-cell transcriptional and B cell receptor profiling on longitudinal blood samples from relapsing rituximab-treated patients and found persistent memory and antibody-secreting cells, a subset of which were specific for the MuSK autoantigen (85). This could explain post-rituximab relapses and, as in SLE (38), highlights the importance of thorough B cell depletion and elimination of autoreactive PCs for durable disease remission.

DIVERSE ROLES FOR B CELLS IN AUTOIMMUNITY AND FURTHER MECHANISTIC INSIGHTS

The diversity of B cell functions including antibody-dependent and -independent effects provides a potential explanation for the efficacy of B cell–targeted therapy in such a wide array of autoimmune diseases (**Figure 2**). Functional versatility of B cells enables them to play either protective or pathogenic roles in autoimmunity (86, 87). B cells may be deleterious through the production of pathogenic autoantibodies, activation of autoreactive T cells, production of proinflammatory cytokines, and organization of ectopic lymphoid tissue. Examples of pathogenic cytokines produced by B cells include GM-CSF, LTα, TNF, and IL-6. ABCs are an interesting B cell population with multiple pathogenic functions in autoimmunity. These B cells express T-bet and were first described in aging and chronically infected mice (88). Subsequent studies highlighted expansions of ABCs in autoimmunity, most notably in mouse and human SLE (7, 9, 89). Although the function of ABCs in autoimmunity is incompletely defined, they have been proposed to serve as antigen-presenting cells (90) and to be a source of class-switched autoantibodies in lupus (88). They may also have proinflammatory cytokine–producing functions (91, 92) that contribute to disease.

Conversely, B cells may prevent or suppress established autoimmunity through anti-inflammatory cytokines such as IL-10 and TGF-β and the expansion of regulatory T cells and/or inhibition of effector T cells (86, 87, 93–95). A regulatory role for B cells has been ascribed to various B cell subsets including transitional B cells, $CD27^+CD24^{hi}$ cells, and $CD1d^+$ cells. Recently, IL-10-expressing regulatory B cells have even been described in the PC compartment, including IgA^+ PCs that can suppress EAE (96), raising the new concept of a regulatory PC. There is also

