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HIGHLIGHTS

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REVIEW

Targeting B cells and plasma cells in autoimmune diseases: From established treatments to novel therapeutic approaches

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Autoimmune diseases are characterized by the recognition of self-antigens by the immune system, which leads to inflammation and tissue damage. B cells are directly and indirectly involved in the pathophysiology of autoimmunity, both via antigen-presentation to T cells and production of proinflammatory cytokines and/or autoantibodies. Consequently, B lineage cells have been identified as therapeutic targets in autoimmune diseases. B cell depleting strategies have proven beneficial in the treatment of rheumatoid arthritis (RA), systemic lupus erythematous (SLE), ANCA-associated vasculitis (AAV), multiple sclerosis (MS), and a wide range of other immune-mediated inflammatory diseases (IMIDs). However, not all patients respond to treatment or may not reach (drug-free) remission. Moreover, B cell depleting therapies do not always target all B cell subsets, such as short-lived and long-lived plasma cells. These cells play an active role in autoimmunity and in certain diseases their depletion would be beneficial to achieve disease remission. In the current review article, we provide an overview of novel strategies to target B lineage cells in autoimmune diseases, with the focus on rheumatic diseases. Both advanced therapies that have recently become available and more experimental treatments that may reach the clinic in the near future are discussed.

Keywords: autoantibodies · autoimmune diseases · B cells · plasma cells · rheumatic diseases

Introduction

Autoimmunity is a hypernym used to describe a disease process in which the immune system inadvertently recognizes self-antigens and reacts against them. B cells are key players in many autoimmune diseases, namely rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), primary Sjögren´s syndrome (pSS), and multiple sclerosis (MS), contributing to the pathogenesis via their antibody-dependent and independent functions [1]. In many of these diseases, autoantibodies may contribute to disease pathogenesis, suggesting a potential role of B cell subsets and terminally differentiated antibody-producing plasma cells (PCs) in autoimmunity. In fact, B lineage cell alterations have been identified both in the peripheral blood and *in situ* in active lesions of patients, often having a different subset distribution

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compared to healthy donors [2, 3]. For example, increased frequencies of peripheral memory B cells and $CD38^+$ plasmablasts were identified in patients with AAV [4] and enriched fractions of circulating transitional B cells and plasmablasts were present in patients with SLE [5]. Moreover, in SLE, RA, and pSS, peripheral memory B cells have been shown to express reduced levels of CD21, which have been attributed with potential (auto)antigen presentation [6]. Besides peripheral blood, B cell alterations were also observed in secondary lymphoid organs, where naïve and memory B cells are found in comparable levels to healthy individuals, but follicular B cells were increased [7].

Naïve B cells originate from stem cell precursors in the bone marrow (BM). In the periphery, naïve B cells can be activated upon antigen recognition via their B cell receptor (BCR), with the presence of T cell co-stimulation within the follicles of secondary lymphoid organs or activated extrafollicularly in a more T cell independent manner [8]. This allows differentiation into memory B cells and (auto)antibody-producing plasmablasts ($CD27^+CD38^+$), short-lived (SL), and long-lived (LL) PCs ($CD38^+CD138^+$). The majority of B lineage cells express the surface markers CD19 and CD20. The expression of CD20 decreases during plasmablast differentiation, and CD20 is absent on the surface of the most differentiated B cell populations in the BM, the LLPCs, of which both $CD19^+$ and $CD19^-$ populations have been identified [9]. Therefore rituximab, a CD20 targeting B cell-depleting monoclonal antibody (mAb) commonly used for the treatment of autoimmunity, has beneficial effects in many different diseases, but does not target the CD20-negative B lineage cells such as the LLPCs [10]. Consequently, intense research efforts have been made to develop therapeutic strategies that also target B lineage cells that currently escape depleting therapies, aiming to overcome the current unmet needs for patients to achieve complete, durable remission.

B lineage cells and their central role in autoimmune diseases

To highlight the role of B lineage cells in autoimmune diseases, we briefly summarize the current evidence for this in selected disorders. RA is characterized by symmetrical peripheral polyarthritis mostly presenting in the hands/feet and can be accompanied by systemic inflammation [11]. The most common autoantibodies are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) [12]. Autoreactive B cells and PCs of RA patients can reside in niches within the inflamed synovium and/or BM, which maintain LLPC survival [3, 13]. Patients with established RA have notable fractions of $CD20^+$ and $CD38^+$ cells within the synovium with significantly higher CD38 expression compared to healthy individuals [14]. Of note, RA patients also exhibit increased CD40/CD40L signaling both in the peripheral blood and the inflamed synovium [15].

SLE has various clinical manifestations, including arthritis, kidney inflammation (lupus nephritis [LN]), and inflammatory skin lesions. Active SLE patients have reduced numbers of circulating naïve B cells and increased PCs, which are capable of generating high antibody titers upon activation [16, 17]. In SLE, naïve B cells are implicated to play an important role during flares, as newly activated naïve B cells of substantial clonality can be found in these conditions. These clonal naïve B and are able to give rise to antibody-secreting cells and remain present in the circulation for months [18]. Common autoantibodies include anti-nuclear antibodies (ANA), anti-dsDNA, antiphospholipid, and anti-Ro antibodies [19]. SLE patients also have increased numbers of anti-dsDNA producing $CD38^+$ plasmablasts [17, 20].

ANCAs mostly target myeloperoxidase (MPO) or proteinase 3 (PR3) and are involved in AAV [21]. ANCAs induce inflammation and endothelial damage, most notably in small-sized blood vessels in the lungs and kidneys of the patients, eventually leading to organ dysfunction [22]. The alterations in B cell composition in patients with AAV, the prominent presence of ANCAs, and preliminary data on dysregulated intracellular signalling pathways in these cells suggest that B cells and PCs are critically involved in the pathogenesis of AAV [23].

pSS is a systemic autoimmune disease in which high levels of B cell activating factor (BAFF) in salivary and lachrymal glands drive B cell activation and autoantibody production [24]; anti-SSA/Ro and anti-La/SS-B are the main autoantibodies in this disease [25].

