HHS Public Access

Author manuscript

Curr Opin Immunol. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Curr Opin Immunol. 2019 December ; 61: 92–99. doi:10.1016/j.coi.2019.09.004.

B cell targeted therapies in autoimmune disease

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Abstract

Purpose of review: FDA approved B cell targeted therapy has expanded to a multitude of autoimmune diseases ranging from organ specific diseases, like pemphigus and multiple sclerosis, to systemic diseases such as ANCA associated vasculitis, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). In this review, we discuss the variability in response to FDA approved B cell targeted therapies with a focus on the diversity of human B cells and plasma cells, and will discuss several of the promising new B cell targeted therapies.

Recent findings: The pathogenic roles for B cells include autoantibody dependent and independent functions whose importance may vary across diseases or even in subsets of patients with the same disease. Recent data has further demonstrated the diversity of human B cell subsets that contribute to disease as well as novel pathways of B cell activation in autoimmune disease. The importance of eliminating autoreactive B cells and plasma cells will be discussed, as well as new approaches to do so.

Summary: The past several years has witnessed significant advances in our knowledge of human B cell subsets and function. This has created a nuanced picture of the diverse ways B cells contribute to autoimmunity and an ever-expanding armamentarium of B cell targeted therapies.

Keywords

B cells; plasma cells; rheumatoid arthritis; lupus; rituximab; proteasome inhibitors; CAR-T

Introduction

Although B cells have long been considered important as producers of antibodies, their antibody independent roles and utility as a major therapeutic target in autoimmune disease has become more prominently appreciated in recent years. In fact, when B cell depletion (BCD) was first being considered as a treatment for autoimmunity in the 1990's it was expected that beneficial effects would correlate with autoantibody reduction. Thus, the success of BCD in pemphigus and neuromyelitis optica where pathogenic autoantibodies are

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

clearly implicated is perhaps not surprising. However, the utility of BCD in such a wide range of diseases including rheumatoid arthritis (RA) and multiple sclerosis (MS) which have traditionally been considered at least in part T cell mediated was initially more surprising (summarized in Table 1). In turn, the variable efficacy in diseases with a strong, though perhaps not exclusive, B cell component including systemic lupus erythematosus (SLE) has been perplexing. These findings have created a paradigm shift in the field, highlighting the follow: 1) the importance of antibody independent B cell functions which include cytokine production and antigen presentation, amongst others and 2) the likely contribution of long-lived plasma cell populations to autoantibody production. In this review we discuss the relevant biological and pathogenic functions of B cells in autoimmunity with a focus on new mechanistic insights over the past year and new therapeutic approaches.

Approaches to B cell targeted therapy

The treatment approaches to target the B cell compartment can be broadly summarized as direct depletion typically with monoclonal antibodies (e.g. rituximab), indirect depletion via survival cytokine blockade (e.g. belimumab), co-stimulatory blockade [1], other approaches to inhibiting B cell activation (e.g. small molecular inhibitors of Btk) [2,3], and more direct plasma cell (PC) targeting [4]. The largest clinical experience has been with anti-CD20 B cell depletion with rituximab though there are now several 2nd generation anti-CD20 agents that are humanized in an effort to reduce immunogenicity including ocrelizumab, obinutuzumab, veltuzumab, and ofatumumab. Some of these second-generation anti-CD20 mAbs have increased binding affinity to the Fc receptor on B cells and increased complement-dependent cytotoxicity (CDC) and/or antibody-dependent cellular cytotoxicity (ADCC) and have been shown to be more potent than rituximab in vitro [5] but not necessarily confirmed in vivo. A number of second-generation anti-CD20s are either approved for limited disease indications or are under investigation (Table 1). Positive topline results were just reported for obinutuzumab in lupus nephritis in the Phase 2 NOBILITY trial. B cell depletion has become a mainstay of treatment of MS, with ocrelizumab approved for the treatment of both relapsing multiple sclerosis (RMS) and primary progressive multiple sclerosis (PPMS) by the FDA in March 2017, notably the first therapy specifically approved for PPMS [6]. Additionally, a humanized anti-CD19 (inebilizumab) was recently shown to reduce rates of attacks in neuromyelitis optica spectrum disorder (N-MOmentum trial) [7].

Variability in efficacy-why?

How can we understand the potent efficacy of B cell depletion therapy in ANCA associated vasculitis, the efficacy in a subset of RA and MS, and the more variable response in SLE? Critical factors to consider include disease and patient heterogeneity with respect to the central role of B cells in pathogenesis and degree of B cell depletion achieved, as well as the diversity of human B cell subsets and their contribution to disease.