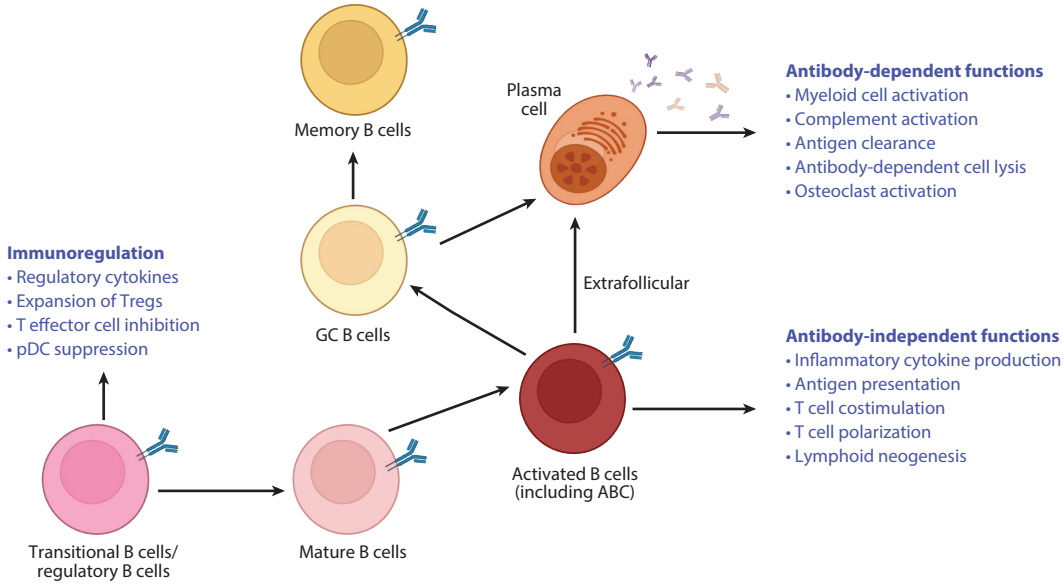


Figure 2

B cell functions in autoimmune disease. B cells can participate in immune reactions via secretion of antibodies (antibody-dependent functions) and antibody-independent functions. Antibody-independent B cell functions can be either proinflammatory or anti-inflammatory depending on the types of cytokines produced and the cells affected. For simplicity, activated B cells are shown as promoting immunity. In addition to cytokine secretion and antigen presentation, ABCs have also been described as poised for plasma cell differentiation and enriched in auto-specificities in autoimmune disease. A variety of anti-inflammatory or regulatory functions for B cells have also been described. Transitional B cells are one population that has been ascribed with a regulatory function, though other B cell subsets can also produce anti-inflammatory cytokines. Abbreviations: ABC, age-associated B cell; GC, germinal center; pDC, plasmacytoid dendritic cell; Treg, regulatory T cell. Figure adapted from images created with BioRender.com.

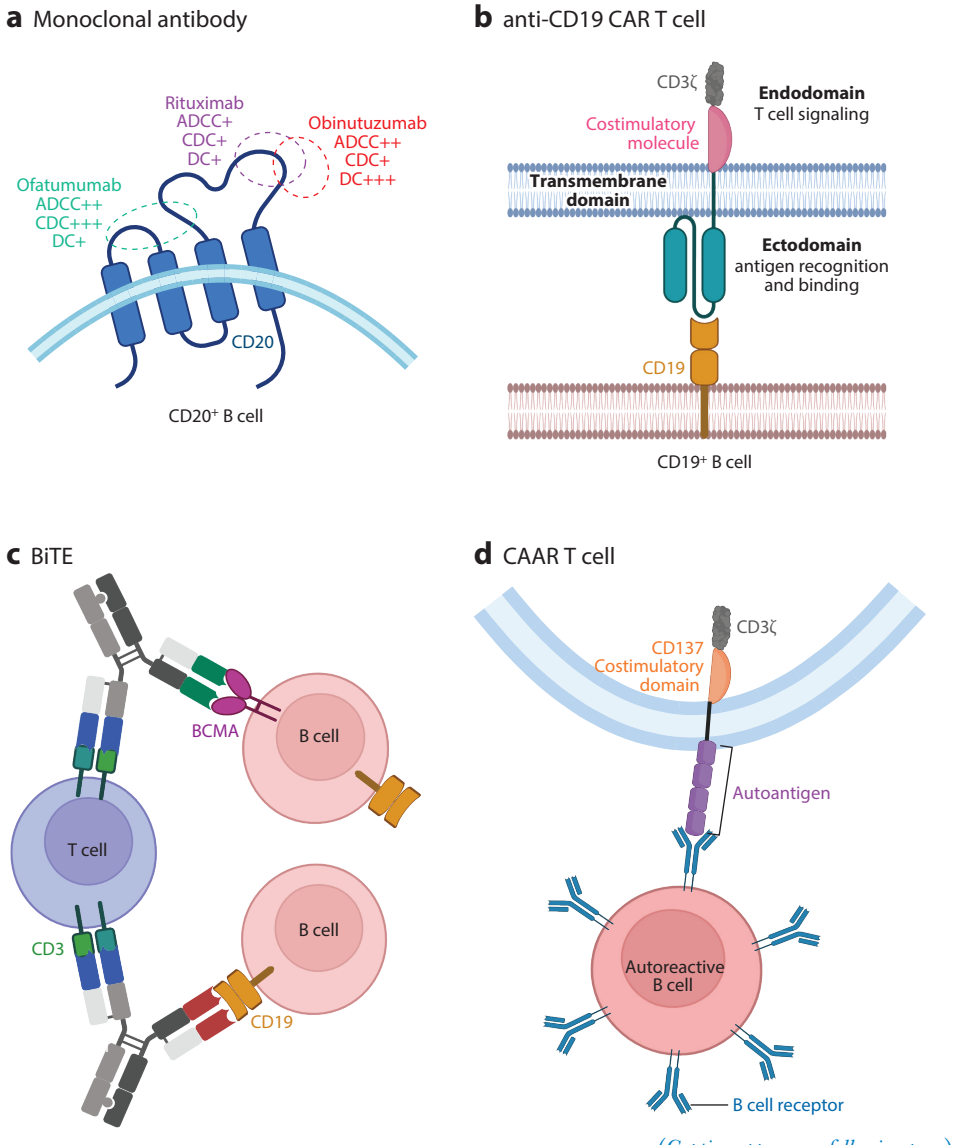
evidence of B cell plasticity with acquisition of regulatory function depending on microenvironmental signals. There are several recent interesting reports of gut microbiota and short-chain fatty acids controlling regulatory B cell development and function (97).

