Opportunities and limitations of B cell depletion approaches in SLE

Stockfelt, M.; Teng, Y.K.O.; Vital, E.M.

nature reviews rheumatology

https://doi.org/10.1038/s41584-024-01210-9

Review article

Check for updates

Opportunities and limitations of B cell depletion approaches in SLE

Marit Stockfelt [1,2], Y. K. Onno Teng [3] & Edward M. Vital [4,5]

Abstract

B cell depletion with rituximab, a chimeric monoclonal antibody that selectively targets B cells by binding CD20, has been used off label in severe and resistant systemic lupus erythematosus (SLE) for over two decades. Several biological mechanisms limit the efficacy of rituximab, including immunological reactions towards the chimeric molecule, increased numbers of residual B cells, including plasmablasts and plasma cells, and a post-treatment surge in B cell-activating factor (BAFF) levels. Consequently, rituximab induces remission in only a proportion of patients, and safety issues limit its use. However, the use of rituximab has established the value of B cell depletion strategies in SLE and has guided the development of several improved B cell depletion therapies for SLE. These include enhanced monoclonal antibodies, modalities that redirect the specificity of patient T cells using chimeric antigen receptor T cells or bispecific T cell engagers, and combination treatment that simultaneously inhibits the BAFF pathway. In this Review, we consider evidence gathered from over two decades of using rituximab in SLE and examine how B cell depletion therapies could be further optimized to achieve immunological and clinical efficacy. In addition, we discuss the prospects of B cell depletion strategies for personalized treatment in SLE based on genetic research and studies in pre-symptomatic individuals.

Sections

[1]Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden. [2]Rheumatology, Sahlgrenska University Hospital, Gothenburg, Sweden. [3]Center of Expertise for Lupus, Vasculitis and Complement-mediated Systemic disease (LuVaCs), Department of Nephrology, Leiden University Medical Center, Leiden, the Netherlands. [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK. [5]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK. e-mail: E.M.J.Vital@leeds.ac.uk

Key points

- Although the B cell depletion agent rituximab failed to reach its primary end points in randomized controlled trials in systemic lupus erythematosus (SLE), favourable clinical experience has led to its frequent off-label use in patients with SLE.
- Deep B cell depletion of prolonged duration has been associated with improved clinical response to rituximab.
- Additional B cell depletion therapies that enhance B cell depletion, reduce immunogenicity, delay relapse of B cell numbers or target memory B cells and plasma cells are under development, although trials comparing these therapies head to head are lacking.
- Innate and non-immune mechanisms that lead to B cell activation, as well as B cell-independent inflammation, might underlie resistance to B cell depletion therapy.
- Although enhanced B cell depletion improves clinical responses in patients with SLE, both B cell-driven mechanisms and innate or non-immune mechanisms might need to be targeted to achieve cure.

Introduction

A role for B cells in the pathogenesis of systemic lupus erythematosus (SLE) has been recognized for decades, and the presence of autoantibodies is a feature of the disease[1]. Rituximab, a chimeric monoclonal IgG1 antibody that selectively targets B cells by binding to CD20 on their surface, was the first B cell depletion agent used in patients with SLE[2,3] (Fig. 1). As many other B cell depletion agents, rituximab was initially developed for the treatment of B cell-derived malignancies. In addition, B cell depletion with rituximab was efficacious in randomized trials in several rheumatic diseases, including patients with rheumatoid arthritis (RA) with insufficient response to TNF inhibitors[4], and the induction and maintenance of remission in antineutrophil cytoplasmic antibody-associated vasculitis[5–8].

Rituximab depletes B cells by several mechanisms (Fig. 1b). It crosslinks its targeted B cells with the activating Fcγ receptor III (FcγRIII) on effector cells such as natural killer (NK) cells and macrophages to induce death of the opsonized B cell through antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), respectively. In addition, B cell depletion can be induced independently of FcγRIII binding. The binding of type I monoclonal antibodies to CD20 on the B cell surface clusters CD20 into lipid rafts. This redistribution increases cell death by complement-dependent cytotoxicity (CDC) and apoptosis[9]. However, clustered complexes are more rapidly internalized, through interactions with inhibitory FcγRIIb qqon the B cell surface, which limits availability for ADCC and ADCP[10]. Some novel therapies include modifications to shift this balance between clustered complexes and non-clustered complexes.

CD20 is specifically expressed on B lineage cells, sparing progenitor cells, some plasmablasts and long-lived plasma cells (Fig. 1a). CD20 function is poorly understood, and its natural ligands remain unknown. In addition to CD20, key targets on B cells include CD19, CD38, B cell maturation antigen (BCMA) and the B cell-activating factor (BAFF) receptor (BAFF-R). These are expressed on different subpopulations of B cells during development (Fig. 1a). Compared with CD20, CD19 has broader expression, including in plasmablasts and plasma cells. CD38 and the BAFF-R have more restricted expression that may direct biological effects towards subpopulations of B cells[11–14].

In this review we examine the biological and clinical efficacy, as well as the limitations of off-label use, of rituximab in SLE and discuss the long-standing evidence showing that deep B cell depletion is important for clinical efficacy. In addition, we explore strategies currently employed to improve B cell depletion therapy, including enhanced monoclonal antibodies, chimeric antigen receptor (CAR) T cells and bispecific T cell engagers (BiTEs) and discuss how to manage long-term safety with B cell depletion. Finally, we examine how recent knowledge about B cell extrinsic mechanisms of SLE pathogenesis illuminate potential limitations of B cell depletion therapies in terms of achieving complete cure of SLE.

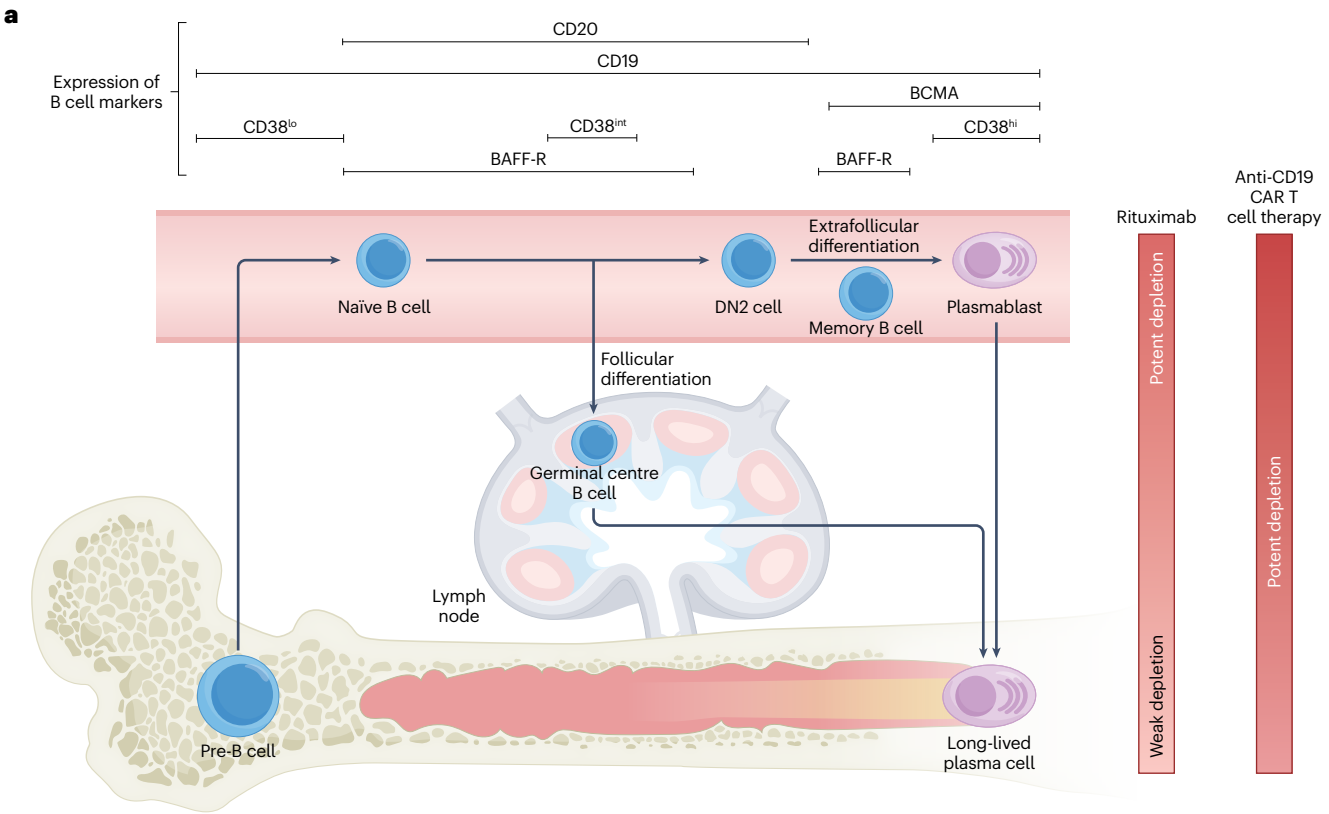
B cell subsets in SLE

In established SLE, the B cell compartment displays several alterations compared to that of healthy individuals, including extrafollicular T cell-independent activation, reduced dependence on B cell receptor (BCR) signalling and B cell lymphopenia[15–17]. Lymphopenia preferentially affects naive B cells, whereas type I interferons (IFNs), which are commonly upregulated in SLE, promote the survival of transitional B cells (Box 1). This leads to an altered composition of the B cell pool with an increased proportion of memory B cells[17–19]. SLE has been described as a prototypic B cell-driven disease that is maintained by mature B cell clones that produce autoantibodies and cytokines and present antigens to autoreactive T cells. However, the extent to which SLE pathogenesis relies on complete and disrupted germinal centre reactions versus extrafollicular B cell maturation is not well clarified[20]. The idea of isolated and intrinsically autoreactive B cell clones that drive disease development might need revisiting as recent evidence points towards the involvement of polyclonally and extrafollicularly activated B cells in the pathogenesis of SLE[15,21,22].

Central T cell tolerance is unlike the first B cell checkpoint in the bone marrow. In central T cell tolerance, expression of the autoimmune regulator protein in thymic epithelial cells ensures exposure of developing T cells to tissue-restricted autoantigens and thereby results in efficient elimination of autoreactive T cell clones. The first checkpoint of B cell tolerance is regulated by exposure to a narrower selection of antigens expressed in the bone marrow, and does not exclude autoreactivity in the naive B cell pool as efficiently. Therefore, an important second checkpoint of B cell tolerance is required to prevent the inappropriate activation of autoreactive naive B cells. Naive B cells, thus, have an elevated threshold for activation and require activation of both BCR signalling and co-stimulatory molecules for an optimal pro-inflammatory response[23]. The RNA-sensing TLR7 pathway is particularly relevant for SLE disease development. After a nuclear antigen has bound its cognate BCR on the B cell surface, the bound complex is internalized and delivered to endosomes containing TLR7 and TLR9 (refs. 23–25) (Box 2). These innate receptors are activated by nuclear and mitochondrial RNA and DNA, and their engagement in concert with BCR ligation provides a second signal that triggers B cell activation[24,25]. The activation of TLR7 is essential to develop an antibody response in SLE-prone mice and was required for the expansion of autoreactive B cells that bind to self nucleotides, including $CD27^{-}IgD^{-}$ double-negative B cells (DN B cells) and plasmablasts[26,27].

The DN B cell population is highly responsive to TLR signalling and shares some properties with murine age-associated B cells. DN stage 2 (DN2) B cells, which are marked by a higher expression of CD11c and T-BET than that of other DN B cell subsets, have increased

levels of TLR7 but lack the TLR regulator TRAF5 (ref. 26). The DN2 B cell subset is expanded in both adults and children with SLE, especially in individuals with African American ancestry and nephritis, and the percentage of DN2 B cells correlates with disease activity and Sm-specific or ribonucleoprotein-specific antibodies[28,29]. DN2 B cells are derived from activated naive B cells, are set to recognize nucleic



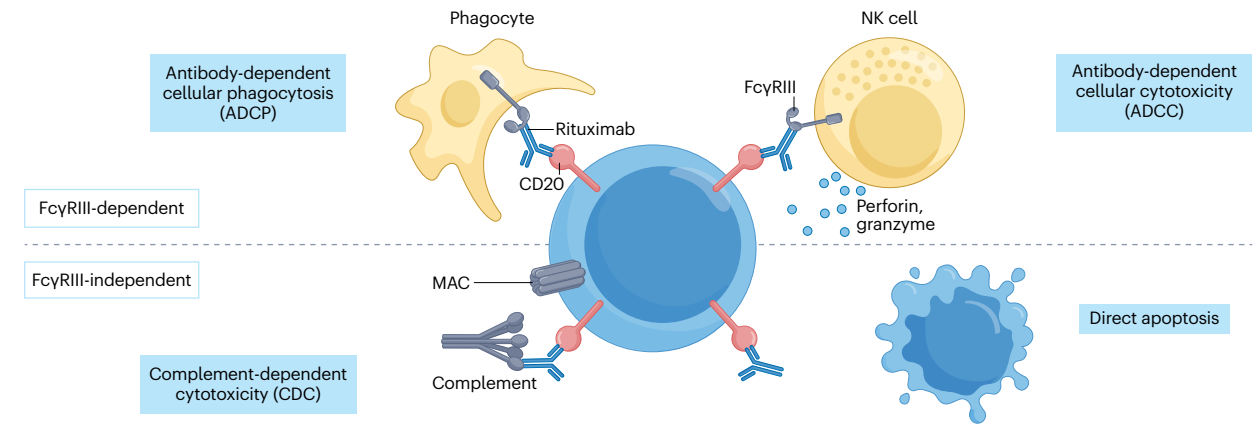


Fig. 1 | Mechanisms of B cell depletion by rituximab. a, B cell subsets express distinct surface markers depending on their differentiation stage. These surface markers can be targeted to direct biological effects towards the various stages of B cell maturation. For example, as rituximab uses CD20 as its target, biological effects are targeted towards B cells prior to the memory and plasma cell stages. B cell subpopulations of special interest for systemic lupus erythematosus (SLE) and their robust and characteristic expression of surface markers are depicted[11–14]. In addition to circulating B cells, which are efficiently targeted by rituximab, lymph node-resident and tissue-resident B cells are also likely to mediate pathology in SLE but are less efficiently depleted by monoclonal antibodies. By virtue of their cellular mechanism of action, chimeric antigen receptor (CAR) T cells are expected to induce more potent depletion in peripheral tissue compared with monoclonal antibody-mediated depletion with rituximab. **b**, Rituximab induces B cell depletion by several different mechanisms, including Fcγ receptor III (FcγRIII)-mediated antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC), as well as complement-dependent cytotoxicity (CDC) and direct induction of apoptosis. BAFF-R, B cell-activating factor receptor; BCMA, B cell maturation antigen; DN2 cell, double-negative stage 2 B cell; MAC, membrane attack complex; NK, natural killer.