MS is a chronic autoimmune, demyelinating disease affecting the CNS, with episodes of inflammation accompanied by neurological manifestations, followed by a remission period or a gradually progressive disease [26]. The presence of oligoclonal immunoglobulin bands and expanded B cells in the neuronal lesions indicates a role of B cells in disease pathogenesis, which is substantiated by the clinical efficacy of anti-CD20 treatment [27, 28].

Novel therapeutic strategies: biologics, combination therapies, and cell-based approaches

In the field of autoimmune diseases much progress has been made in developing target-specific treatment approaches including B cell-targeting therapies [29]. Among these are anti-CD20 therapies and their improved approaches (so-called type II anti-CD20 antibodies), targeting of specific B cell populations (anti-CD38, anti-CD22), modulation of intracellular B cell signaling pathways (Bruton's tyrosine kinase [BTK] inhibitors), co-stimulation blockade (anti-CD40), targeting of B cell survival factors (anti-BAFF), bispecific antibodies (obexelimab), and more recently even cellular immunotherapy approaches (anti-CD19 CAR T cells). We collected the most recent advances in the field focused on therapies that specifically target (subsets of) B lineage cells in autoimmunity demonstrating promising clinical results (Figure 1 and Table 1).

Table 1. Summary of novel therapies against B lineage cells

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
Anti-CD20	Obinutuzumab	SLE	Placebo-controlled, double-blind, randomized study	125 patients (63 patients in treatment group, 62 patients in placebo group)	• 1000 mg of obinutuzumab or placebo at day 1, weeks 2, 24 and 26 • Mycophenolate and corticosteroid	Week 2 Week 24 Week 26 Week 52 Week 104	• Higher percentage of treatment group (35%) achieved CRR compared to placebo (23%) at 52 weeks and 104 weeks (41% vs. 23% respectively) • Higher improvement in renal response with obinutuzumab compared to placebo	[26]
	Ocrelizumab	Relapsing MS	Phase III, double-blind, randomised study	1656 patients (835 patients in OPERA I trial: 410 patients in treatment group, 411 patients in control group; 835 patients in OPERA II trial; 417 patients in treatment group, 418 patients in control group)	• Single dose 100 mg intravenous methylpred-nisolone • 600 mg of ocrelizumab every 24 weeks (two 300 mg infusions on day 1 and 15, single dose afterwards) or 44 μg Interferon β-1a	Week 12 Week 24 Week 48 Week 96	• Significant lower annualised relapse rate with ocrelizumab at 96 weeks in both OPERA I (46%) and OPERA II (47%) trial • Significant lower disability progression rate at 12 weeks (9.1% in pooled treatment group vs. 136.6% in control) and 24 weeks (6.9 vs. 10.5% respectively) • Significant higher disability improvement at 12 weeks (20.7% in pooled treatment group v. 15.6% in control group) • Significant reduction in the number of MRI-detected new brain inflammation areas with ocrelizumab v.s placebo (94% in OPERA I, 95% in OPERA II)	[28]
		PPMS	Phase III, double-blind, placebo-control, randomised study	732 patients (488 in treatment group, 244 in placebo group)	• 600 mg of ocrelizumab every 24 weeks (two 300 mg infusions on day 1 and 15) or placebo for maximum 5 doses	Week 12 Week 24 Week 120	• Significant decrease of disability progression at 12 weeks (32.9% in treatment group vs. 39.3% in placebo group) and 24 weeks (29.6% vs. 35.7% respectively) • Significant lower ambulation speed reduction based on 25-foot walk at 120 weeks (38.9% in treatment group vs. 55.1% in placebo group) • Reduction in lesion volume and number of new lesions in treatment group vs. placebo group (volume lesion increased in placebo group)	[29]

(*Continued*)

Table 1. (Continued)

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
	Ofatumumab	MS	Phase III, double-blind, randomised study	1882 patients (927 patients in ASCLEPIOS I trial: 465 patients in treatment group, 462 patients in control group; 965 patients in ASCLEPIOS II trial; 481 patients in treatment group, 474 patients in control group)	• 20 mg of ofatumumab at day 1, 7, and 14 followed by 20 mg every 4 weeks or 14 mg daily of teriflunomide for up to 30 months	Month 3 Month 6 Month 12 Month 24 Month 30	• Significant decrease in annual relapse rate in ofatumumab group (0.11 in ASCLEPIOS I, 0.10 in ASCLEPLIOS II) v. control group (0.22 in ASCLEPLIOS I, 0.25 in ASCLEPIOS II) • Significant lower disability worsening at in ofatumumab pooled group at 3 months (10.9% vs. 15.0% in control group) and 6 months (8.1% vs. 12.0% in control group) • Higher disability improvement in ofatumumab group (11.0%) vs. control (8.1%) at 6 months • Significant decrease in lesion number in ofatumumab group (0.01 in ASCLEPIOS I, 0.03 in ASCLEPLIOS II) vs. control group (0.4 in ASCLEPLIOS I, 0.51 in ASCLEPIOS II) and new or enlarging lesions (0.72 in ASCLEPIOS I and 0.64 in ASCLEPLIOS II in treatment group vs. 4.00 in ASCLEPLIOS I and 4.15 in ASCLEPIOS II control group) • Significant reduction of sNfL in ofatumumab group vs. control at 3 months (7% in ASCLEPIOS I, 11% in ASCLEPIOS II), 12 months (27% in ASCLEPIOS I, 26% in ASCLEPIOS II), and 24 months (263% in ASCLEPIOS I, 24% in ASCLEPIOS II)	[30]
	Ublituxumab	RRMS	Phase II, double blind, placebo-controlled, randomised study	49 patients (39 in treatment group, 13 in placebo group)	• 150 mg of ublituximab at day 1, 450–600 mg of ublituximab at day 15 and at week 24 in six dosing cohorts or placebo followed by ublituximab at 24 weeks	Week 4 Week 24 Week 48	• Absence of brain lesion at week 24 and 48 after treatment • 7.3% and 10.6% decrease of brain lesion volume at 24 weeks and 48 weeks, respectively • 93% of patients were relapse-free at 48 weeks	[31]