Although regulatory B cells were initially identified as IL-10 producers, recent studies have highlighted the production of other anti-inflammatory cytokines (TGF-β, IL-35) and a role for surface molecules (PD-L1, Tim-1) (reviewed in 98). Regulatory B cell defects, either in numbers or function, have been described in multiple autoimmune diseases (99, 100), as has the emergence or functional normalization of regulatory B cell populations after B cell depletion (101, 102). A regulatory feedback loop between plasmacytoid dendritic cells (pDCs) and B cells was reported, with pDCs secreting IFN-α, enhancing the production of IL-10 by B cells, which in turn suppresses IFN-α production by pDCs. This feedback loop was defective in SLE and normalized after BCDT and reconstitution in some patients (102). In SLE, we and others have observed that a higher fraction of memory B cells and lower fraction of immature transitional B cells during reconstitution correlate with earlier relapse of disease (38, 103, 104), supporting the concept that the outcome of B cell depletion depends on the balance between protective and pathogenic B cell populations (51). An outstanding question in the field is what factors determine the balance between these functions after B cell depletion and reconstitution. We hypothesize that the depth of B cell depletion achieved is one critical factor, as is the cytokine milieu in the bone marrow and periphery (105, 106).

NOVEL EMERGING B CELL–DIRECTED THERAPIES

Chimeric Antigen Receptor T Cells

CAR T cells are one of the most exciting developments in clinical medicine (**Figure 3**). After much work to understand basic immunologic principles, we now have the ability to genetically engineer human T cells and use them to target specific cell populations. Currently, there are six FDA-approved CAR T cell therapies in oncology (107) (**Table 2**). Four therapies for lymphoma and leukemia target CD19 on B cells, and two multiple myeloma (MM) therapies target BCMA. Complete responses are seen in up to 80% of patients with refractory disease (108). Many long-term survivors are said to be cured. There are numerous clinical trials with even newer agents



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Comparison of conventional monoclonal antibody B cell–depletion approaches, CAR T or CAAR T cell therapy, and bispecific antibodies. (*a*) Monoclonal antibodies against CD20 target the extracellular domain of this antigen on B cells and mediate cytotoxicity by ADCC and/or CDC. (*b*) CAR T cell therapies are engineered to express CARs on the T cell surface that recognize and bind to specific antigens, in this case CD19 on B cells. Second-generation CARs include the intracellular domain from either CD28 or CD137 (costimulatory molecule in schematic) between the transmembrane domain and the CD3ζ domain. Once CAR T cells are generated from a patient's T cells, they are expanded and transfused back, where they expand further in vivo and act as effector cells to direct T cell cytotoxicity to CD19-expressing B cells and PCs. (*c*) BiTEs are bispecific T cell engagers cross-linking CD3 on T cells and antigens on other cells, in this case CD19 or BCMA on B cells and PCs. These are approved for some malignancies and have the potential for deep depletion of B cells and/or PCs without having to create autologous CAR T cells for each patient or lymphodeplete prior to treatment. A challenge with this approach is the efficient production of an antibody with two different specificities. There are no published reports yet of this approach in autoimmunity. (*d*) CAAR T cells are a variation on CAR T cells, where the targeted moiety is the autoantigen-specific B cell receptor to specifically deplete autoimmune B cells. Abbreviations: ADCC, antibody-dependent cytotoxicity; BCMA, B cell maturation antigen; BiTE, bispecific T cell engager; CAR, chimeric antibody receptor; CAAR, chimeric autoantibody receptor; CDC, complement-dependent cytotoxicity; DC, dendritic cytotoxicity; PC, plasma cell. Figure adapted from images created with BioRender.com.