Disease heterogeneity

It may be that some patients have B cell independent disease, B cell independent organ manifestations, and/or B cell dependence that varies over the course of disease. As an

example, RA patients can display substantial heterogeneity in synovial histology with variable infiltration of inflammatory cells, suggesting subsets of disease. A recent study reported the cellular and molecular analysis of synovial biopsies in 144 treatment naïve 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 [8]. It is tempting to speculate that a B cell rich synovial pathotype may be predictive of response to B cell depletion therapy, and ongoing studies should elucidate this critical question [9].

The importance of complete pathogenic B cell depletion after anti-CD20

Even with largely B cell dependent disease, response to B cell targeted therapy may vary with the depth of depletion achieved. Indeed, the failure to adequately deplete pathogenic B cells is thought to be an important predictor of incomplete response or early relapse after B cell depletion therapy. Thus, although anti-CD20 is usually effective in depleting B cells from peripheral blood, success in depleting B cells from other sites such as lymph nodes or tertiary lymphoid tissues may be highly variable. In RA, synovial B cells were decreased but not eliminated by rituximab therapy, and higher levels of clinical response correlated with more consistent synovial B cell depletion [10,11]. Similarly, a recent post-hoc analysis of the Lupus Nephritis Assessment with Rituximab (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 [12]. In MS, CNS-compartmentalized inflammation via activated astrocytes may also promote B cell survival and resistance to BCD [13]. Overall, these results raise the possibility that more thorough B cell depletion particularly of pathogenic B cells, possibly with alternative dosing strategies, other B cell depleting agents [14], or combinations of rituximab and belimumab [15], could improve outcomes.

Diversity of B cell functions in disease

It is also likely that the therapeutic effect of B cell depletion does not lie solely in the depletion of B cells since not all of the effects of B cells promote autoimmunity [16]. We have observed that a higher fraction of memory B cells and lower fraction of immature transitional B cells during reconstitution correlates with earlier relapse of disease [17], suggesting that the outcome of B cell depletion depends on the balance between protective and pathogenic B cell populations. This hypothesis is in keeping with the concept of regulatory B cell populations that may dampen autoimmune responses in part via anti-inflammatory cytokine production, such as IL-10. B regulatory cell defects have now been described in both SLE and RA, as well as the emergence or functional normalization of regulatory B cell populations after B cell depletion [18].

B regulatory cell production of anti-inflammatory cytokines is an example of an antibody independent B cell function. However, distinct cytokine producing B cell subsets may contribute to health and disease through either anti-inflammatory or pro-inflammatory functions. In MS, recent reports have supported that BCD may decrease proinflammatory B cells, including a granulocyte macrophage– colony stimulating factor (GM-CSF)–expressing human memory B cell subset [19] and IL-6 expressing B cells that drive T cell activation

and a Th17 phenotype [20]. In contrast, incomplete depletion of pathogenic B cells could contribute to inadequate responses to BCD. For example, in a murine model of MS, a subset of mature B cells was resistant to anti-CD20 and after cessation of treatment repopulated with a high frequency of myelin-reactive B cells. Importantly, these activated B cells were potent antigen presenting cells (APCs) for myelin-specific T cells [21], providing an example of another critical antibody independent role for B cells. A very interesting recent publication in human MS, reported that memory B cells drive proliferation of self-reactive brain-homing CD4+ T cells, which recognize autoantigens expressed in B cells and in brain lesions. Moreover, in vivo BCD effectively reduced T cell activation, providing a potential explanation for the high efficacy of anti-CD20 therapy in a T cell-mediated disease such as MS but also highlighting the importance of effectively eliminating these antigen-presenting memory B cells [22].

Recent studies in RA have identified an unexpected mechanism of B cell cytokine mediated pathogenesis, via production of several factors that impact bone damage in the disease, including RANKL [23–25]. RANKL is preferentially expressed by Fc receptor like 4 (FcRL4) memory B cells enriched in the synovium which also express high levels of CD11c [24,26], an integrin recently described on age-associated B cells (ABC) [27]. One of the drivers of both ABCs and B cell RANKL production is IFN-γ [25] which may be produced by T cells subsets known to be enriched in RA [28] or even B cells themselves [29]. In the latter study in proteoglycan-induced arthritis, B cell depletion led to an increase in T regulatory cells, another potentially important antibody-independent effect. In another study in murine experimental arthritis B cell depletion attenuated bone erosion and osteoclast activation but also reversed osteoblast inhibition [30].