(*Continued*)

Table 1. (Continued)

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
Anti-CD19	Inebilizumab	Relapsing MS	Phase I study	28 patients (27 patients in treatment group, 7 patients in control group)	• 2 intravenous injection of 30, 100 or 600 mg doses at days 1 and 15 • or single subcutaneous injection of 60 or 300 mg dose on day 1 • or placebo	Week 24	• Lower number of new lesion (0.1 in inebilizumab vs. 1.2 in placebo) and enlarging lesions (0.4 in inebilizumab vs. 2.4 in placebo) • Higher percentage free from new inflammatory activity in treatment (75%) vs. placebo (43%)	[34]
Anti-CD22	SM03	RA	Phase II, placebo-controlled, double-blind, randomised study	156 RA patients (3 groups, 52 patients in each group: high dose, low dose, placebo)	• 3600 mg cumulative dose of SM03, or 2400 mg cumulative dose of SM03, or placebo • Previous and continued MTX	Week 8 Week 12 Week 24	• Significant higher ACR20 at week 8 in high-dose group compared to low-dose and placebo groups • Significant higher ACR20 at week 12 and 24 in high-dose (65.3% at week 24) and low-dose (56.9% at week 24) groups compared to placebo (34.0% at week 24) • Significantly higher ACR50 and ACR70 at 24 weeks in high-dose compared to placebo • Significantly higher DAS28 EULAR response in high-dose and low-dose groups compared to placebo at 24 weeks	[37]

(*Continued*)

Table 1. (Continued)

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
	Epratuzumab	SLE	Phase I, open-label study	14 patients	• 360 mg/m^2 every other week for 4 times, in combination with paracetamol and anthistamine	Week 6 Week 10 Week 18 Week 32 post treatment	• Statistical improved clinical manifestations at 6, 10, and 18 weeks • ≥50% increase of BILAG score in 77% of patients at 6 weeks, 71% of patients at 10 weeks, 38% at 18 weeks, and 15% of patients at 32 weeks	[38]
			Phase II, placebo-controlled, double-blind, randomised study	227 patients (39 patients in low dose treatment, 38 patients in second dose, 37 patients in third dose, 37 patients in fourth dose, 38 patients in fifth dose, 38 patients in placebo	• 200 mg epratuzumab cumulative dose (100 mg every other week), or 800 mg epratuzumab cumulative dose (400 mg every other week), or 2400 mg epratuzumab cumulative dose 600 mg weekly), or 2400 mg epratuzumab cumulative dose (1200 mg every other week), or 3600 mg epratuzumab cumulative dose (1800 mg every other week) or placebo	Week 8 Week 12	• Higher proportion of responders in epratuzumab, regardless of dose, compared to placebo • Significant clinical improvement in patients receiving 2400 mg epratuzumab cumulative dose at 12 weeks • Improved BICLA at 8 weeks in 2400 mg epratuzumab group compared to placebo • Improved BILAG score at 12 weeks for 600 mg epratuzumab (51.4%) and 1200 mg epratuzumab (40.5%) compared to placebo (28.9%)	[39]

(*Continued*)

Table 1. (Continued)

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
			Phase II, placebo-controlled, double-blind, randomised study	90 patients (42 patients low dose treatment, 11 patients in high dose treatment, 37 in placebo)	• 360 mg/m^2 epratuzumab or 720 mg/m^2 epratuzumab, or placebo • Patients that continued in SL0006 recived additional 360 mg/m^2 epratuzumab	Week 12 Week 48 Week 120 (SL0006)	• Trial discontinued early for interruption of drug delivery • Improved response in 360 mg/m^2 (44.1%) compared to placebo (30%) but not in 720 mg/m^2 group (20%) • Decreased BILAG scores in both 360 mg/m^2 epratuzumab and 720 mg/m^2 epratuzumab group compared to placebo	[40]
			Phase III, placebo-controlled, double-blind, randomised study	1584 patients (793 patients in EMBODY 1 trial: 265 patients in low dose treatment group, 262 patients in high dose treatment group, 266 patients in control group; 791 patients in EMBODY 2 trial; 266 patients in low dose treatment group, 262 patients in high dose treatment group, 263 patients in control group)	• 600 mg epratuzumb every week (infusion at week 0, 1, 2, and 3) or 1200 mg epratuzumab (infusion at week 0 and 2) or placebo (infusion at week 0, 1, 2, and 3) for each 12-week treatment cycle • 5–60 mg/day of oral corticosteroid	Week 4 Week 12 Week 24 Week 36 Week 48	• No significant difference in BICLA score between groups at 48 weeks • Significant differences in epratuzumab group vs. placebo at weeks 12, 24, and 36. Not consisten in at which dose in EMBODY 1 and EMBODY 2	[41]

(*Continued*)

Table 1. (Continued)

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
		pSS	Phase I/II, open-label study	16 patientys	• 360 mg/m^2 epratuzumab (4 infusions once every 2 weeks)	Week 6 Week 10 Week 18 Month 6	• ≥20 improvement in clinical response in 53% of patients at 6 and 10 weeks • 48% of patients had ≥20 improvement in clinical response at 18 weeks • ≥20 improvement in clinical response in 67% of patients at 6 months • ≥20 improvement in fatigue assessment in 40% of patients at 6 months	[42]
Anti-CD38	Daratumumab	SLE	Case report	2 patients with severe, life-threatening, refractory SLE	• 16 mg/kg body weight of daratumumab 1/week for 4 weeks • Belimumab maintenance therapy 4 months after daratumumab	12 months	• Normalised serum creatinine levels and reduced urine protein levels • Resolution of pericarditis, arthritis, skin rush, musculoskeletal and mucocutanous manifestations • Normalised complement C3 levels • Decreased SLEDAI 2K • 50–60% reduction of anti-dsDNA levels and ANA levels • Transient CD38^{high} and CD19$^+$ B cell reduction • Reduction of type I IFN activity	[13]
		Anti-NMDA AE	Case report	1 patient with severe AE, no consciousness, seizures, in need of external ventilation	• 16 mg/kg body weight of daratumumab 1/week for 8 weeks followed by biweekly injections • Prednisolone • Paracetamol	17 months	• CD19$^+$ B cell, PC, and plasmablast depletion • Return to normal respiratory function, consciousness, interaction with external stimuli and individuals	[47]
		Anti-CASPR2 AE	Case report	1 patient with severe AE, neurological symptoms, personality changes, aggression	• 16 mg/kg body weight of daratumumab 1/week for 13 cycles	Interrupted due to patient death	• Partial neurological symptom remission • Decreased anti-CASPR2-IgG titers in serum and CSF	[46]