designed to improve efficacy and safety. From the point of view of treating autoimmunity, the potential for deep depletion of B cells and/or PCs suggests that CAR T cell therapy may be effective for the large number of autoimmune diseases where B cells and/or PCs play a critical role.

The current vector systems for generation of CAR T cells use HIV-based lentiviral or retroviral sequences (109, 110). The advantage of lentivirus-based constructs is their ability to integrate into DNA even in nonreplicating cells. In the clinically approved third-generation vector systems, the sequences needed for viral packaging (gag and pol), splicing and export of viral transcripts from the nucleus (rev), and viral entry into cells (env) are provided as separate plasmids as a safety measure to guard against production of replication-competent virus. Another important safety measure is deletion of the U3 region of the 3′ long terminal repeat, which creates a self-inactivating lentivirus and disrupts the strong viral promoter that may have contributed to oncogenesis with early retroviral gene therapy approaches.

First-generation CAR constructs had an extracellular targeting domain most often consisting of a single-chain variable region fragment to confer antibody-level specificity, a membrane-proximal hinge or spacer region, a transmembrane domain, and a cytoplasmic signaling domain

Table 2 FDA-approved CAR T cells and bispecifics in oncology

	Drug	Target	Date approved
CAR T	Tisagenlecleucel	CD19	2017
	Axicabtagene ciloleucel	CD19	2017
	Brexucabtagene autoleucel	CD19	2020
	Lisocabtagene maraleucel	CD19	2021
	Idecabtagene vicleucel	BCMA	2021
	Ciltacabtagene autoleucel	BCMA	2022
BiTEs	Blinatumomab	CD3/CD19	2017
	Mosunetuzumab	CD3/CD20	2022
	Teclistamab	CD3/BCMA	2022

Abbreviations: BCMA, B cell maturation antigen; BiTE, bispecific B cell engager; CAR, chimeric antigen receptor; FDA, US Food and Drug Administration.

such as the ζ chain from the T cell antigen receptor (CD3ζ). These first-generation CAR T cells, with a few notable exceptions (111), did not survive long in vivo, due to relatively low production of IL-2, and had limited clinical efficacy in only a small proportion of treated patients (112–114). Second-generation CARs additionally have the intracellular domain from either CD28 or CD137 between the transmembrane domain and the CD3ζ domain. Second-generation CAR constructs proliferate more vigorously and have longer in vivo survival and greater clinical efficacy. Patients are typically pretreated with cyclophosphamide and fludarabine prior to CAR T cell infusion to induce lymphodepletion, which is thought to promote CAR T cell engraftment and proliferation by eliminating homeostatic cytokine sinks and depleting host regulatory T cells that might suppress infused T cell effector function (115, 116). This preconditioning regimen leads to marked peripheral blood cytopenia that generally resolves within two weeks. All currently FDA-approved CAR T cell therapies use second-generation CAR constructs.