Alternate pathways of B cell activation

Recent work in human SLE has defined extra-follicular B cell differentiation pathways as a key source for development of autoreactive plasma cells surprisingly from activated naïve B cell subsets [27,31]. Signals provided by TLR7, IFN-γ, and IL-21 were key, and activated B cells were characterized by the up-regulation of CD11c and the transcription factor T-bet. Multiple other groups have also described CD11c+T-bet+ B cells, initially termed age-associated B cells (ABCs) because they are increased in aged mice. It is now recognized that ABCs are also expanded in autoimmune mice (and humans) and are enriched in autoantibody specificities [32,33]. In mice T-bet was necessary and sufficient for the emergence of this subset [33] and was notably induced by a combination of BCR, IFN-γ, and TLR7 stimulation [34]. Further, it was recently shown that B cell specific deletion of T-bet abrogated autoimmunity in lupus prone mice [35]. In human SLE, ABCs can be driven by the T follicular helper cell derived cytokine IL-21 [36]. Thus, it is likely that this pathogenic B cell population could be reduced by co-stimulatory blocking agents such as therapeutics targeting CD40L, or ICOS, as well as blockade of IL-21 [1]. Whether ABCs are depleted effectively with anti-CD20 or other B cell targeted approaches has not been formally studied.

There is also evidence for two new subsets of helper T cells that are active in peripheral, non-lymphoid tissues. These subsets do not express CXCR5, the chemokine receptor for

CXCL13 and a key marker for Tfh. The first new helper T cell subset, termed Tph (T peripheral helper), was described in peripheral blood and synovial tissue of RA patients [37], Induction of B cell activation and differentiation into plasma cells by Tph is blocked by anti-IL-21 and SLAMF5. The second subset, termed Th10 was described in peripheral blood and renal tissue of SLE patients [38]. T cell help by Th10 is independent of IL-21 and instead is dependent on both IL-10 and succinate. The identification of these new subsets of helper T cells suggests that it might be possible to selectively target T helper cells involved in tissue inflammation in RA and SLE.

Is plasma cell targeting important?

It is important to recognize that BCD with anti-CD20 does do not directly target CD20-PCs. The variable persistence of auto-antibodies after BCDT could be explained by the presence of long-lived PCs and/or the ongoing generation of short-lived plasmablasts, possibly by the extra-follicular pathways described above. The differential contribution of long-lived (LLPC) and short-lived plasma cells (SLPC) to autoimmune disease pathogenesis has been recently reviewed, with pemphigus put forth as a model for SLPC driven disease, Sjogren's a model for LLPC driven disease, and SLE a mixed contribution [39]. One might speculate that the dramatic effect of anti-CD20 in ANCA vasculitis is due to a contribution of both SLPCs and B cell mediated effects on the T cell compartment to the disease process [40]. In normal humoral immunity, a landmark study published over a decade ago now highlighted the long half-life of certain antibody specificities including 11 years for tetanus and over 200 years for certain viruses such as measles [41]. This same group recently conducted a BrdU labeling experiment in rhesus macaques and demonstrated survival of bone marrow-derived plasma cells and durable antibody responses to multiple virus and vaccine antigens for years after sustained memory B cell depletion [42]. Recent studies have also clearly defined populations of long-lived plasma cells in the human bone marrow [43]. In autoimmune lupus mouse models, it is clear that both long-lived and short-lived populations of antibody-secreting cells can contribute to chronic humoral autoimmunity [44]. These observations and the fact that many lupus auto-antibodies are either directly (e.g., antiplatelet antibodies) or indirectly (e.g., anti-nuclear antibodies like anti-double stranded DNA antibodies) pathogenic suggest that long-lived auto-reactive PCs are an important treatment target and have led to intense research into the factors that determine plasma cell longevity (reviewed in [45]).

What's on the horizon?

Plasma cell targeting

Approaches to plasma cell targeting have emerged from the multiple myeloma (MM) field (Table 2). The most established of these with data also in autoimmunity is proteasome inhibition [46]. Both bortezomib and carfilzomib are approved for the treatment of MM and have demonstrated efficacy in mouse models of lupus [47]. Importantly, for the former there is evidence of depletion of long-lived PCs [48]. A recent 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 [49]. An immuno-proteasome inhibitor is currently in Phase 1 b/2 clinical trial in SLE (ClinicalTrials.gov Identifier:). Other approaches to PC targeting that merit investigation in autoimmune disease include anti-CD38 (daratumumab- approved in 2015 for MM), the histone deacetylase (HDAC) inhibitor panobinostat (approved for MM combination therapy in 2015), and a novel monoclonal antibody targeting signaling lymphocytic activation molecule family 7 (SLAMF7) (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 [27].