Box 1 | Interconnections between autoantibodies and the type I interferon system

Studying the early phase of systemic lupus erythematosus (SLE), before the onset of any clinical symptoms, has revealed the early involvement of autoantibodies and the type I interferon (IFN) system in disease development. Loss of humoral tolerance develops progressively during the years preceding onset of disease, and most patients with SLE carry at least one antinuclear antibody (ANA) specificity 6 years before diagnosis[143]. Pathogenic ANAs, especially anti-double-stranded DNA antibodies, can form immune complexes, activate complement, bind apoptotic nucleosomes in the glomeruli and mediate neuronal apoptosis[156,157]. However, some ANAs are benign and can be present during remission[158]. Only a minority of healthy individuals who develop ANA progress to clinical SLE disease[150]. However, even among non-progressors without inflammatory symptoms, ANA positivity is transcriptionally a highly dysregulated state with several abnormalities, including upregulation of IFN production in blood and non-haematopoietic tissues, and the immunological profiles of individuals with ANA positivity are more similar to those of patients with SLE than to those of healthy controls[148,159].

Extracellular nuclear material is a potent stimulus for both antibody production and the type I IFN response, and the progression from ANA positivity to an SLE flare can be predicted on the basis of type I IFN pathway activation in blood and skin[148,150,159]. Most patients with established SLE exhibit sustained upregulation of the type I IFN system, and type I IFN activation has been associated with disease activity and distinct clinical features[160–163]. Local activation of the type I IFN pathway is evident in several organ systems and SLE can be ameliorated by the type I IFN receptor inhibitor anifrolumab[64,159,164–166].

Elevated IFNα protein levels are associated with the presence of ANA and the number of specific autoantibodies is consistently associated with activation of type I IFN system in SLE and other rheumatic diseases[167–169]. Stimulation with type I IFNs upregulate TLR7 expression on B cells, promote BAFF production, and strongly promote B cell differentiation to plasmablasts[170–172]. In addition, exposure to IFNα imprints plasma cells to express high levels of ISG15 mRNA, accompanied by direct secretion of ISG15 protein in SLE[149]. ISG15 has a variety of immune modulatory effects both inside cells and as a soluble mediator. Thus, autoantibodies forming immune complexes can provide an interferonogenic stimulus[173,174]. In return, type I IFN stimulation imprint plasma cells to cause immunomodulatory effects that are independent of their antigen specificity, further contributing to the inflammatory vicious circle of SLE.

acids and seem to develop into antibody-producing cells[26]. This extrafollicular pathway of B cell differentiation seems to promote the development of autoreactive and antibody-producing plasma cells and plasmablasts in SLE.

Plasmablasts are a heterogeneous subset of short-lived, rapidly generated, antibody-producing B lineage cells, often defined on the basis of their $CD19^{+/-}CD27^{++}CD38^{++}$ surface marker profile, that markedly expand early during SLE disease[30]. In viral infections, TLR signalling seems to determine whether plasmablasts develop intrafollicularly or extrafollicularly, and in mice, overexpression of TLR7 increases both spontaneous germinal centre formation and plasmablast development[27,31]. Both a plasmablast gene signature and the proportion of peripheral plasmablasts have been associated with SLE disease activity[32,33]. In the absence of naive and memory B cells, the presence of plasmablasts in circulation might indicate ongoing B cell activity in other tissues. High-sensitivity flow cytometry is necessary to enumerate these rare cells, that are mostly located outside the lymphocyte region and have lower CD19 expression than that of other B cell populations.

Overall, TLR7 signalling has the potential to drive the extrafollicular and polyclonal differentiation of autoreactive B cell populations during SLE. As TLR7-activated B cell populations might contribute to the development of an autoantibody response, the presence of these cells might help explain both the lack of response to rituximab in some patients with SLE and the success of therapeutic strategies involving BAFF inhibition.

Effectiveness and limitations of rituximab

Rituximab in SLE

Although early studies suggested efficacy in SLE, rituximab surprisingly failed to meet the primary and secondary end points in the LUNAR trial of renal SLE and the EXPLORER trial of non-renal SLE[34,35]. Results from both trials indicated biological effects, with rapid depletion of $CD19^{+}$ B cells, improved serology, and normalization of complement factors. However, high doses of background corticosteroids and other immunosuppressive therapies, patient heterogeneity and trial design might have contributed to the failure to meet end points[36]. Regardless, rituximab has been used off-label in patients with SLE for over two decades on the basis of clinical effectiveness in case series, registries and two systematic reviews[37–42]. The clinical response to rituximab is variable and, although many patients need retreatment with rituximab to control disease, the time span before return of clinical symptoms differs considerably across these studies[43,44]. The pattern of relapse is bimodal and for approximately half the patients, relapse occurs within 18 months, whereas the remaining patients seem to benefit from longer periods of remission, sometimes exceeding 4 years[43]. Factors that limit the effects of B cell depletion therapy with rituximab include the presence of residual B cells in circulation and peripheral niches, non-response due to insufficient depletion or B cell-independent disease, and, in a proportion of patients, a sustained reduction in immunoglobulin that is associated with increased risk of serious infection.

Residual B cells in circulation

The level of B cell depletion by rituximab depends on the affinity of FcγRIII to rituximab[45]. FcγRIII allotypes have distinct receptor properties and influence the numbers of residual B cells after treatment with rituximab. In particular, the 158V polymorphism in *FcγRIIIa* increases FcγRIII affinity to IgG1. Patients who are homozygous for this polymorphism have enhanced NK cell-mediated degranulation and require lower serum rituximab levels than patients with other *FcγRIIIa* haplotypes to achieve the same degree of B cell reduction[45,46]. In patients with RA, giving patients with incomplete B cell depletion an extra dose of rituximab 4 weeks after treatment initiation reduced residual B cells and clinical response without increasing adverse events[47]. Similarly, patients with SLE and *FcγRIIIa* genotypes that confer lower affinity to

IgG1 are likely to need increased rituximab doses or B cell depletion by alternative agents to achieve equal biological and clinical responses as patients with higher IgG1 affinity *FcγRIIIa* genotypes.

B cell depletion by rituximab is transient, and many patients with SLE still have detectable B cell levels after two infusions of rituximab. Lower numbers of residual B cells are associated with improved clinical responses in both renal and non-renal SLE[2,43,48–50]. Moreover, the depletion of certain B cell subtypes is associated with clinical response, and transitional B cells are expanded in patients with prolonged clinical response to rituximab[51]. The number of plasmablasts at relapse after rituximab seems to correlate with the titres of double-stranded DNA (dsDNA)-specific autoantibodies, and repopulation by plasmablasts was found to be predictive of disease recurrence[43]. Using high-sensitivity flow cytometry, repopulation with plasmablasts can be identified early; individuals with detectable plasmablasts 6 months after rituximab treatment are at higher risk of clinical relapse within the following 6 months[52]. In these patients, retreatment on the basis of B cell repopulation might have the potential to prevent relapse.

Residual B cells in peripheral niches

Most information about the B cell depletion efficiency of rituximab is based on counts of circulating B cells, which are more accessible than tissue-resident B cells. However, B cells in the blood comprise a minority of total B cell numbers and are not necessarily in homeostasis with tissue B cells[53]. Thus, residual B cells are likely to remain in peripheral niches even after B cell depletion therapy. The numbers of residual renal B cells have been evaluated after rituximab treatment in biopsies from patients with lupus nephritis. B cells were detected in most biopsies, and the presence of renal B cells was associated with poor treatment response even when circulating B cells were low or undetectable[54,55]. In addition, although patients with SLE and a long-term response to rituximab showed an altered B cell composition in the tonsils compared with patients with untreated SLE, germinal centre reactions persisted in these samples[51]. In contrast to the very low levels of circulating memory B cells, this suggests that memory B cell depletion in tissue by rituximab is less effective than in blood.

Similar findings have been reported in other rheumatic diseases. In Sjögren syndrome, rituximab does not affect the presence of clonally related immunoglobulin-producing cells in salivary glands[56]. In RA, B cells remain detectable in the lymph nodes after rituximab treatment[57] and the presence of residual B cells in synovial tissue is associated with disease activity[58–60]. Taken together, although rituximab treatment decreases the number of B cells in secondary lymphoid organs and peripheral tissue, residual B cells often persist in these sites, even in the absence of circulating B cells, suggesting that B cells in secondary lymphoid organs change more slowly than peripheral B cells.

Mechanisms of non-response

The chimeric composition of rituximab with murine variable regions increases immunogenicity and the risks of antidrug reactions. Up to a fifth of patients with SLE who receive rituximab have a good initial response but develop secondary non-depletion and non-response (2NDNR) with repeated use[61]. Symptoms and signs of 2NDNR include a severe infusion reaction that lasts >24 h during the second infusion of a cycle, failure to completely deplete B cells and lack of a clinical response[52]. This is suggestive of an immune reaction against rituximab,

Box 2 | Autoantigens as drivers of B cell activation in SLE

In its symptomatology, a systemic lupus erythematosus (SLE) flare resembles a viral infection, with fatigue, arthralgia and oral ulcers, as well as pleuritis and leukopenia, and both conditions involve immunological reactions directed against nucleotides[175]. However, instead of appropriately eliminating viral RNA and DNA, SLE involves an inappropriate reactivity induced by endogenous nucleotides that manifests in the presence of antinuclear antibodies (ANAs). If these autoantibodies were primarily caused by monoclonal B cell dysfunction (for example, by stochastically arising autoreactive B cells) and perpetuated by T cell help and epitope spreading in germinal centre reactions, then elimination of the resulting clones might be expected to induce a sustained drug-free remission. Cure through elimination of B cell clones has been suggested to be the aim of future B cell-targeted therapy[99]. However, several lines of evidence argue against this theory.

The ANAs observed in SLE comprise antibodies against a diverse mixture of intracellular antigens, including single-stranded and double-stranded DNA, histones and ribonuclear proteins that accumulate leading up to symptom onset[143]. These antigens are not connected by a shared molecular structure, but by their intracellular location and their persistence after defective apoptotic clearance[144,176,177]. SLE susceptibility can be conferred by loss-of-function mutations that increase the availability of these antigens, such as TREX1, which impairs their clearance during apoptosis, or gain-of-function mutations in loci that increase the innate sensing of these antigens, such as STING[145,146,176]. Such antigen generation and sensing is a feature of all nucleated cells, not just the circulating immune system.

In addition, a monogenic TLR7 gain-of-function mutation was recently described leading to typical and severe SLE symptoms[21]. The carrier was a young girl who developed SLE by the age of 7 years with elevated ANA, hypocomplementaemia, inflammatory arthralgia and renal involvement[21]. Additional analyses revealed a further two patients with monogenic variants in TLR7 causing SLE disease[21]. Notably, the gain-of-function mutation in TLR7 caused SLE symptoms in mice by extrafollicular activation of B cells[21]. TLR7 escapes X chromosome inactivation leading to a higher expression in females than in males, and the endogenous X-inactive specific transcript (XIST) contributes a rich source of endogenous TLR7 ligands in female patients with SLE[178]. Thus, the alteration of the sensing of nuclear material by TLR7 is sufficient to induce typical and severe lupus, and may at least partly explain the female bias in SLE.

Hence, the antibody repertoire of SLE is not what one would predict from a series of stochastic B cell autoreactive events with epitope spreading leading to B cell clones as the primary cause of autoreactivity. Instead, these data collectively suggest that B cell autoreactivity is secondary to increased sensitivity to these antigens, and loss of function in clearing these antigens during apoptosis. These latter mechanisms would be predicted to return after any B cell-directed therapy, no matter what intensity of depletion or quality of remission is achieved.