(*Continued*)

Table 1. (Continued)

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
Anti-BAFF	Belimumab	SLE	Phase II, double blind, placebo-controlled, randomised study	52 patients with refractory SLE (26 patients in treatment group, 26 patients in placebo group)	• Rituximab (two 1 g doses administered 2 weeks apart from each other 4–8 weeks before trial) • 10 mg/kg body weight of belimumab at week 0, week 2, week 4 and every 4 weeks for 1 year • Up to 20 mg/day of prednisolone	Week 12 Week 24 Week 52	• Lower IgG anti-dsDNA in treatment (geometric mean 47) compared to placebo (geometric mean 103) at 52 weeks • Decreased risk of flare in treatment compared to placebo (3 flares in belimumab vs. 10 flares in placebo group) • Significant suppression of B cell repopulation in treatment (geometric mean 0.012) vs. placebo (geometric mean 0.037) at 52 weeks	[60]
		pSS + CV	Case report	3 patients with pSS complicated by CV	• Rituximab • 200 mg/week belimumab		• Improved renal manifestations • Remission of cutaneous erosions • Decreased ESSADAI	[61]
		AVV	Multinational, multicentre, double blind, placebo-controlled, randomised study	105 patients with AAV (53 in treatment group and 52 in placebo group)	• Azathrioprine 2mg/kg daily • ≤10 mg/day glucocorticoid • 10 mg/kg of belimumab at days 0, 14, 28, and every 28 days	Until study completion or relapse	• No reduction of AVV risk of relapse in treatment group	[64]
		CV	Pilot study	4 patients with refractory CV	• 10 mg/kg belimumab on days 0, 14, 28 and then every month in association with rituximab	Month 3 Month 6 Months 18, 14, 35 and 24 (end of follow up)	• Improved (n = 1) and stabilized (n = 2) neuropathy • Urinary tract infections (n = 1) and osteomyelitis (n = 1) • Complete resolution of cutaneous and/or articular manifestations (n = 3)	[63]

(*Continued*)

Table 1. (Continued)

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
		pSS + CV	Case report	1 patient with type II CV with pSS refractory to rituximab	• Twelve months after second induction therapy with rituximab (discontinuation), subcutaneous belimumab (200 mg/week) and hydroxychloro-quine (200 mg)	More than 6 months	• Abated fatigue, purpura, poly-arthralgia, proteinuria, haematuria and dysmorphic casts • No relapses of CV or bacterial pneumonia for > 6 months	[62]
Anti-CD40	BI 655064	RA	Phase IIa, placebo-controlled, double-blind, randomised study	67 RA patients seropositive for either RF or ACPA (44 patients in treatment group, 23 patients in placebo group)	• 120 mg of BI 655064 or placebo weekly • ≥15 mg/week MTX (dose ≥7.5 mg/week in patients who didn't tolerate higher dose)	8 weeks 12 weeks	• 68.2% of treatment group reached ACR20 compared to placebo (45.5%) • 36.4% and 18.2% of treatment reached ACR50 and ACR70 respectively, compared to placebo (18.2% and 13.6%, respectively) • Significant decrease of IgG, IgM, IgA-RF, and IgG-RF titers at 12 weeks • Significant CD19+IgD-CD27-CD95+ memory B cells at 12 weeks • Decreased IL-6, MMP3, and RANKL at 8 and 12 weeks • Relatively safe, with higher reported adverse events in placebo group (78.3%) compared to treatment (65.9%)	[69]
	Dapirolizumab pegol (DZP)	SLE	Phase IIa, double-blind, placebo-controlled, randomised study	182 patients (45 in lower dose treatment group, 45 in medium dose treatment group, 47 in high dose treatment group, 45 in placebo group)	• Intravenous 6 mg/kg DZP or 24 mg/kg DZP, or 45 mg/kg DZP, or placebo every 4 weeks up to 24-week period • 10–40 mg/day corticosteroid	Week 24 Week 48	• Improved clinical measure of disease activity in treatment vs. placebo regardless of dose at 24 weeks • Lower BILAG sever flare numbers in DZP 6 mg/kg (4), 24 mg/kg (0), and 45 mg/kg (1) vs. placebo (7) • Greater reduction of anti-dsDNA and improvement of C3 and C4 levels in treatment groups vs. placebo • Less cumulative number of flares at 48 weeks in DZP 24 mg/kg (5) and 45mg/kg (5) vs. placebo (12) and 6 mg/kg (12)	[68]

(*Continued*)

Table 1. (Continued)

