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REVIEW ARTICLE

B Cell Depletion Therapy in Systemic Lupus Erythematosus, Where Are We Now, Where Are We Going?

Teresa V. Gouveia[1*], Lucía B. Molinero[2*], David A. Isenberg[3*].

[1] Department of Internal Medicine, Centro Hospitalar Lisboa-Norte, Lisboa, Portugal.
[2] Department of Internal Medicine, Hospital Provincial del Centenario, Rosario, Argentina.
[3] Centre for Rheumatology, Department of Medicine, University College London, London, United Kingdom

*These authors contributed equally to this work.

Corresponding author: d.isenberg@ucl.ac.uk

ABSTRACT
Systemic lupus erythematosus (SLE) is a life-threatening autoimmune disease, which involves the production of class-switched autoantibodies against intracellular antigens, particularly nuclear antigens, leading to tissue damage and immune complex deposition in multiple organs. Strategies for B cell modulation include direct depletion using monoclonal antibodies, such as rituximab, or indirect impairment of survival via targeting B cell activating factors, notably belimumab. While the pursuit of autoreactive B cell modulation has yielded progress, challenges persist, including modest therapeutic responses, allergic reactions and infections. Thus, to overcome these challenges and focus on achieving a more effective B cell depletion, new strategies may involve fully humanized monoclonal antibodies, such as obinutuzumab, which demonstrated promising results in the NOBILITY study, involving patients with lupus nephritis, Another approach is the use of chimeric antigen receptor T cells therapy, a strategy that has been approved for the treatment of patients with relapsed or refractory B-cell malignancies and has been shown in lupus patients to lead to a rapid and sustained breakdown of the B cell-mediated autoimmune response, reported to lead to drug-free remission of refractory SLE. In addition, combinations of existing therapies and innovative cellular approaches, such rituximab plus belimumab, have been studied. There have now been four studies describing the use of a rituximab plus belimumab in lupus nephritis and non-renal lupus. In the BEAT-LUPUS, the primary endpoint (reduction in anti-double strand DNA) was achieved, however, in BLISS-BELIEVE study the primary endpoint (Systemic Lupus Erythematosus Disease Activity Index 2000) was not met. The CALIBRATE trial was a safety study. The SynBioSe 1 study demonstrated clinical improvement, as indicated by the Systemic Lupus Erythematosus Disease Activity Index and Lupus Low Disease Activity State indices.
This review will provide a brief review of the established conventional approaches to B cell depletion and then discuss the trends towards innovative concepts aimed at achieving this goal.
Keywords: B cell depletion; CAR-T cell; Systemic lupus erythematosu

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous, unpredictable autoimmune disease characterized by class-switched antibodies to intracellular antigens, particularly nuclear antigens. These antibodies can bind directly to tissues or form immune complexes causing damage in multiple organs [1]. As producers of autoantibodies, an adaptative immune response is mediated by B cells, making them the main target of different therapies that lead to direct depletion or indirectly, through the use of monoclonal antibodies (mAbs) [2,3].

Proposed B cell therapeutic targets have included direct depletion of B cell expressed surface molecules such as CD20 (targeted by rituximab). Alternatively, mAb function can be influenced by targeting B cell activating factors such as B cell activating factor (BAFF) and a proliferation inducing ligand (APRIL). These mAbs indirectly affect B cell survival. For example, belimumab, the first biologic agent to be approved for use in SLE and lupus nephritis (LN), inhibits BAFF [4].

Although rituximab did not meet its primary endpoints in major clinical trials, its utility has been recognised in many open label studies and it is recommended in the guidelines for the therapy of LN, by both the American College of Rheumatology (ACR) [5] and European Alliance of Associations for Rheumatology (EULAR) [6]. It can be rapid in onset and has been used to treat diverse SLE clinical features. Unfortunately, it may be associated with side effects which limit its use. In contrast belimumab has met its primary endpoints in four clinical trials [7–10] but it remains relatively expensive, slow in onset and the National Institute of Health (NICE) restrict its use, in the United Kingdom.

There remains an ongoing need to achieve B cell depletion by other means. The most novel approach is chimeric antigen-receptor (CAR) T cell therapy against the CD19 receptor on B cells claims that it induces rapid remission of refractory SLE [11].

This review will briefly review the use of the now conventional forms of B cell therapy then focus on new ideas about how this might be achieved.

Conventional B cell depletion therapy

The generation of autoantibodies against nuclear proteins, in particular double-stranded DNA (dsDNA) characterizes SLE. Anti-dsDNA antibodies are thought to be involved in its pathogenesis [12] which provides a justification to use therapies targeting B-cell [13]. Based on their mechanisms-of-action, CD20 mAbs are divided into Type I and II [14] (TABLE 1).