CAR-T therapy

At the cutting edge of B cell depletion therapy is the use of T lymphocytes that have been modified to express chimeric antigen receptors (CARs). These chimeric receptors consist of an antigen-specific recognition domain which is fused to T cell signaling machinery. By fusion of antigen-specific receptors, CAR T cells are able to target specific cell-types for destruction. For instance, fusion of anti-CD19 allows for CAR T cells to eliminate B cells. CD19-targeted CAR T cells have served as a useful modality in refractory B cell lymphoma patients where tumor remission can be obtained [50]. This technique holds promise for translation into autoimmune disease and has recently been studied in lupus-like mouse model. CD19-targeted CAR CD8+ T cells were able to induce sustained remission in both NZB/W and MRL-lpr lupus-like mouse models [51]. Titers of dsDNA antibodies fell in the mice, less immunoglobulin light chain messenger RNA was detectable in the kidneys, and proteinuria improved to baseline suggesting improvement in lupus nephritis. However, immunoglobulin light chains continued to be expressed in the bone marrow and spleens of the treated NZB/W mice suggesting that not all plasma cells were destroyed by the CD19-targeted CAR CD8+ T cells, and indeed long-lived CD19- plasma cells would not be expected to be targeted [52]. Nevertheless, this study is significant because it suggests that T cells from an autoimmune mouse strain can successfully be utilized as functional CAR T cells even in lupus.

A problem with using CD19 targeted CAR T cells for antibody mediated autoimmune disease is that long lived plasma cells do not express CD19 [43]. Thus, alternative approaches should be considered. Targeting plasma cells directly using B cell maturation antigen (BCMA)-CAR T cells is being developed for multiple myeloma [53]. It will be interesting to see the effects of BCMA targeted CAR T cells on autoantibodies produced by long lived plasma cells. However, it seems likely that durable responses may be have the same problem as proteasome inhibitors, i.e. repopulation of pathogenic plasma cells from the memory B cell population.

The possibility of more specific autoreactive PC targeting is also exciting. For instance, chimeric autoantibody receptor (CAAR) T cells are also under development and have been tested in a mouse model of pemphigus vulgaris, an autoimmune skin disease where pathogenic B cells make antibodies against desmoglein 3. In this case, the T cells are made

to express desmoglein 3 and pathogenic B cells that recognize this antigen are then targeted for destruction [54], allowing for more specific pathogenic B cell depletion.

Conclusions

Accumulating data indicates that B cells contribute to autoimmune disease through multiple mechanisms that include both autoantibody-dependent and independent functions. Thus, B cell targeted therapies are effective in a surprisingly broad range of conditions including clearly autoantibody driven like pemphigus and more complex diseases such as RA and MS that are also mediated by multiple cell types in addition to B cells. Importantly, antibody independent functions for B cells including antigen presentation, cytokine production, T cell activation and polarization, and organization of other inflammatory cells, likely explain the remarkable efficacy of B cell depletion therapy in diseases previously thought to be predominantly T cell driven. Accumulating data indicates that B cells display considerable phenotypic diversity, with multiple activation pathways, and it is important to recognize that not all of the effects of B cells promote autoimmunity. Thus, the therapeutic benefit of B cell targeted therapy will depend on the balance of pathogenic and protective B cell functions, as well as the relative contribution of B cells to disease vs. plasma cells and other cell populations. Additionally, novel agents to deplete and/or modulate B cell numbers or function continue to be developed. A major question in the field is whether it will be possible in the future to thoroughly deplete disease driving B cell subsets.

Acknowledgments

Dr. Barnas was supported by the Rheumatology Research Foundation. Dr. Looney was supported by a grant from the Alliance for Lupus Research, Pfizer, Inc., and the Rosenfeld Professorship. Dr. Anolik was supported by the NIH (grant NIAID R01-AI-077674, National Institute of Arthritis and Musculoskeletal and Skin Diseases Accelerating Medicines Partnership Grant 1UH2-AR-067690, NIAMS R21AR071670), and the Bertha and Louis Weinstein Research Fund.