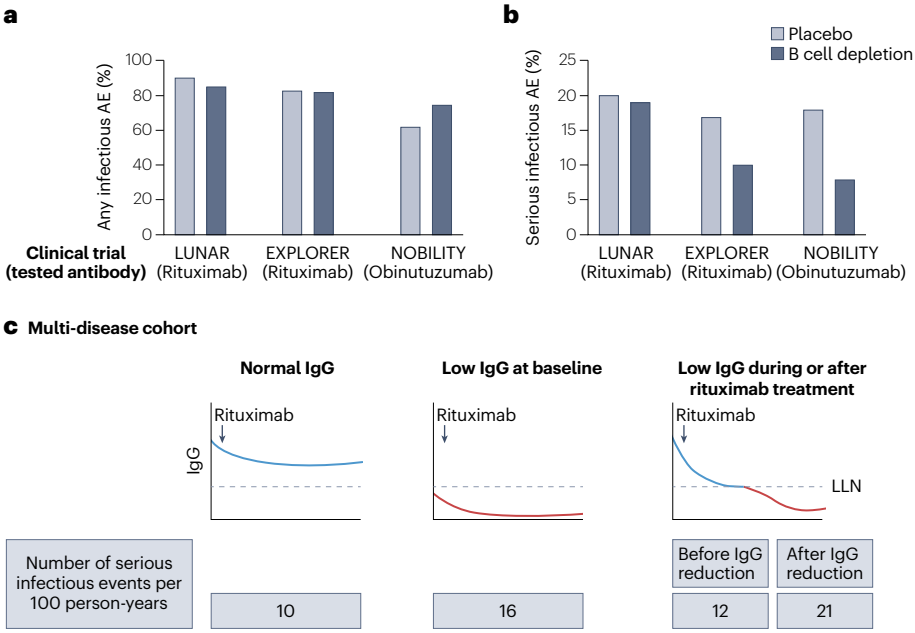


Fig. 2 | No evidence for increased risk of infections by B cell depletion across multiple trials. Across multiple trials of patients with systemic lupus erythematosus (SLE), there is no evidence for increased risk of any (part **a**) or serious (part **b**) infections following B cell depletion therapy compared with placebo[34,35,67]. However, in a mixed cohort of patients with rheumatic diseases (part **c**), patients with low IgG levels at baseline or patients with hypogammaglobulinaemia during treatment had increased risk of serious infection after treatment with rituximab[72]. Active SLE is associated with increased risk of infection (part **d**), and this risk may be reduced by treatment. However, sustained B cell depletion is likely to cause hypogammaglobulinaemia, which is associated with increased risk of infection. AE, adverse event; LLN, lower limit of normal.

and the presence of rituximab-specific antibodies is common in patients with SLE who develop 2NDNR. Thus, in primary responders to rituximab, subsequent treatment failure might occur because of insufficient B cell depletion, and tailored strategies to optimize depletion can restore clinical response.

Patients with mucocutaneous disease and, in particular, with chronic cutaneous lupus erythematosus (CCLE) have a low clinical response rate to rituximab[52,62]. In these patients, the level of B cell depletion is not associated with CCLE response rates, CCLE non-response is not associated with low response in other domains, and new cutaneous lesions erupt during the period of B cell depletion, suggesting that a primary non-response with B cell-independent inflammation is probably involved in CCLE[62]. Indeed, CCLE is initiated by keratinocyte apoptosis, which leads to exposure of nuclear antigens and type I IFN production. Thus, patients with CCLE might be better suited to a between-class switch to type I IFN targeted therapy[63,64]

Managing long-term safety

A common misconception is that B cell depletion inherently increases the risk of infection[65]. Across multiple trials in SLE, no significant differences in the proportion of adverse or serious adverse events were found between placebo and B cell depletion agents, and infection rates were numerically lower in treated patients than in those receiving placebo (Fig. 2a,b). In registry data of patients with moderate-to-severe

SLE, rituximab, the BAFF inhibitor belimumab and standard immunosuppression were associated with similar rates of serious infection[66]. Although patients with SLE might be sometimes told that treatment with rituximab might increase the risk of infection, a general increase in serious infections has not been observed[34,35,67]. Patients with SLE are likely to have an increased risk of infection due to their disease and their treatment with glucocorticoids[68]. While suppressing immunity, specific targeting of B cells with rituximab can allow glucocorticoid tapering and normalization of other immune cells and molecules, which might potentially improve the endogenous defence against infections.

In the case of COVID-19, treatment with B cell depletion agents was initially associated with a higher risk of severe infection in patients with immune-mediated disease[69]. However, vaccination offered protection with every new dose received[70]. Together with the decreased immunogenicity of the virus, the risk of severe COVID-19 infection in patients with systemic rheumatic diseases abated towards the end of the pandemic[71].

In around 15% of patients, repeated rituximab treatment leads to hypogammaglobulinaemia[38]. In a multi-disease cohort, low IgG at baseline was associated with an increased risk of serious infections, and a reduction in IgG levels occurring during or after treatment doubled the risk compared with normal IgG levels[72] (Fig. 2c). Immunoglobulin levels are probably sustained by long-lived plasma cells, and although targeting CD20-positive B cells does not affect plasma cells directly, it reduces the number of plasma cell precursors. Exposure to cyclophosphamide and glucocorticoids, as well as multimorbidity, also increase the risk of hypogammaglobulinaemia[72–74]. Thus, although B cell depletion is desirable for active disease and does not affect the short-term risk of infection, in a proportion of patients, repeated rituximab treatment leads to a reduction in immunoglobulin levels that is associated with an increased risk of serious infections (Fig. 2d). This calls for a tailored approach to B cell depletion. While acknowledging the infectious risks of alternative treatment options, monitoring of immunoglobulin levels before each cycle of rituximab allows an individualized risk–benefit analysis.

B cell depletion therapies beyond rituximab

Several B cell depletion therapies are under development in SLE. These include two types of enhanced monoclonal antibodies that are specific to CD20: type I anti-CD20 antibodies have the ability to reorganize the CD20 molecule into lipid rafts, whereas type II anti-CD20 antibodies affect CD20 distribution in the plasma membrane to a lesser extent. Type I monoclonal antibodies include, in addition to rituximab, ocrelizumab and ofatumumab, which are humanized and fully human, respectively, to ensure reduced immunogenicity. The afucosylated type II monoclonal CD20-specific antibody obinutuzumab, as well as CAR T cells and BiTEs that redirect T cells towards B cell targets, have been developed to achieve deeper B cell depletion. In addition, combination treatment with BAFF inhibition using ianalumab, and plasma cell-directed treatment with the proteasome inhibitor bortezomib or the CD38-specific antibody daratumumab are treatment strategies designed to improve and direct B cell depletion. An overview of the mechanisms of emergent B cell depletion therapies is presented in Fig. 3.

Type I anti-CD20 antibodies

The chimeric nature of rituximab occasionally induces immune reactivity, and the formation of antidrug antibodies often impairs clinical

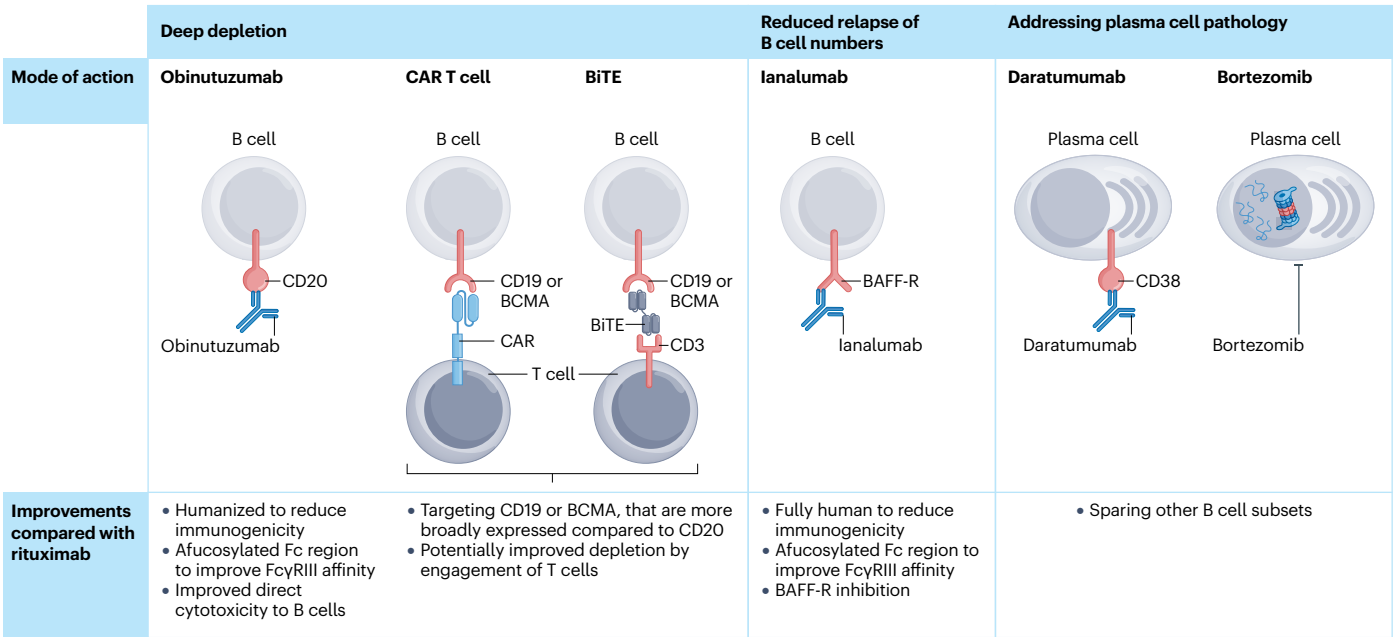


Fig. 3 | Emergent B lineage depletion therapies in SLE. The emergent B cell depletion therapies use various modes of action that confer distinct advantages compared with rituximab for B cell depletion. Deep B cell depletion is attempted through the actions of type II monoclonal antibodies against CD20, such as obinutuzumab, or by chimeric antigen receptor (CAR) T cells and bispecific T cell engagers (BiTEs) that target CD19 or B cell maturation antigen (BCMA). A combination of B cell depletion and inhibition of B cell-activating factor receptor (BAFF-R) with ianalumab could reduce the relapse of B cell numbers after B cell depletion and potentially prolong the duration of the treatment effect. In patients with evidence of plasma cell involvement and antibody-mediated inflammation, treatment with the CD38-specific monoclonal antibody daratumumab or a proteasome inhibitor such as bortezomib might be more targeted to the pathology of their individual systemic lupus erythematosus (SLE) disease. FcγRIII, Fcγ receptor III.

effects and reduces safety. One humanized (ocrelizumab) and one fully human (ofatumumab) type I monoclonal antibodies are, thus, currently under evaluation in SLE. Ofatumumab is a type I anti-CD20 IgG1 monoclonal antibody that targets both the large and the small external loops of CD20, recognizing epitopes that are distinct from those targeted by rituximab. Ofatumumab was shown to be well tolerated in a single-centre case series, and achieved B cell depletion in 12 out of 14 patients with SLE. In this setting, 6 months after treatment with ofatumumab six of the 12 patients with lupus nephritis had achieved renal remission[75]. Treatment with ofatumumab also showed clinical effects in smaller case series in patients with juvenile SLE or lupus nephritis[76,77]. However, this was not the case for ocrelizumab, a humanized IgG1 monoclonal antibody that recognizes the same epitope as rituximab on the large extracellular loop of CD20. A study evaluating ocrelizumab along with background immunosuppressive therapy in patients with lupus nephritis was terminated early owing to an increased risk of serious infections, some of which were fatal, in patients receiving background mycophenolate mofetil (MMF). At the time of study termination and despite efficient B cell depletion in peripheral blood, renal responses were not significantly better in patients receiving ocrelizumab plus MMF than in those receiving placebo[78]. Thus, following the results of these trials, alternative type I anti-CD20 antibodies have not yet demonstrated promise regarding efficacy.

Type II anti-CD20 antibodies

Obinutuzumab is a humanized type II monoclonal antibody targeting CD20, and recognizes an overlapping epitope together with rituximab but at a different orientation[79]. Obinutuzumab is less efficient at clustering CD20 into lipid rafts than type I monoclonal antibodies such as rituximab. Although this limits cellular death through CDC, it also reduces internalization of the CD20–obinutuzumab complex, thereby increasing ADCC. In total, this leads to a net improvement in B cell depletion[9,80–82]. In addition, the Fc region of obinutuzumab is afucosylated to improve affinity to FcγRIII on effector cells. This enhances B cell depletion through ADCC[80,82]. In direct comparison with rituximab, obinutuzumab displays improved B cell depletion through FcγRIII-mediated activation of NK cells and ADCC, and obinutuzumab is also more potent in inducing direct cell death[80,82].