The remarkable efficacy of CAR T cells for refractory B cell and PC malignancies has been associated with significant toxicities. Chief among these toxicities are cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Manifestations of mild to moderate CRS include fever, headache, fatigue, myalgia, arthralgia, rash, and diarrhea. Hypotension, vascular leak, and multi-organ failure can be seen with severe CRS. ICANS is associated with neurological dysfunction ranging from inattention and disorientation to coma. Other rare neurological toxicities may also include transverse myelitis, acute disseminated encephalomyelopathy, and Guillain-Barré syndrome. In addition, BCMA-targeted CAR T cell therapy has been associated with a delayed-movement disorder. Severe (grade 3 or higher) CRS is estimated to occur in 4–77% of cases, and severe ICANS occurs in 9–40% (108). Rates vary with CAR design, disease burden, and infused cell dose. CRS usually occurs within 2–3 days of CAR T cell infusion. ICANS usually occurs a bit later, although delayed-onset CRS weeks after infusion has also been observed. Severe CRS is a risk factor for ICANS, but ICANS can occur in isolation. CRS and ICANS were associated with 5.4% mortality in early second-generation CAR T cell clinical trials (117), but with early steroids and/or tocilizumab treatment, recovery can be rapid and long-term outcomes very good. Because of these complications, the FDA requires a Risk Evaluation and Mitigation Strategy (REMS) program for each CAR T cell therapy. Administering facilities must be enrolled in the REMS program and ensure that providers are trained in the management of CRS and ICANS. In addition to CRS and ICANS, a potential consequence of long-term B cell or PC depletion by CAR T cell therapy is hypogammaglobulinemia (<500 mg/dL), which has been estimated to occur in 18–74% of patients, with infections requiring hospitalization occurring in about 10–20% of patients (118).

An increasing number of published studies have used CAR T cells to treat autoimmune disease, which has caused a great deal of excitement (119). This excitement should be tempered by the relatively small number of patients reported and the potential for bias in publishing positive results among cancer patients with concurrent autoimmune conditions. At the time of writing, only six individual cases and two small case series of CAR T cell therapy of autoimmune conditions have been published (120–127), comprising a few dozen patients with NMO, SLE, antiphospholipid syndrome (APLS), antisynthetase syndrome, and systemic sclerosis.

As an initial proof of principle, two patients that were treated for diffuse large B cell lymphoma had secondary beneficial effects on their autoimmunity. The first patient had SLE and was treated with dual-specificity CAR T cells that recognized both CD19 and BCMA (124). The patient had a good clinical response, and with the dual anti-CD19 and anti-BCMA specificity also had a marked drop in all immunoglobulins. The second patient had APLS and was treated with anti-CD19 CAR T cells, with subsequent disappearance of high-titer anticardiolipin IgM. The interpretation of these results was complicated by prior treatment with chemotherapy that included rituximab.

Georg Schett's group in Erlangen, Germany, has reported on patients with SLE, antisynthetase syndrome, and systemic sclerosis treated with anti-CD19 CAR T cells (120–123). The CAR transgene consisted of the anti-CD19 scFV FMC63, the hinge region of CD8a, TNFSFR19 transmembrane domain, 4–1BB costimulatory domain, and CD3ζ signaling domain (128, 129). $CD3^+$ lymphocytes were enriched from apheresis, transduced with lentivirus comprising the CAR transgene, and expanded in vitro. In a case series, five SLE patients were treated with a cyclophosphamide and fludarabine preconditioning regimen before anti-CD19 CAR T cell transfer (121). All five achieved complete remission of disease activity off systemic immunosuppressive medications. There were fevers in three patients (grade 1 CRS) treated with an antipyretic, and one patient received a single dose of tocilizumab. There were no manifestations of ICANS. SLEDAI-2K disease activity scores ranged from 8 to 16 (mean 12) at baseline compared to 0 in all five patients by 3–4 months after CAR T cell infusion. There were no relapses of SLE during follow-up off lupus medications (5–17 months, mean 9.8 months). By 3 months, anti-dsDNA antibody titer was below the upper limit of normal and C3 had normalized. Patients exhibited expansion of CAR T cells after infusion, with CAR T cells constituting 11.5–58.1% of CD3 T cells by day 9. B cells were undetectable by day 2 but began to reconstitute by day 63 to day 142 (mean 110). Upon reconstitution, naive B cells ($CD21^+CD27^-$) were markedly expanded while memory B cells ($CD21^+CD27^-$), activated memory B cells ($CD11c^+CD21^{lo}$), and plasmablasts ($CD20^-CD38^+$) were very few or absent. Recovery of transitional B cells, which may behave as B regulatory cells, was not analyzed in this report, but studies with CD19-targeting CAR T cells in malignancies have reported robust expansion of this cell population (130). No infections were reported during follow-up, and antibodies to vaccine antigens were mostly preserved, especially for long-lived responses to childhood viral vaccines (measles, rubella, mumps, varicella). While failure to deplete protective antibody titers is a good outcome from a safety perspective, it will be of interest to determine whether patients with high titers of more long-lived autoantibodies such as anti-RNP/Sm, anti-SSA/SSB, or anti–β2 glycoprotein I may also achieve disease remission with CD19-directed CAR T cell therapy, or whether a BCMA- or other PC-directed CAR T cell therapy would be more desirable for these conditions.