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
BTK inhibitor	Fenebrutinib	RA	Phase II, placebo-controlled study	Two cohorts: 480 RA patients with MTX inadequate response (40 patients in fenebrutinib 50 mg/daily, 109 patients in fenebrutinib 150 mg/daily, 110 patients in fenebrutinib 200 mg twice daily) 98 RA patients with anti-TNF inadequate response (48 patients in fenebrutinib 200 mg twice daily, 50 placebo)	• Fenebrutinib 50 mg, 150 mg or 200 mg twice daily according to study protocol	Week 1 Week 2 Week 4 Week 8 Week 12	• In cohort 1, higher percentage of ACR50 in 150 mg/day fenebrutinib group (28%) and 200 mg twice daily group (35%) compared to placebo (15%) at 12 weeks • In cohort 2, higher percentage of patients achieving ACR50 in fenebrutinib 200 mg twice daily (25%) vs. placebo (12%) • Significant fenebrutinib effect on CCL4 and RF • Significant change in B cell biomarkers after treatment	[76]
BTK inhibitor Bispecific antibodies	Evobrutinib	Relapsing MS	Phase II, double-blind, placebo-controlled, randomised study	267 patients (52 patients in low dose treatment group, 53 in medium dose treatment group, 54 in high dose treatment, 54 in dimethyl fumarate group, 54 in placebo group)	• 25 mg once daily, or 75 mg once daily, or 75 mg twice daily of evobrutinib, or placebo or dimethyl fumarate	Week 12 Week 16 Week 20 Week 24 Week 84 (extension phase)	• Lower mean number of lesions between weeks 12 and 24 in 75 mg/kg once daily (1.69±4.69) and twice daily (1.15±3.70) vs. 25 mg/kg (4.06±8.02), placebo (3.85±5.44) and dimethyl fumarate (4.78±22.05) • Lower relapse rate at 24 weeks in 75 mg/kg once daily (0.13) and twice daily (0.08) vs. 25 mg/kg (0.57), placebo (0.37) and dimethyl fumarate (0.20)	[77]

(*Continued*)

Table 1. (Continued)

Target receptor	Drug name	Disease	Type of study	Study population	Intervention	Time of follow-up	Results	Reference
	Obexelimab (XmAb5871)	SLE	Phase II, randomized, double-blind, placebo-controlled study	104 patients (52 patients in treatment group, 52 patients in placebo group)	• Every other week administration of XmAb5871 or placebo at 5 mg/kg by IV infusion over 1–2 hours for up to a total of 16 doses (30 weeks)	Followed for 6 weeks following the last dose for a total study period of up to 40 weeks	• Primary endpoint (the proportion with no loss of improvement by Day 225) was met by 21 (42%) of XmAb5871-treated patients vs 12 (28.6%) of the placebo group • No difference in patients with or without anti-dsDNA and/or ENA antibodies • Time to flare significantly longer in the XmAb5871 group • All in all, XmAb5871 was well-tolerated	[81]
Cell-based approach	Anti-CD19 CAR T cell	SLE	Case report	1 severe refractory SLE patient	• Infusion of 1.1 × 10^6 CD19 CAR T cells per kilogram of body weight	Week 7 Week 21 Week 33 Week 44	• Decreased anti-ds DNA levels • Normalised C3 and C4 levels • Decreased proteinuria • Decreased SLEDAI with SELENA modification	[85]

SLE, systemic lupus erythematosus; CRR, complete renal response; MS, multiple sclerosis; MRI, magnetic resonance imaging; PPMS, primary progressive MS; sNfL, serum neurofilament light chain; RRMS, relapsing remitting MS; RA, rheumatoid arthritis; MTX, methotrexate; ACR20, American College of Rheumatology 20% response rate; ACR50, American College of Rheumatology 50% response rate; ACR70, American College of Rheumatology 70% response rate; DAS28, disease activity score 28; EULAR, European Alliance of Associations for Rheumatology; BILAG score, British Isles Lupus Assessment Group score; BICLA, BILAG-based Combined Lupus Assessment; pSS, primary Sjögren´s syndrome; C3, complement 3; SLEDAI 2K, Systemic Lupus Erythematosus Disease Activity Index 2000; ANA, anti-nuclear antibody; IFN, interferon; Anti-NMDA, Anti-N-methyl-D-aspartate; AE, autoimmune encephalitis; PC, plasma cell; Anti-CASPR2, Contactin-associated protein-like 2; CSF, cerebrospinal fluid; IgG, immunoglobulin G; BAFF, B-cell activating factor; CV, cryoglobulinaemic vasculitis; ESSADAI, EULAR Sjogren's syndrome disease activity index; AVV, Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; IgM, immunoglobulin M; IgA, immunoglobulin A; IL-6, interleukin-6; MMP3, Matrix metalloproteinase 3; RANKL, Receptor activator of nuclear factor kappa-B ligand; DZP, Dapirolizumab pegol; C4, complement; 4BTK, Bruton's tyrosine kinase; TNF, tumour necrosis factor; CCL4, chemokine ligand 4; ENA, extractable nuclear antigens; Car T-cell, chimeric antigen receptor (CAR) T-cell; SELENA, Safety of Estrogens in Lupus National Assessment.