In the NOBILITY phase II randomized controlled trial (RCT), obinutuzumab or placebo infusions were administered during weeks 1, 2, 24 and 26 together with standard-of-care[83]. The addition of obinutuzumab led to rapid depletion of peripheral B cells, including memory B cells, plasmablasts and naive B cells[67]. These biological effects were associated with an increased proportion of patients who reached complete renal response by week 52, together with significantly improved estimated glomerular filtration rate and proteinuria. In a post hoc analysis, obinutuzumab also decreased the risk of lupus nephritis flares[84]. The treatment was well tolerated with similar numbers of adverse events in the treatment group and the placebo group[67]. The REGENCY phase III RCT is a randomized double-blind placebo-controlled trial of the efficacy and safety of obinutuzumab together with MMF and glucocorticoids in lupus nephritis, including a total of 271 patients, that appears to have met its primary end point, as announced in the company's press release[85,86]. Here, a higher proportion of patients were reported to have achieved the primary end point of complete renal response when treated with obinutuzumab compared with patients receiving standard therapy. This indicates that improved B cell depletion may translate to clinical efficacy in SLE, and it may come down to the safety profile of obinutuzumab to determine its place as a novel B cell-targeted treatment strategy in SLE.

CAR T cells

CAR-expressing T cells combine direct antigen recognition with the effector mechanisms of T cells. Thereby, ordinary immune checkpoints are bypassed, and the CAR T cell is activated in an MHC-independent manner[87]. Adoptive transfer of CAR T cells directed towards the CD19 antigen was approved in 2017 for the treatment of two types of refractory B cell-derived malignancies. Long-term effects vary depending on the type of malignancy, but CAR T cells induced durable remission for a proportion of the patients with the longest follow-up extending over a decade[88]. In SLE, CAR T cells targeting CD19 were first administered in 2021 as part of a compassionate use scheme to a woman with severe and refractory SLE despite several treatments, including rituximab and belimumab[89]. After leukapheresis, autologous T cells were activated and transduced with a lentiviral anti-CD19 CAR vector, expanded in vitro, and returned to the patient's blood. As the CAR T cells expanded, B cells were depleted, serology normalized, and clinical remission was achieved.

This first case report was followed by two publications detailing the treatment of a total of eight patients with refractory and multiorgan SLE, four of whom had previously failed rituximab[90,91]. In all patients, drug-free remission was achieved by 6 months after autologous CAR T cell delivery, and remission was accompanied by seroconversion, normalization of complement levels, and disappearance of proteinuria. CAR T cells rapidly expanded until day 9 after transfer and then rapidly declined. B cells were absent a few days after infusion but reappeared after about 100 days. The repopulating B cells were preferentially non-class-switched, whereas the numbers of memory B cells remained reduced and plasmablasts were low to absent. Despite the reappearance of B cells, no clinical relapse occurred during a follow-up period of 6–29 months.

In patients with B cell lymphoma and other malignancies that are treated with CAR T cells, adverse events are common and include cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenias, hypogammaglobulinaemia and infections[88,92]. In the patients with SLE who have received CAR T cells so far, toxic effects have been mostly mild, possibly attributable to a lower load of B cells in SLE than in B cell-derived malignancies[89–91]. It is noteworthy that long-term follow-up in cancer research has shown a non-trivial risk of non-relapse mortality. In a meta-analysis, around half of the non-relapse mortality cases were caused by infections, but almost 8% were attributed to the development of other malignant diseases[93]. In addition, case reports have described T cell-derived malignancies following CAR T cell therapy[94]. These observations highlight the need for long-term follow-up to ensure maintained remission and safety of CAR T cell therapies in SLE and other autoimmune diseases. The substantially lower mortality in SLE than in malignant disease increases the impact of long-term outcomes on the choice of therapy.

CAR T cells targeting CD19 are currently under evaluation in several phase I and II studies and some new technologies are under very early investigation in SLE, as described below. A case report described a patient with SLE and B cell lymphoma treated with CAR T cells designed to target both CD19 and BCMA[95]. This treatment would be expected to affect plasma cells to a larger degree, as BCMA is predominantly expressed on mature B cells. B cells were depleted but had recovered to normal levels by 9 months after infusion. The disease remained stable until follow-up 23 months after treatment. However, there was a marked reduction in total immunoglobulin levels, and the patient received prophylactic treatment with intravenous immunoglobulin to limit the risk of infection.

Various types of immune cells, including NK cells, can be transformed to produce CAR construct expressing therapies, as demonstrated by CAR regulatory T (T_{reg}) cells targeting CD19 that improved serology and delayed lymphopenia in SLE-prone mice[96]. In addition, chimeric autoantibody receptor T cells could be designed to specifically target the B cells that produce autoantibodies involved in disease pathogenesis, a concept established in pemphigus vulgaris that could be applicable to autoantibodies in SLE, such as anti-dsDNA or anti-C1q[97].

An argument for the use of CAR T cells in autoimmunity is that their cellular mechanism of B cell killing might be superior to that of monoclonal antibodies. In addition, CAR T cells might have improved penetrance to peripheral tissues and secondary lymphoid organs where pathogenic B cells reside[98]. In comparison with rituximab, depletion of peripheral B cells and immunoglobulin levels were similar, but a complete depletion of $CD19^+$ and $CD20^+$ B cells was observed in the lymph nodes of patients treated with CAR T cells but not in the lymph nodes of patients treated with rituximab[98].

CAR T cell therapies have also been suggested to potentially achieve long-term clinical remission[90]. Across patients with malignant diseases that received CAR T cell therapy, at least a proportion have remained in remission for over a decade, despite the reduction in CAR T cell numbers and the B cell repopulation that occur over time[88]. However, this information cannot be directly applied to autoimmune diseases. B cell malignancies are initiated by single expanded B cell clones, and after elimination of such clonotypes it is less probable that the same disease-causing mutation would arise de novo. By contrast, SLE involves polyclonal B cell activation directed towards several distinct nuclear and intracellular antigens[15]. Even after initial depletion of autoreactive B cell clones, continuous exposure of such antigens is expected to drive new autoreactive B cell clones in the context of a susceptible host.

In addition, CAR T cell therapies differ from strategies that are based on monoclonal antibodies in terms of patient effort and economic costs. At present, CAR T cells are not produced at scale, and most protocols involve the use of autologous T cells[99]. Pretreatment conditioning, leukapheresis and initial follow-up is a time-consuming process requiring long periods of hospitalization for the patient and large initial costs for the healthcare system. These costs could be mitigated in the long term if CAR T cells survive and expand, creating a pool of T cells with the potential to respond even before disease is clinically evident. In addition, the development of allogenic CAR T cells could reduce the logistic requirements and improve treatment availability[100]. The first available report of use of allogeneic anti-CD19 CAR T cells in rheumatic disease included one patient with severe myositis and two patients with systemic sclerosis[101]. To prevent rejection and improve persistence, genes for the T cell receptor and certain MHC molecules were knocked out using CRISPR–CAS9-based gene editing. The treatment was well tolerated, disease activity was reduced, and quality of life improved for the three participants. This is a rapidly developing field, and advances in T cell engineering and manufacturing of off-the-shelf CAR T cell products might increase availability and reduce the time requirement for future patients, as well as reduce costs for the healthcare system.

Overall, although the promise of CAR T cell therapy has generated much excitement, the therapy is still nascent, and it needs to be emphasized that no controlled studies have been reported so far. The obvious comparator arm in such studies would be monoclonal antibody-mediated B cell depletion with type I or type II antibodies. Moreover, key questions must be answered before it can be concluded that CAR T cells are qualitatively better than monoclonal antibodies in terms of B cell depletion or a long-term cure in SLE. These include their comparative efficacy and added value both regarding immunological biomarkers and clinical outcome. In addition, a large, powered study with defined primary and secondary outcomes and long-term follow-up will be essential to understand the safety and efficacy of CAR T cells in SLE.

Bispecific T cell engagers

Unlike monoclonal antibodies, which recognize only one antigen, T cell-engaging bispecific antibodies simultaneously engage two surface antigens: one on a target cell, and one on an endogenous T cell, which is redirected to the target. BiTEs are small, flexible bispecific antibodies that lack an Fc region. The first approved BiTE still in use, blinatumomab, was used in relapsed or refractory acute lymphoblastic leukaemia[102]. Blinatumomab depletes B cells by connecting two single-chain variable immunoglobulin fragments, recognizing CD19 and CD3ε, respectively[102]. As the B and T cells are brought into proximity, the T cell is activated in a polyclonal manner and secretes perforin that lyses the B cell[103]. Blinatumomab has since been administered in one patient with rapidly progressive systemic sclerosis, with swift improvement of symptoms[104], as well as in a case series of six patients with severe resistant RA[105]. Circulating B cells, and particularly the $CD27^+$ memory B cell subset, were reduced and serology improved in all patients with RA who received blinatumomab. Clinically, the numbers of tender and swollen joints decreased, and remission was achieved. In two out of three patients who had a synovial biopsy, blinatumomab completely depleted synovial B cells. This deep depletion may be influenced by the broader range of expression of CD19, which probably leads to additional plasmablast and plasma cell killing with blinatumomab compared with approaches targeting CD20. In addition, the T cell engagement and killing mechanisms of BiTEs are likely to be superior to monoclonal antibody-mediated killing, although this has not yet been proven.

Teclistamab, a BiTE recognizing CD3 and BCMA, also showed efficacy in one patient with active lupus nephritis[106], as well as in four patients with other rheumatic diseases, including systemic sclerosis, idiopathic inflammatory myositis, primary Sjögren syndrome and RA[107]. During the first few weeks after treatment, B cells were depleted, especially the plasmablast and plasma cell subsets, and serology and disease activity scores normalized. Several of the patients showed grade 1–2 cytokine release syndrome, infections and hypogammaglobulinaemia, side effects that have previously been reported with the use of teclistamab in patients with multiple myeloma[108].

BiTEs are similar to CAR T cells in that they both require a functional T cell compartment, and several adverse reactions are shared, including cytokine-release syndrome and ICANS. However, similar to monoclonal antibodies, BiTEs are recombinant off-the-shelf proteins without interpatient variability. This gives the advantage of a short time from decision to infusion without the need for patient conditioning. The short half-life of BiTEs also means that continuous treatment might be required for long-term effects to be achieved. Overall, BiTEs have emerged as a promising therapeutic modality in SLE, and further investigations in SLE are planned.

Combination with BAFF receptor blockade

B cell activation and survival is promoted by BAFF, and BAFF inhibition with belimumab has been shown to reduce disease activity in a

Glossary

B cell-activating factor
Also called B lymphocyte stimulator; a potent B cell activator and survival factor that promotes B cell maturation.

Double-negative B cells
B cells that have class switched and lack expression of IgD but also the memory marker CD27. Of these, DN2 cells have higher expression of CD11c and T-BET and are increased in the circulation in patients with SLE.

Fcγ receptor III
Activating Fc receptor that mediates interaction between the Fc domain of antibodies and FcγR-bearing effector cells.

Plasmablasts
A heterogeneous subset of short-lived circulating antibody-producing cells that might lie outside a $CD19^+$ lymphocyte gate in flow cytometry and can be defined as $CD3^-CD14^-CD19^{+/-}CD38^{++}CD27^{++}$ mononuclear cells.

Transitional B cells
B cells that have successfully recombined their surface receptor and exited the bone marrow but are not yet fully mature. Depending on their stage of transition, they can be $CD24^{hi}CD38^{hi}$.

proportion of patients with refractory SLE[109,110]. A proliferation-inducing ligand (APRIL) shares some cell surface receptors with BAFF and also has a key role in B cell maturation and survival[111]. The BAFF and APRIL inhibitors telitacicept and atacicept have both shown some efficacy in phase II studies of SLE[112–114].

The concentration of BAFF is elevated in patients with SLE after treatment with rituximab, and these increased BAFF levels have been associated with disease relapse and higher disease activity[115–117]. In mice, excess BAFF was able to rescue self-reactive early B cells from deletion and improved survival of new B cells emerging from the bone marrow[118,119]. The BAFF receptor (BAFF-R) is highly expressed on certain B cell subpopulations[13,14], and combining B cell depletion with BAFF-R inhibition has the potential to delay B cell repopulation and provide longer duration of remission after B cell depletion.

Ianalumab is a human anti-BAFF-R IgG1 monoclonal antibody that combines B cell depletion with blockade of BAFF-R-mediated signalling. Ianalumab is afucosylated, thereby ensuring enhanced depletion through interaction with FcγRIII-bearing cells, and can be administered subcutaneously. Ianalumab was not internalized by acute leukaemia B cells, and it showed enhanced depletion of chronic leukaemia B cells by ADCC compared with monoclonal antibodies directed towards CD20 (refs. 120,121). In a phase IIb trial in Sjögren syndrome, ianalumab reduced disease activity and was overall well tolerated[122]. Preliminary interim data from the phase II SIRIUS RCT in SLE demonstrated both efficacy and safety, with a larger number of patients achieving SLE responder index 4 (SRI-4) response with sustained steroid reduction in the treatment arm compared with patients receiving placebo[123,124].

The combination of B cell depletion and BAFF inhibition with belimumab has been evaluated in several trials. In the CALIBRATE, SYNBIOSE and BLISS-BELIEVE studies, B cell depletion and serology improved[125–127]. Although the CALIBRATE and BLISS-BELIEVE studies did not demonstrate clinical improvement by combination treatment, belimumab was found to reduce the risk of severe flare in the BEAT-LUPUS trial[125,127,128]. Thus, the results of the SYNBIOSE-2 phase III RCT that is currently in progress in patients with anti-dsDNA-positive, severe SLE are anticipated with interest[129]. Indeed, combination treatment might be particularly relevant in patients who have tested positive for anti-dsDNA autoantibodies and, in particular, for anti-dsDNA antibodies of the IgA2 subtype, as these antibodies have emerged as a relevant predictor for clinical response of belimumab after rituximab[115,130]. In the BLISS-BELIEVE trial, the combination treatment seemed more effective in the subgroup that was anti-dsDNA-positive at baseline[127]. Thus, when there is biological response to rituximab but insufficient depletion, add-on therapy with belimumab might be beneficial, especially in patients with high anti-dsDNA autoantibody titres.