Case reports of patients with refractory antisynthetase syndrome with myositis and pneumonitis and severe refractory systemic sclerosis were also recently reported (120, 123, 131). The patient with anti-Jo-1 myositis had an excellent clinical response, with resolution of muscle inflammation by serum creatinine kinase measurements and thigh muscle MRI, near normalization of strength, improved respiratory symptoms, and regression of alveolitis on chest CT (computed tomography). Anti-Jo-1 antibody levels were 331 U/L initially and 5 U/L after treatment (normal cutoff was 25 U/L). Fever was present for three days and was treated with tocilizumab. IgG was low before CAR T cell therapy and decreased slightly, resulting in initiation of low-dose IVIG (10 g per month). The patient with RNA polymerase III diffuse systemic sclerosis also tolerated treatment well, with only a brief fever, and improved clinically in terms of skin involvement, joint tenderness, tendon friction rub, and Raynaud syndrome. In addition, ANA (antinuclear antibody) and anti–RNA polymerase antibodies turned negative, and both cardiac PET scan and lung diffusion capacity improved.

A phase 1 trial has been published using anti-BCMA CAR T cells to treat patients with NMO (126). Twelve patients with NMO were treated with a cyclophosphamide and fludarabine preconditioning regimen, followed by infusion of CAR T cells. All infused patients had grade 3 or higher hematologic adverse reactions presumably due to preconditioning. All patients also had grade 1 or 2 cytokine release syndrome; none had grade 3 or higher CRS. Infections occurred in 58% of patients, and serious adverse reactions occurred in 5 patients, including three cytomegalovirus infections and 1 pneumonia. Hypogammaglobulinemia developed in 11 patients. Anti-AQP4 IgG

decreased in all patients and became seronegative by 3 and 12 months in 70% and 83% of patients, respectively. In general, patients did clinically well with discontinuation of other therapies, but 1 patient did flare after infusion with visual changes at 14 months. This patient also had increasing anti-AQP4 levels starting at 12 weeks. Two patients with concomitant Sjögren syndrome had a dramatic decrease in anti-SSA antibodies. Salivary flow improved in one of the patients with Sjögren syndrome. Joint symptoms improved in another patient with concomitant RA.

To mitigate infectious adverse events associated with anti-BCMA CAR T cell therapy of autoimmune disease, infusion of RNA-electroporated anti-BCMA CAR T cells, without preconditioning, was evaluated in a phase 1a/2b study for myasthenia gravis (132). Because the electroporated RNA dilutes out with each cell division, PC depletion is expected to be transient. The dose-escalation study had 14 participants; 7 received the maximum tolerated dose and completed study follow-up. Mean improvements in multiple measures of disease activity were observed after infusion, which exceeded the minimum clinically important difference. No dose-limiting toxicity, CRS, ICANS, or serious infections were observed. One participant experienced a possibly related serious adverse event from grade 3 urticaria (potentially attributable to immune reaction against the chimeric scFv), and some participants experienced headache ($N = 6$), nausea ($N = 5$), and/or fever ($N = 4$) that resolved within 24 h of infusion and were not associated with IL-6, IL-2, or TNF production. However, correlative assays did not demonstrate strong evidence of PC targeting after infusion, as soluble BCMA remained unchanged, total serum IgG decreased 18%, acetylcholine receptor antibody titers decreased 22%, and muscle-specific tyrosine kinase autoantibody titers were unchanged.