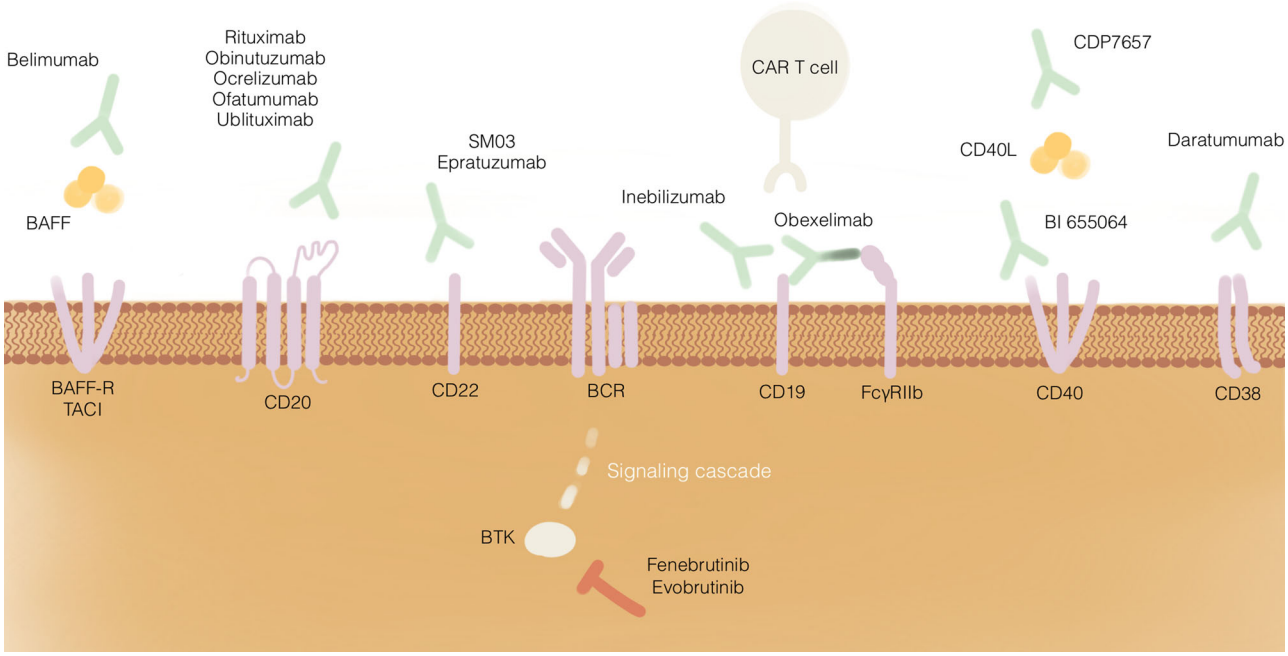

Figure 1. Selection of novel B-cell targeting therapeutic strategies in autoimmune diseases. Pink, receptors on the B cell membrane; green, biologic-based therapies (bispecific antibody in darker green); orange, ligands; gray, CAR T cell; white, intracellular signaling molecules; coral, small molecule inhibitors. Abbreviations: BAFF, B cell activating factor; BAFF-R, B cell activating factor receptor; TACI, transmembrane activator and cyclophilin ligand interactor; BCR, B cell receptor; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor.

Anti-CD20

CD20 is a transmembrane receptor expressed on the majority of B lineage cells, with the exception of pro-B cells and PC [30]. Anti-CD20 B cell-depleting therapies are very effective in many autoimmune disorders and include types I (rituximab) and II (obinutuzumab). In lymph nodes of patients with RA, rituximab treatment (B cell depleting therapy) significantly reduced naïve, unswitched memory B cells and follicular B cells. However, switched memory B cells remained unaltered, probably favoring relapses [7]. In SLE and RA patients, obinutuzumab caused a superior and sustained induction of direct B cell death *in vitro* compared to type I [31] through antibody-dependent cellular cytotoxicity (ADCC) [32]. Its efficacy and safety were tested in in a randomized, double-blind, placebo-controlled trial (NOBILITY) [33], when added to standard therapy, and its superior complete renal response compared to placebo correlated with decreased serum IgM and anti-dsDNA antibodies, and normalized complement levels. However, stable IgG and pre-existing antibody levels suggested the survival of $CD20^-$ PCs, regardless of the durable peripheral depletion of naïve and memory B cells and plasmablasts. No relevant safety issues were reported and a current global phase III trial is to be completed in 2025 [34]. Hence, type II anti-CD20 antibodies might more efficiently achieve long-term remission through a more durable B cell depletion, and represent an alternative for patients refractory to rituximab.

Rituximab has been used as off-label treatment for MS [28], and additional type I anti-CD20 treatments including ocrelizumab, ofatumumab, and ublituximab have been investigated. Ocrelizumab has a 2–5 fold increased ADCC activity compared to rituximab [10], and its testing in MS patients (OPERA I and II, ORATORIO study) lead to reduced relapse rate and MRI progression and lower markers of neuronal damage, while showing a favorable safety profile [35, 36]. Consequently, ocrelizumab is now approved for the treatment of MS [28]. Ofatumumab binds a distinct epitope from rituximab, and has greater complement-dependent cytotoxicity (CDC) activity [10]. Ofatumumab suppressed relapses and progression in MS in two phase II clinical trials (ASCLEPIOS I and II), with only minimal side effects [37]. B cell depletion by ublituximab is mediated mostly by ADCC and significantly prevented relapses, disease progression and radiological disease activity in a 48-wk phase II study on MS [38].

Anti-CD19

CD19 is a surface marker specific for B cells, which expression starts during early B cell development in the BM throughout the PC stage. However, as mentioned earlier, some PC may be negative for CD19 [9]. CD19 is an essential component of the BCR signaling complex, triggering the aggregation of engaged BCRs in microclusters on the cell surface and hereby acts as regulator of BCR activation [39]. This makes that a strict regulation of CD19 expression is required, since its upregulation may break peripheral tolerance and lead to autoimmune processes [40], and its downregulation may lead to impaired maintenance of memory B cells and antibody titers [41]. Altogether, these expression profile and function in the B cell lineage makes CD19

an appropriate target for pan B cell depletion [42]. Inebilizumab is an anti-CD19 afucosylated mAb with strong ADCC activity [43]. A phase I trial has found inebilizumab to be safe in MS patients and to reduce lesion formation, but additional phase II/III trials are not yet available [44].

Anti-CD22

CD22 is a transmembrane receptor expressed mainly on B cells that is able to crosslink the BCR. Upon CD22 activation, BCR signaling is reduced, enabling the regulating B cell survival, activation, and migration [45]. SM03 is a recombinant human/mouse chimeric mAb that targets the extracellular portion of CD22 on B cells with a good safety profile in both SLE and RA patients [46]. In a clinical in RA patients under MTX treatment, both high and low dose of SM03 caused improved clinical scores, and was relatively safe and well tolerated [47]. Epratuzumab is an humanized mAb that targets CD22 with modest ADCC activity [10]. In SLE, epratuzumab was found safe and able to significantly reduce disease activity in a small phase I, open label study [48]. Epratuzumab efficacy was later confirmed by three phase II studies (EMBLEM, ALLEVIATE-1, and ALLEVIATE-2) [49, 50]. However, two phase III studies reported no significant difference between treatment and placebo groups (EMBODY-1 and EMBODY-2) [51]. A phase I/II trial on pSS found that epratuzumab was relatively safe, improved clinical response in more than half of study patients, and significantly improved also fatigue and global assessment [52].