Targeting plasma cells

Plasma cells are important for autoantibody production but are unresponsive to anti-CD20-directed B cell depletion. In addition, $CD19^{low}$ antibody-secreting cell populations are abundant in patients with active SLE and correlate with disease activity[131]. The maintenance of vaccination responses after both rituximab and CAR T cell treatment suggests that memory B cells and long-lived plasma cells are likely to resist depletion strategies[91,132]. Treatment directed specifically towards plasma cells might be beneficial in certain patients, particularly when there is evidence for antibody-mediated inflammation. Daratumumab is a monoclonal antibody targeting CD38, which is highly expressed on plasmablasts and plasma cells[11,12]. After ligation of CD38, daratumumab induces cell death through ADCC, ADCP and CDC.

A few patients with SLE have been treated with daratumumab thus far. In two patients, daratumumab depleted plasma cells, reduced dsDNA-specific antibodies, and decreased SLE disease activity index scores[133]. In addition, daratumumab decreased type I IFN pathway activation in these patients. The titre of vaccine-induced response to tetanus toxoid declined. Responses were sustained at follow-up 3 years after treatment[134]. These initial results were followed by a case series of six patients with refractory lupus nephritis[135]. Three of these patients receiving daratumumab experienced a complete renal response, whereas two patients had a partial renal response during follow-up until 12 months. Commonly reported adverse events have been hypogammaglobulinaemia, infusion reactions and infections[136].

Another way to target plasma cells is through proteasome inhibition. The proteasome destroys proteins marked for degradation, and its inhibition cause the accumulation of misfolded proteins which leads to apoptosis[137]. Plasma cells are especially vulnerable to proteasome inhibitors owing to their high rate of protein production during antibody synthesis[137]. Thus, treatment of patients with SLE with the proteasome inhibitor bortezomib led to rapid depletion of plasma cells while other B cells were mostly unchanged[138]. Bortezomib initially showed promise in case series; in one study in lupus nephritis, four out of five patients achieved a complete or partial response, and in three studies, each including 12 patients, disease activity declined and serology improved[138–141]. However, bortezomib displayed significant toxicity, with reduction in total immunoglobulins and vaccination responses, and has frequently been discontinued. In an RCT that included 14 patients, four out of eight in the bortezomib group discontinued treatment due to adverse effects, and although SRI was numerically higher in the treatment group, it was not significantly affected by treatment[142]. Thus, adverse reactions may limit the use of bortezomib, and its initial promise has not been corroborated by subsequent trials.

Choice of therapy after rituximab failure

In case of treatment failure with rituximab, the choice of subsequent therapy can be guided by the residual B cell count (Fig. 4). This necessitates high-sensitivity flow cytometry and directs treatment towards

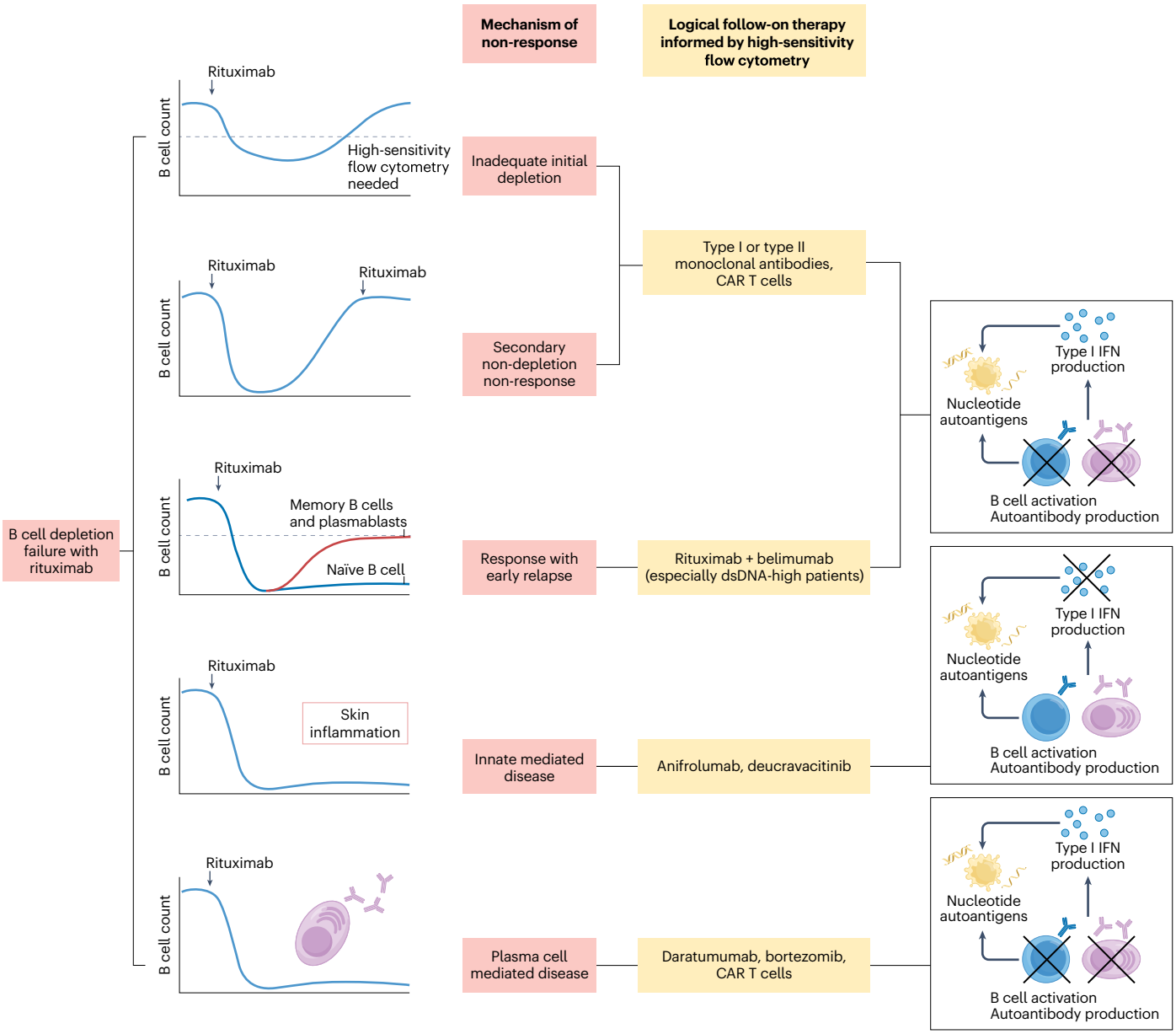


Fig. 4 | Options after B cell depletion failure with rituximab with currently licensed or off-label drugs. The choice of therapy after B cell depletion failure with rituximab can be guided by the B cell count. High-sensitivity flow cytometry is needed to measure rare B cell subpopulations and determine residual B cell counts, and might help stratify patients with systemic lupus erythematosus. In case of inadequate initial depletion or secondary non-depletion non-response, the logical follow-on therapy would be to use another type I or II monoclonal antibody against CD20, such as obinutuzumab, or chimeric antigen receptor (CAR) T cells, to improve depletion. When there is a biological response but early relapse, add-on therapy with the B cell-activating factor receptor inhibitor belimumab might be beneficial, especially in patients with high anti-dsDNA antibody titres. When disease, particularly disease involving skin inflammation, is mediated by innate immune cells or by plasma cells, treatment could be designed to target these pathways instead. dsDNA, double-stranded DNA; IFN, interferon.

the active immunological mechanisms in the individual disease. In case of inadequate initial B cell depletion or 2NDNR, given the prior good response to rituximab, the logical follow-on therapy would be improved depletion with another type I or II monoclonal antibody against CD20. Switching to one of the alternative CD20-targeting monoclonal antibodies ocrelizumab, ofatumumab or obinutuzumab restored depletion and clinical response in patients with 2NDNR[52]. This within-class switch was more effective than switching to a BAFF inhibitor[61]. In the future, CAR T cells and BiTEs might become options in this treatment arsenal. When there is B cell depletion with early relapse, add-on therapy with belimumab might be beneficial, especially in patients with high anti-dsDNA autoantibody titres. When B cells are depleted without clinical response, disease may be mediated not by B cells but by innate cells or plasma cells, and treatment could be designed to target these pathways instead.

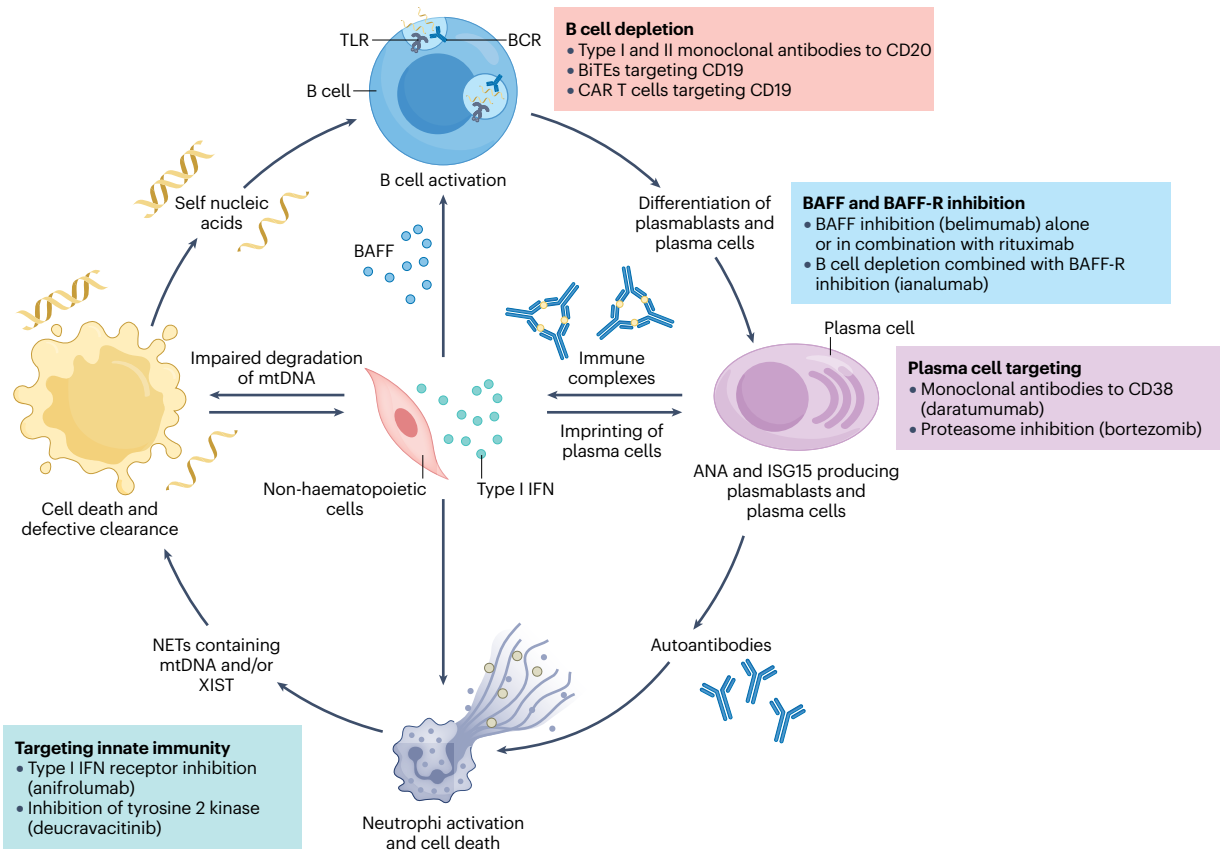


Fig. 5 | B cell-intrinsic and B cell-extrinsic mechanisms in SLE pathogenesis. Cell death, impaired degradation of extracellular nucleotides, impaired mitophagy of damaged mitochondria, and exposure to ultraviolet light have been associated with presentation of autoantigens to autoreactive B cells in systemic lupus erythematosus (SLE). After binding to their cognate B cell receptors (BCR), autoantigens are taken up in endosomes in the B cell. With simultaneous TLR7 stimulation, the B cell is activated and can differentiate intrafollicularly or extrafollicularly to become an antibody-producing cell. Extracellular nucleotides such as the X-inactive specific transcript (XIST) long non-coding RNA also induce type I interferon (IFN) production from non-haematopoietic cells. Mitochondrial DNA (mtDNA) is highly immunogenic and induces an interferon response, especially in its oxidized form. In most cells, damaged mitochondria are removed by mitophagy, through which an endophagosome sequesters mtDNA and fuses with a lysosome. However, neutrophils are constitutively unable to perform mitophagy and may instead extrude complexes of mtDNA and protein in neutrophil extracellular traps (NETs)[151,152]. Ribonucleoprotein-containing immune complexes and TLR activation increase NET formation and the extrusion of mtDNA[152–154]. Type I IFN in turn impairs the degradation of mtDNA[155]. Type I IFN and its downstream mediators stimulate B cell-activating factor (BAFF) production and B cell activation, induce B cell differentiation to plasmablasts, and imprint plasma cells. Immune complexes are formed in the presence of sufficient amounts of autoantigen and add another interferonogenic stimulus. Both type I IFN and certain antinuclear antibodies (ANAs) induce neutrophil death through NETosis, through which intracellular autoantigens are exposed, further contributing to the inflammatory vicious circle. Treatments that specifically deplete B cells and plasma cells are depicted, as well as treatments that may supersede B cell depletion, including inhibition of BAFF and innate pathways using currently licensed or off-label drugs. BAFF-R, BAFF receptor; BiTEs, bispecific T cell engagers.