Many more patients with autoimmune disease have been treated with CAR T cells in ongoing clinical trials whose data are not yet publicly available (133–135) (see **Table 1** for a summary of some of these trials). A reassuring observation thus far is that toxicity due to CRS or ICANS appears to be less than in patients with malignancies, although risks might vary with different CAR designs. Unanswered questions include the role of preconditioning regimens in clinical efficacy and whether reduced dose cytotoxic therapy can achieve similar therapeutic effects. CAR T cell therapy has the potential for deep depletion of the cellular components of humoral autoimmunity, and it is tempting to speculate that such depletion results in a global reset of immune tolerance through reestablishing balance between proinflammatory and anti-inflammatory B cell subsets. Early expansion of transitional B cells, which have been reported to have regulatory properties, might theoretically restrain autoimmune T cells and help control recurrence of autoimmunity. Results from the many ongoing trials of CAR T cells in autoimmunity will be critical for establishing efficacy and safety.

Chimeric Autoantibody Receptor T Cells

As a precision approach to antibody-mediated disease, a novel approach for antigen-specific B cell depletion known as chimeric autoantibody receptor (CAAR) T cells has been evaluated in both preclinical studies and phase 1 clinical trials (136–138). Because the B cell receptor is a membrane-bound immunoglobulin identical in specificity to the autoantibody that an autoreactive B cell will secrete once activated, depletion of these autoimmune B cell populations should theoretically be possible by using the autoantigen as the extracellular targeting domain of the CAAR to direct T cell cytotoxicity (**Figure 3**).

Phase 1 dose-escalation studies of desmoglein 3 CAAR T cells (DSG3-CAART) in mucosal pemphigus vulgaris and muscle-specific tyrosine kinase CAAR T cells in MuSK myasthenia gravis are currently enrolling subjects (NCT04422912 and NCT05451212). Preliminary results from the DSG3-CAART study indicate that DSG3-CAART is well tolerated, with no dose-limiting toxicities. DSG3-CAART is associated with transient improvements in disease activity in a subset

of patients without a clear pattern of change in anti-DSG3 autoantibody levels. Dose-dependent persistence in the first 29 days after infusion was observed from 2×10^7 to 7.5×10^9 transduced cells without preconditioning, which reached a plateau at a dose of 2.5×10^9 transduced cells. Addition of intravenous immunoglobulin and cyclophosphamide preconditioning modestly impacted DSG3-CAART persistence and was associated with transient leukopenia (less than two weeks) and increased serum IL-15. Additional cohorts will be studied to evaluate combination cyclophosphamide and fludarabine preconditioning regimens on DSG3-CAART persistence, safety, and efficacy.

Bispecific Antibodies

Bispecific T cell engagers (BiTEs) (monoclonal antibodies cross-linking CD3 on T cells and targeting B cell or PC surface antigens) are another class of very promising therapeutic agents for cell depletion. Bispecific antibodies cross-linking CD3 on T cells with CD20, CD19, or BCMA have the potential for deep depletion of B cells and/or PCs without requiring autologous CAR T cells to be created for each patient (139, 140). Moreover, lymphodepletion is not required. Three T cell–redirecting bispecific antibodies that target B cells and/or PCs are FDA approved for treatment of refractory B cell malignancies (blinatumomab is anti-CD3/anti-CD19 and mosunetuzumab is anti-CD3/anti-CD20) and myeloma (teclistamab is anti-CD3/anti-BCMA) (**Table 2**), and many additional bispecific antibodies are in late-phase trials. The reported rates of complete response are good: 52% for blinatumomab in diffuse large B cell lymphoma, 60% for mosunetuzumab in follicular lymphoma, and 28% for teclistamab in MM. Though BiTEs targeting B cells and PCs could be a promising approach to treat autoimmune diseases, they have not yet been studied.