Anti-CD38

CD38 is differentially expressed among different B lineage cell populations. High expression levels can be detected in transitional B cells, germinal center B cells, and PCs. CD38 expression is also present albeit at relatively low levels in B cell precursors and naïve B cells, whereas it is hardly detectable in other B lineage cells [53, 54]. CD38 is part of the BCR co-receptor complex. Upon activation, CD38 is able to associate with CD19 leading to the spatial reorganization of CD19 and BCR molecules on B cell surface. This action of CD38 contributes to the regulation of the BCR activation threshold [55]. Moreover, CD38 is involved in cell differentiation and inflammatory cytokine production [53]. Daratumumab is an anti-CD38 mAb approved for the treatment of multiple myeloma which induces PC depletion via CDC and ADCC [56]. Anti-CD38 also depletes PCs and plasmablasts ex vivo in peripheral blood mononuclear cells (PBMCs) from patients with RA and SLE [57]. Daratumumab treatment of two patients with severe, life-threatening, refractory SLE, followed by maintenance therapy with belimumab, induced complete resolution of lupus-associated clinical manifestations, decreased disease activity scores, and reduced the anti-dsDNA levels. Therapy was well-tolerated and patients generally did not present adverse effects. Moreover, daratumumab induced a transient reduction of $CD38^{high}$ cells and $CD19^{+}$ B cells, and type I IFN activity [20].

Off-label use of daratumumab to treat patients with autoimmune encephalitis (AE) refractory to other immunosuppressants (i.e. rituximab) lead to depletion of PCs and plasmablasts, as well as reduced autoantibody titers [58], and was accompanied by a significant amelioration of clinical signs and symptoms [59].

Anti-BAFF

BAFF belongs to the TNF superfamily, and is essential for the proliferation and survival of B cells [60]. Belimumab is a human mAb with affinity for the soluble [61], and transmembrane [62] forms of BAFF, which has proven to be an effective therapy for SLE [63, 64], including LN [65], but not for RA, pSS and AAV [66]. The occurrence of relapses in these diseases after B cell depletion could be due to the higher BAFF levels [67–69]. Hence, the combination of rituximab and belimumab could be an alternative for patients with refractory disease [70, 71].

Treatment of SLE patients with belimumab after rituximab in a phase II, double-blind, placebo-controlled clinical trial [72] significantly reduced levels of anti-dsDNA antibodies and lowered the risk of severe flares without relevant safety findings. Similar benefits were observed in three patients with pSS or type II cryoglobulinaemic vasculitis (CV) treated with belimumab after rituximab or obinutuzumab failure [73]. Interestingly, the combination of belimumab and hydroxychloroquine successfully controlled the disease in one patient who developed allergic reactions to rituximab [74]. In line with previous findings, the use of belimumab after rituximab treatment in CV patients [75] improved clinical symptoms, decreased or depleted cryoglobulins, and normalized complement levels, without severe infections. However, the combination of belimumab after maintenance of remission with azathioprine and glucocorticoids in AAV [76] did not statistically reduce the risk of relapse compared with the placebo group, except for the absence of relapses if rituximab was used as induction therapy. Although promising, these studies also reported an increased risk of infections, which may require further refinement of treatment schemes [73, 75].

Anti-CD40/CD40L

CD40 is a membrane glycoprotein that belongs to the TNF receptor superfamily. It is expressed on B cells and is involved in the regulation of their proliferation, activation, differentiation into antibody-producing cells, and isotype switch. CD40L is expressed on activated $CD4^{+}$ T cells and platelets [77, 78], the latter which became activated upon treatment with the initial anti-CD40L antibodies ruplizumab and toralizumab, leading to their clinical failure. To overcome this issue, dapirolizumab pegol (CDP7657), a humanized mAb against CD40L lacking the Fc-portion to avoid aspecific platelet activation was generated [79]. CDP7657 was well tolerated in a phase II trial in SLE, patients having improved

clinical manifestations despite results not being statistically significant [80]. BI 655064 is a novel anti-human CD40 mAb that prevents binding of CD40L to its receptor, as it selectively binds to CD40 on B cells from whole blood, blocking CD40L-induced B cell proliferation and abrogating IgG and IgM production both *in vitro* and *in vivo* experiments [77]. In seropositive RA patients (i.e., RF or ACPA) with active disease, BI 655064 was relatively safe, significantly decreased both IgG and IgM, as well as autoantibody levels, and caused a significant reduction of memory B cells. Furthermore, reduction of inflammation and bone-remodelling markers, and improved clinical manifestations were reported [81]. Further studies are warranted to determine the full potential of this target in systemic autoimmune diseases.

BTK inhibitors

BTK is a member of the TEC family of non-receptor tyrosine kinases, crucial for BCR signaling in B cells [82], and with higher activity in autoimmune diseases, including SLE [83], AAV [84], and RA and pSS [85]. Due to off-target effects and irreversible binding of the first-generation BTK inhibitors [86], more specific and safer second-generation inhibitors (i.e., fenebrutinib) were designed to treat autoimmunity [87]. A phase II placebo- and active-controlled study analyzed the efficacy of fenebrutinib in patients with active RA refractory to conventional therapies [88], resulting in beneficial clinical outcomes compared to the placebo group. Interestingly, fenebrutinib not only downregulated autoantibody levels (IgM-RF and ACPA) and IgG, but also IgM and IgA, of which the latter two were not reduced by adalimumab (TNF inhibitor), despite having comparable efficacy and safety profiles. Among several limitations, the potential long-term adverse effects caused by the general reduction of immunoglobulins in this study should be studied in more detail. Evobrutinib permanently binds and deactivates BTK, affecting B cell activation and differentiation to PCs [28]. Treatment of MS patients in a phase II study caused reduction of lesion in patients after treatment independently from the dose, although no effect was seen on relapses and progression of disability [89]. A phase III trial is currently investigating the effect of evobrutinib on MS, and results are expected after trial completion in 2023 [90].