Further limitations of B cell depletion in SLE

In the larger perspective, a limitation of B cell depletion therapeutic strategies in SLE involves the complex immunology underpinning the SLE disease. First, the autoreactivity of B cells in SLE does not develop in isolation but is induced by TLR7-triggered hyperresponsiveness of the immune system secondary to autoantigen exposure (Box 2). During progression to SLE, the autoantibody repertoire is expanded recognizing a broader range of various intracellular targets, including nucleotides and their binding proteins[143]. The recognized proteins are molecularly dissimilar but share an adjacent intracellular location[144]. Processes that increase the extracellular availability of these autoantigens are likely to precede the accumulating loss of B cell tolerance[145,146]. Accordingly, single-gene variants sufficient to cause severe and typical lupus mainly affect the removal and sensing of extracellular nucleotides and waste[147]. These initiating and perpetuating processes would be expected to be maintained even after complete B cell depletion.

Second, lupus develops successively over a period of several years, and innate immune mechanisms have a prominent role during early disease development. Indeed, IFN-stimulated genes were found to be upregulated in antinuclear antibody (ANA)-positive individuals who later developed SLE but not in ANA-positive individuals who remained healthy[148]. In these individuals, as in patients with established SLE, autoantibody production is heavily interconnected with the type I IFN system (Box 1).

Together, these studies of the complex non-immune and innate involvement in SLE development are compatible with a model in which

increased availability, elevated sensing of nucleic autoantigens, or both, lead to potent TLR signalling that triggers type I IFN production and extrafollicular B cell differentiation. Once established, innate immune signalling and B cells will stimulate each other, leading to a vicious circle of immune activation and damage in SLE (Fig. 5).

This vicious circle might underly a major limitation of B cell depletion therapies. If polyclonally activated B cells function within a network of cellular interactions and are activated and imprinted by their microenvironment, these innate and non-immune mechanisms would remain present in patients with SLE even in a state of full depletion of B cells[15,149]. If so, this would mean that fundamental pathophysiological mechanisms of SLE are not dependent on B cells and might be unresponsive to B cell therapy.

If this is the case, the degree to which relapse would occur after complete depletion of B cells is unknown. Considering that only a small fraction of individuals with ANA positivity develop SLE, despite widespread immune abnormalities, it is conceivable that a similar small but substantial proportion of patients might relapse after deep B cell depletion with antibody-based or cellular therapy in the future, whereas the majority of patients receiving such treatments might be able to live with stable subclinical autoimmunity[150]. However, the genetic and immune abnormalities that once caused SLE might also eventually lead to relapse in most patients after a brief or longer period of remission. Although B cell depletion may lead to clinical quiescence, it is expected that patients with SLE will remain immunologically complex.

Conclusions

Rituximab efficacy has been long known to depend on the depth and duration of B cell depletion. Improved B cell depletion mechanisms of therapeutics that are based on monoclonal antibodies, such as obinutuzumab and ianalumab, or on B cell targeting by T cells (for example using BiTEs or CAR T cells), are likely to translate into clinical efficacy. The multifaceted nature of SLE means that there will probably be occasion for several different treatment options and argues for personalized treatment according to the underlying immunological networks that are activated in individual patients with SLE. Predictive biomarkers that enable us to choose the treatment option with the highest likelihood of improvement for the clinical and immunological disease pattern of the individual patient, balancing short-term and long-term cost, toxicity and patient effort in the process, will be required for aiding clinical decisions.

However, the extent to which the various treatment options will be used remains unclear. So far, there are few direct comparisons between the treatment modalities regarding immunological and biological effects and no head-to-head trials comparing clinical efficacy. Planned studies of B cell depletion agents seldom compare them with existing monoclonal antibody-mediated B cell depletion regarding biomarkers or clinical outcome.

While awaiting head-to-head trials, targeting the active immunological pathways of the individual disease may have promise for optimizing treatment in each patient, given the complex nature of the SLE disease. Measuring B cell subpopulations might be relevant to evaluating disease activity, determining the immunological efficacy of B cell depletion and aiding in the decision to continue or discontinue B cell depletion therapy. To guide therapeutic B cell targeting in patients with SLE, a thorough understanding of the pathophysiology of B cells in relation to other immune abnormalities in SLE and of the limitations of B cell depletion therapies are required. The clinician's interpretation of how B cells are activated in SLE determines how we predict if B cell depletion therapies will work. If B cells are intrafollicularly activated by T cell interactions resulting in isolated clones of intrinsically autoreactive cells, then depleting these clones deeply enough could cure the disease. However, if B cells are polyclonally and extrafollicularly activated, a long-term cure for SLE will probably need to equally target B cell-driven, innate and non-immune mechanisms.

Published online: 15 January 2025

References

1. Aringer, M. et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol.* **71**, 1400–1412 (2019).
2. Looney, R. J. et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. *Arthritis Rheum.* **50**, 2580–2589 (2004).
3. Leandro, M. J., Edwards, J. C., Cambridge, G., Ehrenstein, M. R. & Isenberg, D. A. An open study of B lymphocyte depletion in systemic lupus erythematosus. *Arthritis Rheum.* **46**, 2673–2677 (2002).
4. Cohen, S. B. et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum.* **54**, 2793–2806 (2006).
5. Jones, R. B. et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N. Engl. J. Med.* **363**, 211–220 (2010).
6. Smith, R. M. et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. *Ann. Rheum. Dis.* **79**, 1243–1249 (2020).
7. Guillevin, L. et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N. Engl. J. Med.* **371**, 1771–1780 (2014).
8. Specks, U. et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N. Engl. J. Med.* **369**, 417–427 (2013).
9. Reddy, V. et al. Internalization of rituximab and the efficiency of B cell depletion in rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Rheumatol.* **67**, 2046–2055 (2015).
10. Lim, S. H. et al. Fc gamma receptor IIb on target B cells promotes rituximab internalization and reduces clinical efficacy. *Blood* **118**, 2530–2540 (2011).
11. Cole, S. et al. Integrative analysis reveals CD38 as a therapeutic target for plasma cell-rich pre-disease and established rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Res. Ther.* **20**, 85 (2018).
12. Clavarino, G. et al. Novel strategy for phenotypic characterization of human B lymphocytes from precursors to effector cells by flow cytometry. *PLoS ONE* **11**, e0162209 (2016).
13. Álvarez Gómez, J. A. et al. BAFF system expression in double negative 2, activated naïve and activated memory B cells in systemic lupus erythematosus. *Front. Immunol.* **14**, 1235937 (2023).
14. Rodig, S. J., Shahsafaei, A., Li, B., Mackay, C. R. & Dorfman, D. M. BAFF-R, the major B cell-activating factor receptor, is expressed on most mature B cells and B-cell lymphoproliferative disorders. *Hum. Pathol.* **36**, 1113–1119 (2005).
15. Tipton, C. M. et al. Diversity, cellular origin and autoreactivity of antibody-secreting cell population expansions in acute systemic lupus erythematosus. *Nat. Immunol.* **16**, 755–765 (2015).
16. Rivero, S. J., Díaz-Jouanen, E. & Alarcón-Segovia, D. Lymphopenia in systemic lupus erythematosus. Clinical, diagnostic, and prognostic significance. *Arthritis Rheum.* **21**, 295–305 (1978).
17. Dörner, T. & Lipsky, P. E. The essential roles of memory B cells in the pathogenesis of systemic lupus erythematosus. *Nat. Rev. Rheumatol.* **20**, 770–782 (2024).
18. Odendahl, M. et al. Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus. *J. Immunol.* **165**, 5970–5979 (2000).
19. Liu, M. et al. Type I interferons promote the survival and proinflammatory properties of transitional B cells in systemic lupus erythematosus patients. *Cell. Mol. Immunol.* **16**, 367–379 (2019).
20. Suurmond, J. et al. Patterns of ANA$^+$ B cells for SLE patient stratification. *JCI Insight* **4**, e127885 (2019).
21. Brown, G. J. et al. TLR7 gain-of-function genetic variation causes human lupus. *Nature* **605**, 349–356 (2022).
22. Suurmond, J. et al. Loss of an IgG plasma cell checkpoint in patients with lupus. *J. Allergy Clin. Immunol.* **143**, 1586–1597 (2019).
23. Eckl-Dorna, J. & Batista, F. D. BCR-mediated uptake of antigen linked to TLR9 ligand stimulates B-cell proliferation and antigen-specific plasma cell formation. *Blood* **113**, 3969–3977 (2009).
24. Lau, C. M. et al. RNA-associated autoantigens activate B cells by combined B cell antigen receptor/Toll-like receptor 7 engagement. *J. Exp. Med.* **202**, 1171–1177 (2005).
25. Leadbetter, E. A. et al. Chromatin–IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature* **416**, 603–607 (2002).
26. Jenks, S. A. et al. Distinct effector B cells induced by unregulated Toll-like receptor 7 contribute to pathogenic responses in systemic lupus erythematosus. *Immunity* **49**, 725–739.e6 (2018).