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Highlights

- Two key paradigm shifts in the field of B cell targeted therapies which will be further highlighted here include 1) the importance of antibody independent B cell functions and 2) the contribution of long-lived plasma cell populations to autoantibody production.
- Autoantibody independent B cell functions include cytokine production and antigen presentation and likely explain the efficacy of B cell depletion in prominently T cell mediated autoimmune disease.
- The relative contribution of antibody independent functions for B cells vs. short lived vs. long lived plasma cell populations contributes to heterogeneity in response to B cell depletion.
- New B cell and plasma cell targeted therapies on the horizon include Btk inhibitors, novel co-stimulatory blockade or Tfh targeting, proteasome inhibitors, CAR-T therapy, and novel monoclonal antibodies targeting CD38 and SLAMF7.

Table 1:

B Cell Depletion Strategies in Autoimmune Disease

First Generation		**FDA Approved Indications and Orphan Drug Designations**
CD20	Rituximab	• Chronic Lymphocytic Leukemia (CLL) • Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) • Non-Hodgkin's Lymphoma (NHL) • Pemphigus Vulgaris • Rheumatoid arthritis • Orphan Designation: Rassmussen's encephalitis • Orphan Designation: Immune Thrombocytopenic Purpura
BLyS (BAFF)	Belimumab	• Active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy without severe active lupus nephritis or active central nervous system lupus
Second Generation		FDA Approved Indications and Orphan Drug Designation
CD20	Obinutuzumab	• Chronic lymphocytic leukemia • Follicular lymphoma refractory to rituximab • Stage II bulky, III or IV follicular lymphoma
CD20	Ocrelizumab	• Relapsing or primary progressive forms of multiple sclerosis
CD20	Ofatumumab	• Chronic lymphocytic leukemia
CD20	Veltuzumab	• Orphan drug designation: Chronic lymphocytic leukemia • Orphan drug designation: Immune thrombocytopenic purpura • Orphan drug designation: Pemphigus

B cell depletion strategies currently employed in autoimmune disease and malignancy. Rituximab and belimumab are currently approved cytolytic monoclonal antibodies within rheumatology. Second generation CD20 agents are now also finding use in autoimmune diseases such as immune thrombocytopenia, pemphigus and multiple sclerosis. Current and withdrawn orphan drug designations can be found in the Orphan Designated and or Approved Products database on the FDA website (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/).

Table 2:

B cell therapeutics on the horizon.

BTK Inhibitors	**FDA Approved Indications and Orphan Drug Designations**
Acalabrutinib	• Refractory mantle cell carcinoma • Orphan Designation: Chronic lymphocytic leukemia (CLL) • Orphan Designation: Waldenstrom macroglobulinemia
Ibrutinib	• Chronic graft versus host disease after failure of systemic therapy • Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) • Mantle Zone Lymphoma with prior anti-CD20 therapy • Refractory mantle cell lymphoma • Waldenstrom's macroglobulinemia • Orphan Designation: Gastric cancer • Orphan Designation: Multiple myeloma • Orphan Designation: Diffuse large B-cell lymphoma • Orphan Designation: Follicular lymphoma • Orphan Designation: pancreatic cancer
CD19-CAR T Cells	FDA Approved Indications and Orphan Drug Designations
Axicabtagene Ciloleucel	• Relapsed or refractory large B-cell lymphoma
Tisagenlecleucel	• Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma • Pediatric and Young Adult Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia (ALL)
Histone Deacetylase Inhibitors	FDA Approved Indications and Orphan Drug Designations
Panobinostat	• Refractory multiple myeloma
Monoclonal Antibodies	FDA Approved Indications and Orphan Drug Designations
Daratumumab (CD38)	• Refractory multiple myeloma • Orphan Designation: Follicular lymphoma, diffuse large B-cell lymphoma • Orphan Designation: Systemic light-chain (AL) amyloidosis
Elotuzumab (SLAMF7)	• Refractory multiple myeloma
Proteosome Inhibitors	FDA Approved Indications and Orphan Drug Designations
Bortezomib	• Mantle cell lymphoma • Multiple myeloma • Orphan Designation: neurofibromatosis type 2 (NF2)
Carfilzomib	• Refractory multiple myeloma
Ixazomib	• Refractory multiple myeloma • Orphan Designation: Systemic light chain (AL) amyloidosis

B cell therapeutics on the horizon. Multiple strategies have been FDA approved in lymphoma and multiple myeloma which may have utility in autoimmune disease. Strategies used in multiple myeloma also target plasma cells. Current FDA indications and orphan drug designations are listed.