OTHER PLASMA CELL–TARGETING APPROACHES

Approaches to PC targeting have emerged from the MM field. The most established of these for autoimmunity is proteasome inhibition (141). Both bortezomib and carfilzomib are approved for the treatment of MM and have demonstrated efficacy in mouse models of lupus (14, 142). Importantly, for the former there is evidence of depletion of long-lived PCs (142). A study of 8 SLE patients treated with bortezomib demonstrated a significant reduction in autoantibodies, including a 50% depletion of $CD138^+$ PCs in the bone marrow of 1 patient (including putative long-lived $CD19^-$ PCs) but with a rapid repopulation of short-lived PCs and autoantibodies after treatment withdrawal. The authors speculate that proteasome inhibition may need to be combined with other targeted B cell therapies to impact precursor cells for sustained response (15). An immuno-proteasome inhibitor is currently in a phase 1b/2 clinical trial for SLE (NCT03393013). Other approaches to PC targeting that merit investigation in autoimmune disease include anti-CD38 (daratumumab, approved in 2015 for MM), the histone deacetylase inhibitor panobinostat (approved for MM combination therapy in 2015), and a novel monoclonal antibody targeting SLAMF7 (signaling lymphocytic activation molecule family 7) (elotuzumab, approved in 2018 for relapsed/refractory MM) (4). The latter is particularly interesting, as this pathway appears to be upregulated in both PCs and age/autoimmunity-associated B cells (7).

FUTURE PERSPECTIVES

B cell–directed therapies in autoimmunity have come a long way over the last two decades, now with FDA-approved agents in rheumatoid arthritis, ANCA-associated vasculitis, systemic lupus erythematosus, multiple sclerosis, neuromyelitis optica, and pemphigus vulgaris. Most approvals are for CD20-targeting antibodies, with one approval for an antibody targeting CD19 and another for an antibody targeting BAFF. However, the currently approved agents are not effective

in many patients. Anti-CD20 in combination with anti-BAFF therapy has been tested in SLE without notable improvement in disease outcomes. Combining anti-CD20 or anti-CD19 with TACI-Ig, which would block both BAFF and APRIL, might be more effective but so far has not been tested. Bispecific T cell engagers targeting B cells and PCs have already established themselves in cancer immunotherapy, and it would be of interest to determine whether they can induce durable remissions of autoimmune diseases. An alternative approach is to selectively deplete just the autoimmune B cells so that general depletion of B cells is avoided. Ongoing clinical trials will determine whether such strategies are effective in autoimmune diseases but will likely be limited to conditions where the autoantigen is well defined, such as mucosal pemphigus vulgaris and MuSK myasthenia gravis.

Ultimately, durable remission off systemic immunosuppressives is the ideal outcome of autoimmune disease therapy. Current BCDT treatment paradigms require repeated infusion regimens to maintain disease remission. Inadequate depletion of memory B cells by the approved agents targeting CD19 or CD20 is associated with a poor response and appears to be the major limitation of this approach. Depletion in tissue has been especially problematic. Additionally, understanding how to achieve immune system recovery without the reemergence of autoimmune disease will be a critical area for study going forward. The preliminary data with anti-CD19 CAR T cells in lupus, scleroderma, and myositis demonstrate that durable disease remission with this approach is possible when deep B cell depletion is achieved. How often clinically significant autoimmunity recurs after CAR T cell therapy, and whether favorable B cell repletion occurs in all autoimmune disease patients undergoing CAR T cell therapy, remains to be determined. In diseases where long-lived PCs, which are mostly CD19 negative, are producing clinically important autoantibodies, anti-BCMA CAR T cells may prove effective. Evaluation in more patients, longer-term follow-up, inclusion of controls, and confirmation by other groups are all needed to validate this approach. Additional therapies that have proven effective in malignancies are also being tested in refractory patients with a variety of severe autoimmune diseases. It will be interesting to see which diseases and disease manifestations respond well to such therapies and define the optimal timing of treatment to prevent organ damage and ensure the best long-term results.

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