27. Walsh, E. R. et al. Dual signaling by innate and adaptive immune receptors is required for TLR7-induced B-cell-mediated autoimmunity. *Proc. Natl Acad. Sci. USA* **109**, 16276–16281 (2012).
28. Wei, C. et al. A new population of cells lacking expression of CD27 represents a notable component of the B cell memory compartment in systemic lupus erythematosus. *J. Immunol.* **178**, 6624–6633 (2007).
29. Baxter, R. M. et al. Expansion of extrafollicular B and T cell subsets in childhood-onset systemic lupus erythematosus. *Front. Immunol.* **14**, 1208282 (2023).
30. Sasaki, T. et al. Longitudinal immune cell profiling in patients with early systemic lupus erythematosus. *Arthritis Rheumatol.* **74**, 1808–1821 (2022).
31. Lam, J. H. & Baumgarth, N. Toll-like receptor mediated inflammation directs B cells towards protective antiviral extrafollicular responses. *Nat. Commun.* **14**, 3979 (2023).
32. Jacobi, A. M. et al. HLA-DR^{high}/CD27^{high} plasmablasts indicate active disease in patients with systemic lupus erythematosus. *Ann. Rheum. Dis.* **69**, 305–308 (2010).
33. Banchereau, R. et al. Personalized immunomonitoring uncovers molecular networks that stratify lupus patients. *Cell* **165**, 551–565 (2016).
34. Rovin, B. H. et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum.* **64**, 1215–1226 (2012).
35. Merrill, J. T. et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum.* **62**, 222–233 (2010).
36. Reddy, V., Jayne, D., Close, D. & Isenberg, D. B-cell depletion in SLE: clinical and trial experience with rituximab and ocrelizumab and implications for study design. *Arthritis Res. Ther.* **15**, S2 (2013).
37. McCarthy, E. M. et al. Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register. *Rheumatology* **57**, 470–479 (2018).
38. Aguiar, R., Araújo, C., Martins-Coelho, G. & Isenberg, D. Use of rituximab in systemic lupus erythematosus: a single center experience over 14 years. *Arthritis Care Res.* **69**, 257–262 (2017).
39. Díaz-Lagares, C. et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. *Autoimmun. Rev.* **11**, 357–364 (2012).
40. Lan, L., Han, F. & Chen, J. H. Efficacy and safety of rituximab therapy for systemic lupus erythematosus: a systematic review and meta-analysis. *J. Zhejiang Univ. Sci. B* **13**, 731–744 (2012).
41. Ramos-Casals, M., Soto, M. J., Cuadrado, M. J. & Khamashta, M. A. Rituximab in systemic lupus erythematosus: a systematic review of off-label use in 188 cases. *Lupus* **18**, 767–776 (2009).
42. Galarza-Maldonado, C. et al. The administration of low doses of rituximab followed by hydroxychloroquine, prednisone and low doses of mycophenolate mofetil is an effective therapy in Latin American patients with active systemic lupus erythematosus. *Autoimmun. Rev.* **10**, 108–111 (2010).
43. Vital, E. M. et al. B cell biomarkers of rituximab responses in systemic lupus erythematosus. *Arthritis Rheum.* **63**, 3038–3047 (2011).
44. Turner-Stokes, T. et al. The efficacy of repeated treatment with B-cell depletion therapy in systemic lupus erythematosus: an evaluation. *Rheumatology* **50**, 1401–1408 (2011).
45. Anolik, J. H. et al. The relationship of FcγRIIIa genotype to degree of B cell depletion by rituximab in the treatment of systemic lupus erythematosus. *Arthritis Rheum.* **48**, 455–459 (2003).
46. Robinson, J. I. et al. Comprehensive genetic and functional analyses of Fc gamma receptors influence on response to rituximab therapy for autoimmunity. *EBioMedicine* **86**, 104343 (2022).
47. Vital, E. M., Dass, S., Buch, M. H., Rawstron, A. C. & Emery, P. An extra dose of rituximab improves clinical response in rheumatoid arthritis patients with initial incomplete B cell depletion: a randomised controlled trial. *Ann. Rheum. Dis.* **74**, 1195–1201 (2015).
48. Albert, D. et al. Variability in the biological response to anti-CD20 B cell depletion in systemic lupus erythaematosus. *Ann. Rheum. Dis.* **67**, 1724–1731 (2008).
49. Gomez Mendez, L. M. et al. Peripheral blood B cell depletion after rituximab and complete response in lupus nephritis. *Clin. J. Am. Soc. Nephrol.* **13**, 1502–1509 (2018).
50. Anolik, J. H. et al. Rituximab improves peripheral B cell abnormalities in human systemic lupus erythematosus. *Arthritis Rheum.* **50**, 3580–3590 (2004).
51. Anolik, J. H. et al. Delayed memory B cell recovery in peripheral blood and lymphoid tissue in systemic lupus erythematosus after B cell depletion therapy. *Arthritis Rheum.* **56**, 3044–3056 (2007).
52. Md Yusof, M. Y. et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. *Ann. Rheum. Dis.* **76**, 1829–1836 (2017).
53. Weisel, N. M. et al. Comprehensive analyses of B-cell compartments across the human body reveal novel subsets and a gut-resident memory phenotype. *Blood* **136**, 2774–2785 (2020).
54. Gunnarsson, I. et al. Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. *Arthritis Rheum.* **56**, 1263–1272 (2007).
55. Reddy, V. R. et al. Disparity in peripheral and renal B-cell depletion with rituximab in systemic lupus erythematosus: an opportunity for obinutuzumab? *Rheumatology* **61**, 2894–2904 (2022).
56. Nishath, H. et al. Persistence of immunoglobulin-producing cells in parotid salivary glands of patients with primary Sjögren's syndrome after B cell depletion therapy. *Ann. Rheum. Dis.* **71**, 1881 (2012).
57. Ramwadhdoebe, T. H. et al. Effect of rituximab treatment on T and B cell subsets in lymph node biopsies of patients with rheumatoid arthritis. *Rheumatology* **58**, 1075–1085 (2019).
58. Thurlings, R. M. et al. Clinical response, pharmacokinetics, development of human anti-chimaeric antibodies, and synovial tissue response to rituximab treatment in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **69**, 409–412 (2010).
59. Teng, Y. K., Levarht, E. W., Toes, R. E., Huizinga, T. W. & van Laar, J. M. Residual inflammation after rituximab treatment is associated with sustained synovial plasma cell infiltration and enhanced B cell repopulation. *Ann. Rheum. Dis.* **68**, 1011–1016 (2009).
60. Kavanaugh, A. et al. Assessment of rituximab's immunomodulatory synovial effects (ARISE trial). 1: clinical and synovial biomarker results. *Ann. Rheum. Dis.* **67**, 402–408 (2008).
61. Hassan, S. U., Md Yusof, M. Y., Emery, P., Dass, S. & Vital, E. M. Biologic sequencing in systemic lupus erythematosus: after secondary non-response to rituximab, switching to humanised anti-CD20 agent is more effective than belimumab. *Front. Med.* **7**, 498 (2020).
62. Vital, E. M. et al. Brief report: responses to rituximab suggest B cell-independent inflammation in cutaneous systemic lupus erythematosus. *Arthritis Rheumatol.* **67**, 1586–1591 (2015).
63. Bao, A., Petri, M. A., Fava, A. & Kang, J. Case series of anifrolumab for treatment of cutaneous lupus erythematosus and lupus-related mucocutaneous manifestations in patients with SLE. *Lupus Sci. Med.* **10**, e001007 (2023).
64. Morand, E. F. et al. Trial of anifrolumab in active systemic lupus erythematosus. *N. Engl. J. Med.* **382**, 211–221 (2020).
65. He, J. & Li, Z. Dilemma of immunosuppression and infection risk in systemic lupus erythematosus. *Rheumatology* **62**, i22–i29 (2023).
66. Rodziewicz, M. et al. Early infection risk in patients with systemic lupus erythematosus treated with rituximab or belimumab from the British Isles Lupus Assessment Group Biologics Register (BILA-BR): a prospective longitudinal study. *Lancet Rheumatol.* **5**, e284–e292 (2023).
67. Furie, R. A. et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **81**, 100–107 (2022).
68. Migita, K. et al. Glucocorticoid therapy and the risk of infection in patients with newly diagnosed autoimmune disease. *Medicine* **92**, 285–293 (2013).
69. Patel, N. J. et al. Coronavirus disease 2019 outcomes among recipients of anti-CD20 monoclonal antibodies for immune-mediated diseases: a comparative cohort study. *ACR Open. Rheumatol.* **4**, 238–246 (2022).
70. Md Yusof, M. Y. et al. Breakthrough SARS-CoV-2 infections and prediction of moderate-to-severe outcomes during rituximab therapy in patients with rheumatic and musculoskeletal diseases in the UK: a single-centre cohort study. *Lancet Rheumatol.* **5**, e88–e98 (2023).
71. Kawano, Y. et al. Temporal trends in COVID-19 outcomes among patients with systemic autoimmune rheumatic diseases: from the first wave through the initial Omicron wave. *Ann. Rheum. Dis.* **81**, 1742–1749 (2022).
72. Md Yusof, M. Y. et al. Predicting severe infection and effects of hypogammaglobulinemia during therapy with rituximab in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol.* **71**, 1812–1823 (2019).
73. Fassbinder, T. et al. Differential effects of cyclophosphamide and mycophenolate mofetil on cellular and serological parameters in patients with systemic lupus erythematosus. *Arthritis Res. Ther.* **17**, 92 (2015).
74. Marco, H. et al. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. *BMC Musculoskelet. Disord.* **15**, 178 (2014).
75. Masoud, S., McAdoo, S. P., Bedi, R., Cairns, T. D. & Lightstone, L. Ofatumumab for B cell depletion in patients with systemic lupus erythematosus who are allergic to rituximab. *Rheumatology* **57**, 1156–1161 (2018).
76. Cinar, O. K. et al. Ofatumumab use in juvenile systemic lupus erythematosus: a single centre experience. *Lupus* **30**, 527–530 (2021).
77. Haarhaus, M. L., Svenungsson, E. & Gunnarsson, I. Ofatumumab treatment in lupus nephritis patients. *Clin. Kidney J.* **9**, 552–555 (2016).
78. Mysler, E. F. et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. *Arthritis Rheum.* **65**, 2368–2379 (2013).
79. Niederfellner, G. et al. Epitope characterization and crystal structure of GA101 provide insights into the molecular basis for type I/II distinction of CD20 antibodies. *Blood* **118**, 358–367 (2011).
80. Herter, S. et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. *Mol. Cancer Ther.* **12**, 2031–2042 (2013).
81. Tipton, T. R. W. et al. Antigenic modulation limits the effector cell mechanisms employed by type I anti-CD20 monoclonal antibodies. *Blood* **125**, 1901–1909 (2015).
82. Reddy, V. et al. Obinutuzumab induces superior B-cell cytotoxicity to rituximab in rheumatoid arthritis and systemic lupus erythematosus patient samples. *Rheumatology* **56**, 1227–1237 (2017).
83. US National Library of Medicine. *ClinicalTrials.gov* clinicaltrials.gov/study/NCT02550652 (2024).
84. Rovin, B. H. et al. Kidney outcomes and preservation of kidney function with obinutuzumab in patients with lupus nephritis: a post hoc analysis of the NOBILITY trial. *Arthritis Rheumatol.* **76**, 247–254 (2024).