Bispecific antibodies targeting B cells

Bispecific antibodies (bsAbs) emerge as a potentially more directed and effective therapeutic strategy through the simultaneous recognition of two different target molecules that would allow for more specific targeting of specific immune cells, modulation of their functions, or their neutralization [91]. Although initially developed for cancer treatment, other bsAb applications exist. For instance, obexelimab is a monoclonal antibody targeting CD19 on B cells that also engages the FcγRIIb, a receptor that inhibits B cell function [92]. Via this co-engagement, obexelimab is able to supress activation, while avoiding B cell depletion. Treatment of SLE patients in a phase II clinical trial did not meet the primary endpoint, but did increase the time to flares [93]. Interestingly, the authors have now demonstrated better responses to obexelimab in patients with a marked expression profile of B cell and PC pathways, rather than those with a strong inflammatory signature [92]. Of note, obexelimab also suppressed B cell activation in PBMCs from RA patients [94]. Consequently, bsAbs seem to be a promising therapeutic strategy given the positive results in cancer and preliminary studies in autoimmunity [91, 95]. However, further fine-tuning needs to be performed, as some trials had to be discontinued in autoimmune diseases due to failure in demonstrating clinical improvement [91].

Cell based approaches: CAR T cell therapy

To target B lineage cells that currently escape conventional antibody or small molecule-based approaches, due to lack of certain surface markers or their location in specific niches, and inspired by the successful outcomes in cancer [96], an immunotherapeutic approach using Chimeric Antigen Receptor (CAR) T cells has gained interest to potentially treat autoimmunity. In this approach, a chimeric receptor on autologous T cells of the patient targeting the marker of interest results in elimination of the cells that express it. In a pioneering study, anti-CD19 CAR T cells were generated to treat an SLE patient refractory to diverse treatments [97], leading to complete depletion of circulating B cells, and clinical and serological patient remission. In addition, the decrease in anti-dsDNA autoantibodies suggested that $CD19^+$ plasmablasts were their main source. Recently, the same research group reported beneficial effects of this treatment in 4 additional patients with refractory SLE, showing complete loss of ANA and dsDNA antibodies and even clinical remission in some cases [98]. Importantly, all patients achieved low disease activity and could stop all SLE-specific medication, with no significant side effects, suggesting that anti-CD19 CAR T cell therapy may be a potential strategy to treat refractory SLE and achieve long-term remission. Two other novel cell-based therapies are under investigation for the treatment of autoimmunity, namely the chimeric autoantibody receptor (CAAR) T cells [99] and the B-cell-targeting antigen receptor (BAR) T regulatory and cytotoxic T cells [100], which aim to target the autoreactive B cells in these diseases.

Concluding remarks and future perspectives

B lineage cells play an important role in many autoimmune diseases. Initial attempts to treat autoimmunity by peripheral B cell depletion strategies using the anti-CD20 antibody rituximab were largely beneficial, but not in all patients and induction of relapse-free long-term remission is scarce, mainly due to inability of this approach to eliminate LLPCs. Perhaps, intervention in the earliest phases of autoimmune diseases may improve efficacy and/or delay onset of clinical overt disease, as was demonstrated for RA in the PRAIRI trial [101]. Similarly, a recent study by Werner

et al. was performed in which B cells were depleted in the preclinical phase of murine experimental SLE. This B cell targeting approach resulted not only in a delayed onset of disease, but also in a reduction of clinical features including less tissue damage and reduced autoantibody production [102]. Moreover, some of the currently available biological therapies are not completely specific for B lineage cells, causing off-target effects and/or incomplete therapeutic responses (i.e. anti-CD38 therapy also targets $CD38^+$ regulatory T cells) [103]. Hence, there is been a need for therapies specifically targeting the autoreactive B cell populations, including those that reside in survival niches in the BM and/or lymph nodes. Innovative research efforts have resulted in promising approaches, including biologics and cellular immunotherapies, which may also be able to modulate B cell function rather than merely depleting B lineage cells.

We explored the latest therapeutic strategies targeting B lineage cells and conclude that most novel therapies improved clinical manifestations with limited safety issues. However, this remains to be formally proven in larger studies. Most approaches, depending on their mechanism of action, downregulated activation or depleted B lineage cells (either pan-B cells or specific subtypes), resulting in a decrease or abrogation of autoantibody production by plasmablasts and PCs. Novel therapies were found to be effective regardless of the disease studied, reinforcing the need to better explore shared pathological mechanisms. Nevertheless, targeting of PCs was not always effective, which remains to be an important issue to tackle. Even though anti-CD38 therapy seems promising, increased knowledge on PCs in BM and/or lymph nodes of patients with autoimmune diseases would certainly be helpful in designing more focused therapeutic approaches.

These studies also had some limitations, and although severe adverse events were mostly lacking, infections are frequently reported side effects. Other potential side effects are lymphopenia and hypogammaglobulinemia, which might manifest after treatment. Indeed, rituximab treatment is associated with both IgM and IgG hypogammaglobulinemia, with a frequency range between 10% and 58% for IgM and between 1.5% and 66.7% for IgG. The proportion of patients with IgM hypogammaglobulinemia increases proportionally to the number of rituximab cycles, and IgM levels remain persistently lower than pre-treatment even after $CD20^+$ B cell repopulation [104]. However, only a small percentage of patients that experience IgM and IgG hypogammaglobulinemia also experience increased frequency of infection, which were reduced after IgG replacement therapy [105, 106]. Furthermore, most of the studies explored were either case reports or phase II clinical trials, with short follow-up time. Consequently, trials with a longer follow-up period should be designed to determine potential long-term adverse events of IgG, IgM, and IgA reduction, including effects on vaccination recall responses. Finally, the small sample size of some of the pilot studies and case reports need to be taken into account, necessitating larger trials to formally test efficacy and safety.

Altogether, these findings clearly demonstrate that B cell-directed research is moving into the right direction, getting closer and closer to achieving complete remission in patients with autoimmune diseases. Most of the aforementioned trials and studies are currently in the next phase, and many sophisticated strategies, including CAR, CAAR, and BAR T cells, bsAbs, and small molecule inhibitors of B cell-intrinsic signaling pathways are currently aiming to refine their mechanism of action to eventually fill the unmet therapeutic need in these diseases and improve the lives of patients.

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