85. Genentech. Positive phase III results for Genentech's Gazyva show superiority to standard therapy alone in people with lupus nephritis. *Genentech* www.gene.com/media/press-releases/15038/2024-09-25/positive-phase-iii-results-for-genentech (2024).
86. US National Library of Medicine. *ClinicalTrials.gov* clinicaltrials.gov/study/NCT04221477 (2024).
87. Sterner, R. C. & Sterner, R. M. CAR-T cell therapy: current limitations and potential strategies. *Blood Cancer J.* **11**, 69 (2021).
88. Cappell, K. M. & Kochenderfer, J. N. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat. Rev. Clin. Oncol.* **20**, 359–371 (2023).
89. Mougiakakos, D. et al. CD19-targeted CAR T cells in refractory systemic lupus erythematosus. *N. Engl. J. Med.* **385**, 567–569 (2021).
90. Mackensen, A. et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat. Med.* **28**, 2124–2132 (2022).
91. Müller, F. et al. CD19 CAR T-cell therapy in autoimmune disease – a case series with follow-up. *N. Engl. J. Med.* **390**, 687–700 (2024).
92. Neelapu, S. S. et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N. Engl. J. Med.* **377**, 2531–2544 (2017).
93. Cordas dos Santos, D. M. et al. A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy. *Nat. Med.* **30**, 2667–2678 (2024).
94. Verdun, N. & Marks, P. Secondary cancers after chimeric antigen receptor T-cell therapy. *N. Engl. J. Med.* **390**, 584–586 (2024).
95. Zhang, W. et al. Treatment of systemic lupus erythematosus using BCMA-CD19 compound CAR. *Stem Cell Rev. Rep.* **17**, 2120–2123 (2021).
96. Doglio, M. et al. Regulatory T cells expressing CD19-targeted chimeric antigen receptor restore homeostasis in systemic lupus erythematosus. *Nat. Commun.* **15**, 2542 (2024).
97. Lee, J. et al. Antigen-specific B cell depletion for precision therapy of mucosal pemphigus vulgaris. *J. Clin. Invest.* **130**, 6317–6324 (2020).
98. Tur, C. et al. CD19-CAR T-cell therapy induces deep tissue depletion of B cells. *Ann. Rheum. Dis.* https://doi.org/10.1136/ard-2024-226142 (2024).
99. Schett, G., Mackensen, A. & Mougiakakos, D. CAR T-cell therapy in autoimmune diseases. *Lancet* **402**, 2034–2044 (2023).
100. Labanieh, L. & Mackall, C. L. CAR immune cells: design principles, resistance and the next generation. *Nature* **614**, 635–648 (2023).
101. Wang, X. et al. Allogeneic CD19-targeted CAR-T therapy in patients with severe myositis and systemic sclerosis. *Cell* **187**, 4890–4904.e9 (2024).
102. Klein, C., Brinkmann, U., Reichert, J. M. & Kontermann, R. E. The present and future of bispecific antibodies for cancer therapy. *Nat. Rev. Drug. Discov.* **23**, 301–319 (2024).
103. Gruen, M., Bommert, K. & Bargou, R. C. T-cell-mediated lysis of B cells induced by a CD19xCD3 bispecific single-chain antibody is perforin dependent and death receptor independent. *Cancer Immunol. Immunother.* **53**, 625–632 (2004).
104. Subklewe, M. et al. Application of blinatumomab, a bispecific anti-CD3/CD19 T-cell engager, in treating severe systemic sclerosis: a case study. *Eur. J. Cancer* **204**, 114071 (2024).
105. Bucci, L. et al. Bispecific T cell engager therapy for refractory rheumatoid arthritis. *Nat. Med.* **30**, 1593–1601 (2024).
106. Alexander, T., Krönke, J., Cheng, Q., Keller, U. & Krönke, G. Teclistamab-induced remission in refractory systemic lupus erythematosus. *N. Engl. J. Med.* **391**, 864–866 (2024).
107. Hagen, M. et al. BCMA-targeted T-cell-engager therapy for autoimmune disease. *N. Engl. J. Med.* **391**, 867–869 (2024).
108. Moreau, P. et al. Teclistamab in relapsed or refractory multiple myeloma. *N. Engl. J. Med.* **387**, 495–505 (2022).
109. Parodis, I. et al. Attainment of remission and low disease activity after treatment with belimumab in patients with systemic lupus erythematosus: a post-hoc analysis of pooled data from five randomised clinical trials. *Lancet Rheumatol.* **6**, e751–e761 (2024).
110. Furie, R. et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum.* **63**, 3918–3930 (2011).
111. Vincent, F. B., Morand, E. F., Schneider, P. & Mackay, F. The BAFF/APRIL system in SLE pathogenesis. *Nat. Rev. Rheumatol.* **10**, 365–373 (2014).
112. Wu, D. et al. Telitacicept in patients with active systemic lupus erythematosus: results of a phase 2b, randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **83**, 475 (2024).
113. Merrill, J. T. et al. Efficacy and safety of atacicept in patients with systemic lupus erythematosus: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled, parallel-arm, phase IIb study. *Arthritis Rheumatol.* **70**, 266–276 (2018).
114. Isenberg, D. et al. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). *Ann. Rheum. Dis.* **74**, 2006–2015 (2015).
115. Carter, L. M., Isenberg, D. A. & Ehrenstein, M. R. Elevated serum BAFF levels are associated with rising anti-double-stranded DNA antibody levels and disease flare following B cell depletion therapy in systemic lupus erythematosus. *Arthritis Rheum.* **65**, 2672–2679 (2013).
116. Cambridge, G. et al. B cell depletion therapy in systemic lupus erythematosus: relationships among serum B lymphocyte stimulator levels, autoantibody profile and clinical response. *Ann. Rheum. Dis.* **67**, 1011–1016 (2008).
117. Vallerskog, T. et al. Differential effects on BAFF and APRIL levels in rituximab-treated patients with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Res. Ther.* **8**, R167 (2006).
118. Thien, M. et al. Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. *Immunity* **20**, 785–798 (2004).
119. Hsu, B. L., Harless, S. M., Lindsley, R. C., Hilbert, D. M. & Cancro, M. P. Cutting edge: BLyS enables survival of transitional and mature B cells through distinct mediators. *J. Immunol.* **168**, 5993–5996 (2002).
120. Parameswaran, R. et al. Effector-mediated eradication of precursor B acute lymphoblastic leukemia with a novel Fc-engineered monoclonal antibody targeting the BAFF-R. *Mol. Cancer Ther.* **13**, 1567–1577 (2014).
121. McWilliams, E. M. et al. Anti-BAFF-R antibody VAY-736 demonstrates promising preclinical activity in CLL and enhances effectiveness of ibrutinib. *Blood Adv.* **3**, 447–460 (2019).
122. Bowman, S. J. et al. Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled, phase 2b dose-finding trial. *Lancet* **399**, 161–171 (2022).
123. Lee, S.-S. et al. Interim safety and efficacy of subcutaneous (s.c.) dose ianalumab (VAY736; anti-BAFF-R mAb) administered monthly over 28 weeks in patients with systemic lupus erythematosus (SLE) [abstract LO-021]. *Lupus Sci. Med.* **10** (Suppl. 1), A17–A18 (2023).
124. Cortés-Hernández, J. et al. Safety and efficacy of subcutaneous (s.c.) dose ianalumab (VAY736; anti-BAFFR mAb) administered monthly over 28 weeks in patients with systemic lupus erythematosus (SLE) [abstract POS0120]. *Ann. Rheum. Dis.* **82**, 275–276 (2023).
125. Atisha-Fregoso, Y. et al. Phase II randomized trial of rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis. *Arthritis Rheumatol.* **73**, 121–131 (2021).
126. Kraaij, T. et al. Long-term effects of combined B-cell immunomodulation with rituximab and belimumab in severe, refractory systemic lupus erythematosus: 2-year results. *Nephrol. Dial. Transpl.* **36**, 1474–1483 (2021).
127. Aranow, C. et al. Efficacy and safety of sequential therapy with subcutaneous belimumab and one cycle of rituximab in patients with systemic lupus erythematosus: the phase 3, randomised, placebo-controlled BLISS-BELIEVE study. *Ann. Rheum. Dis.* **83**, 1502–1512 (2024).
128. Shipa, M. et al. Effectiveness of belimumab after rituximab in systemic lupus erythematosus: a randomized controlled trial. *Ann. Intern. Med.* **174**, 1647–1657 (2021).
129. van Schaik, M. et al. Efficacy of belimumab combined with rituximab in severe systemic lupus erythematosus: study protocol for the phase 3, multicenter, randomized, open-label Synbiose 2 trial. *Trials* **23**, 939 (2022).
130. Shipa, M. et al. Identification of biomarkers to stratify response to B-cell-targeted therapies in systemic lupus erythematosus: an exploratory analysis of a randomised controlled trial. *Lancet Rheumatol.* **5**, e24–e35 (2023).
131. Chen, W. et al. Distinct transcriptomes and autocrine cytokines underpin maturation and survival of antibody-secreting cells in systemic lupus erythematosus. *Nat. Commun.* **15**, 1899 (2024).
132. Cambridge, G. et al. B cell depletion therapy in systemic lupus erythematosus: effect on autoantibody and antimicrobial antibody profiles. *Arthritis Rheumatol.* **54**, 3612–3622 (2006).
133. Ostendorf, L. et al. Targeting CD38 with daratumumab in refractory systemic lupus erythematosus. *N. Engl. J. Med.* **383**, 1149–1155 (2020).
134. Alexander, T. et al. Sustained responses after anti-CD38 treatment with daratumumab in two patients with refractory systemic lupus erythematosus. *Ann. Rheum. Dis.* **82**, 1497–1499 (2023).
135. Roccatello, D. et al. Daratumumab monotherapy for refractory lupus nephritis. *Nat. Med.* **29**, 2041–2047 (2023).
136. Holzer, M. T. et al. Daratumumab for autoimmune diseases: a systematic review. *RMD Open* **9**, e003604 (2023).
137. Obeng, E. A. et al. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. *Blood* **107**, 4907–4916 (2006).
138. Alexander, T. et al. The proteasome inhibitior bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. *Ann. Rheum. Dis.* **74**, 1474–1478 (2015).
139. Segarra, A. et al. Efficacy and safety of bortezomib in refractory lupus nephritis: a single-center experience. *Lupus* **29**, 118–125 (2020).
140. Zhang, H. et al. The short-term efficacy of bortezomib combined with glucocorticoids for the treatment of refractory lupus nephritis. *Lupus* **26**, 952–958 (2017).
141. Walhelm, T. et al. Clinical experience of proteasome inhibitor bortezomib regarding efficacy and safety in severe systemic lupus erythematosus: a nationwide study. *Front. Immunol.* **12**, 756941 (2021).
142. Ishii, T. et al. Multicenter double-blind randomized controlled trial to evaluate the effectiveness and safety of bortezomib as a treatment for refractory systemic lupus erythematosus. *Mod. Rheumatol.* **28**, 986–992 (2018).
143. Arbuckle, M. R. et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N. Engl. J. Med.* **349**, 1526–1533 (2003).
144. Shao, W. H. & Cohen, P. L. Disturbances of apoptotic cell clearance in systemic lupus erythematosus. *Arthritis Res. Ther.* **13**, 202 (2011).
145. Grieves, J. L. et al. Exonuclease TREX1 degrades double-stranded DNA to prevent spontaneous lupus-like inflammatory disease. *Proc. Natl Acad. Sci. USA* **112**, 5117–5122 (2015).
146. Lee-Kirsch, M. A. et al. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 are associated with systemic lupus erythematosus. *Nat. Genet.* **39**, 1065–1067 (2007).

147. Vinuesa, C. G., Shen, N. & Ware, T. Genetics of SLE: mechanistic insights from monogenic disease and disease-associated variants. *Nat. Rev. Nephrol.* **19**, 558–572 (2023).
148. Carter, L. M. et al. Blood RNA-sequencing across the continuum of ANA-positive autoimmunity reveals insights into initiating immunopathology. *Ann. Rheum. Dis.* **83**, 1322–1334 (2024).
149. Care, M. A. et al. Network analysis identifies proinflammatory plasma cell polarization for secretion of ISG15 in human autoimmunity. *J. Immunol.* **197**, 1447–1459 (2016).
150. Md Yuzaiful Md, Y. et al. Prediction of autoimmune connective tissue disease in an at-risk cohort: prognostic value of a novel two-score system for interferon status. *Ann. Rheum. Dis.* **77**, 1432 (2018).
151. Lood, C. et al. Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. *Nat. Med.* **22**, 146–153 (2016).
152. Caielli, S. et al. Oxidized mitochondrial nucleoids released by neutrophils drive type I interferon production in human lupus. *J. Exp. Med.* **213**, 697–713 (2016).
153. Lood, C., Arve, S., Ledbetter, J. & Elkon, K. B. TLR7/8 activation in neutrophils impairs immune complex phagocytosis through shedding of FcgRIIA. *J. Exp. Med.* **214**, 2103–2119 (2017).
154. Garcia-Romo, G. S. et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci. Transl. Med.* **3**, 73ra20 (2011).
155. Gkirtzimanaki, K. et al. IFNα impairs autophagic degradation of mtDNA promoting autoreactivity of SLE monocytes in a STING-dependent fashion. *Cell Rep.* **25**, 921–933.e5 (2018).
156. Kalaaji, M. et al. Glomerular apoptotic nucleosomes are central target structures for nephritogenic antibodies in human SLE nephritis. *Kidney Int.* **71**, 664–672 (2007).
157. DeGiorgio, L. A. et al. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. *Nat. Med.* **7**, 1189–1193 (2001).
158. Yurasov, S. et al. Persistent expression of autoantibodies in SLE patients in remission. *J. Exp. Med.* **203**, 2255–2261 (2006).
159. Psarras, A. et al. Functionally impaired plasmacytoid dendritic cells and non-haematopoietic sources of type I interferon characterize human autoimmunity. *Nat. Commun.* **11**, 6149 (2020).
160. Baechler, E. C. et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc. Natl Acad. Sci. USA* **100**, 2610–2615 (2003).
161. Mathian, A. et al. Ultrasensitive serum interferon-α quantification during SLE remission identifies patients at risk for relapse. *Ann. Rheum. Dis.* **78**, 1669–1676 (2019).
162. Stockfelt, M. et al. Plasma interferon-alpha protein levels during pregnancy are associated with lower birth weight in systemic lupus erythematosus. *Rheumatology* https://doi.org/10.1093/rheumatology/keae332 (2024).
163. Laurent, A. et al. Burden of systemic lupus erythematosus in clinical practice: baseline data from the SLE Prospective Observational Cohort Study (SPOCS) by interferon gene signature. *Lupus Sci. Med.* **10**, e001032 (2023).
164. Castellano, G. et al. Local synthesis of interferon-alpha in lupus nephritis is associated with type I interferons signature and LMP7 induction in renal tubular epithelial cells. *Arthritis Res. Ther.* **17**, 72 (2015).
165. Toukap, A. N. et al. Identification of distinct gene expression profiles in the synovium of patients with systemic lupus erythematosus. *Arthritis Rheum.* **56**, 1579–1588 (2007).
166. Stockfelt, M. et al. Activated low-density granulocytes in peripheral and intervillous blood and neutrophil inflammation in placentas from SLE pregnancies. *Lupus Sci. Med* **8**, e000463 (2021).
167. Reynolds, J. A. et al. Type I interferon in patients with systemic autoimmune rheumatic disease is associated with haematological abnormalities and specific autoantibody profiles. *Arthritis Res. Ther.* **21**, 147 (2019).
168. Torell, A. et al. Low $CD4^+$ T cell count is related to specific anti-nuclear antibodies, IFNα protein positivity and disease activity in systemic lupus erythematosus pregnancy. *Arthritis Res. Ther.* **26**, 65 (2024).
169. Stockfelt, M. et al. Plasma interferon-alpha is associated with double-positivity for autoantibodies but is not a predictor of remission in early rheumatoid arthritis – a spin-off study of the NORD-STAR randomized clinical trial. *Arthritis Res. Ther.* **23**, 189 (2021).
170. Bekeredjian-Ding, I. B. et al. Plasmacytoid dendritic cells control TLR7 sensitivity of naive B cells via type I IFN. *J. Immunol.* **174**, 4043–4050 (2005).
171. Jego, G. et al. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. *Immunity* **19**, 225–234 (2003).
172. Ittah, M. et al. B cell-activating factor of the tumor necrosis factor family (BAFF) is expressed under stimulation by interferon in salivary gland epithelial cells in primary Sjögren's syndrome. *Arthritis Res. Ther.* **8**, R51 (2006).
173. Eloranta, M. L. et al. Regulation of the interferon-α production induced by RNA-containing immune complexes in plasmacytoid dendritic cells. *Arthritis Rheum.* **60**, 2418–2427 (2009).
174. Hua, J., Kirou, K., Lee, C. & Crow, M. K. Functional assay of type I interferon in systemic lupus erythematosus plasma and association with anti-RNA binding protein autoantibodies. *Arthritis Rheum.* **54**, 1906–1916 (2006).
175. Chasset, F. et al. Rare diseases that mimic systemic lupus erythematosus (lupus mimickers). *Joint Bone Spine* **86**, 165–171 (2019).
176. König, N. et al. Familial chilblain lupus due to a gain-of-function mutation in STING. *Ann. Rheum. Dis.* **76**, 468–472 (2017).
177. Tsokos, G. C., Lo, M. S., Costa Reis, P. & Sullivan, K. E. New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat. Rev. Rheumatol.* **12**, 716–730 (2016).
178. Crawford, J. D. et al. The XIST lncRNA is a sex-specific reservoir of TLR7 ligands in SLE. *JCI Insight* **8**, e169344 (2023).

Author contributions

All authors researched data for the article. All authors contributed substantially to discussion of the content. M.S. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

M.S. declares no competing interests. E.M.V. has received consultancy fees from Roche, GSK, AstraZeneca, UCB, Otsuka, BMS, Pfizer, Abbvie, Pfizer, Alpine, Alumis, Merck, BMS, Aurinia Pharmaceuticals, Lilly and Novartis, and has also received research grants paid to his employer from AstraZeneca and Sandoz. Y.K.O.T. has received grants/research support from the Dutch Arthritis Foundation, Autoimmune Research & Collaboration (ARCH) Foundation, Dutch Kidney Foundation, Netherlands Organization for Scientific Research, GSK, CSL Vifor and LUMC, and has received consulting fees from AstraZeneca, Alexion, GSK, Novartis, Otsuka Pharmaceuticals and Vifor Pharma.

Additional information

Peer review information *Nature Reviews Rheumatology* thanks William Stohl, Gregg Silverman and Muhammad Shipa for their contribution to the peer review of this work.