TABLE 1. Types of anti CD20 monoclonal antibodies

TYPE	**I**	**II**
Epitope	Class I	Class II
Complement-dependent cytotoxicity	High	Low
Antibody-dependent cell mediated cytotoxicity	Yes	Yes
Apoptosis induction	Caspase dependent	Caspase independent. Lysosome mediated
Examples	Rituximab; Ofatumumab; Ocrelizumab	Obinutuzumab

Rituximab, a chimeric anti-CD20 mAb with 20% mouse variable region [15], was the first biologic drug used in SLE targeting B cells. Rituximab met its primary endpoints in trials of patients with rheumatoid arthritis [16–18]; vasculitis [19], and membranous nephropathy [20]. Many open label studies in SLE reported encouraging results [21–24] and a striking reduction in the use of concomitant steroids [25,26]. However, two large controlled trials of patients with extra-renal lupus (EXPLORER study) [27] and LN (LUNAR study) [28] failed to achieve their primary endpoints, probably because the patients recruited were treated with substantial amount of background medications notably high doses of steroids and immunosuppressants for many weeks as well receiving rituximab or placebo [29].

Nevertheless, numerous studies continue to demonstrate the effectiveness of rituximab [30]. Recently, Chen et al. [31] investigated the efficacy and safety of rituximab maintenance therapy compared with traditional immunosuppressive agent (ISA) maintenance therapy in patients with relapsing or refractory SLE who had received at least one course of rituximab induction treatment. Patients with a clinical response to rituximab were divided into two groups based on their maintenance therapy in the first 12 months: the rituximab and ISA group. The relapse-free survival times were compared between them. Of 82 patients included, 67 (81.7%) had a clinical response at 6 months. Rituximab maintenance therapy was given to 34 (50.7%) and ISA maintenance therapy in the remaining 33 (49.3%) patients. After a median

follow-up of 24 months, 13 (19.4%) had experienced disease relapse, three and 10 in the rituximab group and ISA groups respectively. The rituximab group had a higher relapse-free survival rate than the ISA group suggesting long-term rituximab maintenance therapy has high efficacy and an acceptable safety record in relapsing or refractory SLE patients who had a clinical response to rituximab induction therapy.

Intriguingly, there is evidence that clinical presentation, prognosis and treatment response varies between different racial groups and geographical locations. SLE occurs more frequently in African, Asian and Hispanic individuals who also have an increased risk of severe and more damaging disease [32]. Thus, renal disease is notably more common and has a higher mortality in patients of African ancestry [33]. There is also a slower response to conventional treatment and high disease activity seen in black and Hispanic patients [34]. In contrast, there is evidence that rituximab had a greater beneficial effect in black and Hispanic patients with active extrarenal SLE [35,36]. The overall renal response was better in rituximab treated black patients compared to placebo [27].

Is the prevalence of LN more common in the black population for socio-economic or genetic reasons? This is difficult to unentangle in the USA. However, in the United Kingdom, where medicine is free at the point of entry into the health care system, Adler et al. [37] showed black populations were more likely to have renal disease than Caucasians, suggesting that the differences are likely to be genetic. Prospective studies are needed to evaluate the impact of B cell depletion on patients of diverse ethnicity.

B cell activating factors blockage

Belimumab was the first biological drug to be approved in 2011 by Federal Drug Administration (FDA) for treatment in SLE patients. This mAb inhibits a B lymphocyte stimulator (BlyS), an indirect regulator of B cell survival. Following prolonged belimumab treatment, there is preservation of transitional 1 (T1) cell, while T3 and naïve B cells show a substantial reduction of around 90%. There is a significant depletion observed in class-switched memory B cells, B1, and plasmablasts [38]. It has met its endpoints in four trials [7–10], including active LN [39] and patients of various ethnic backgrounds.

Another approach involves atacicept and telitacicept, which inhibits both BAFF and APRIL. Blocking both cytokines impacts mature B and plasma cells by disrupting B cell survival post the T1 transitional stage, while preserving B cell progenitors and memory B cells [40–43].

Atacicept decreases levels of serum IgG, IgM, and IgA, and causes reductions in mature and overall circulating B cell counts [40,44]. A study [41] aiming to prevent lupus flare documented improved serologies but no clinical difference between atacicept 75mg and placebo for flare rate was found. Unfortunately, the premature discontinuation of the more potent high-dose group was prompted by two cases of fatal infections, one being due to leptospirosis, which is not a common cause of death in SLE. The mortality rate in this study mirrored that observed in belimumab trials, and later analysis identified a significant advantage for the 150mg arm compared to the lower dosage and placebo groups. Another trial of atacicept for LN was halted due to the development of hypogammaglobuline-mia and severe pneumonia [45] among 3 out of 4 patients receiving treatment. Notably the serum IgG decreased before atacicept was given, the reductions were due to mycophenolate mofetil (MMF) [46]. The ADDRESS II study [47] presented encouraging efficacy findings, showing reductions in disease activity and severe flare for atacicept 75mg and 150mg vs placebo among individuals with elevated clinical and serologic disease activity, with an acceptable safety profile.

Telitacicept, another dual inhibitor structurally similar to atacicept, was approved in 2021 in China to treat patients with active SLE. Wang et al. [48] assessed the efficacy and safety of telitacicept in SLE patients, who received telitacicept 160mg or placebo weekly for 52 weeks. It met its primary endpoint with significantly greater proportion of patients in the telitacicept 160 mg group achieving a Systemic Lupus Erythematosus Responder Index (SRI) 4 response: placebo n= 64 (38.1%) vs Telitacicept n= 38 (82.6%): $p<0.001$. Rapid and sustained increase of C3 and C4 and reduction of IgM, IgG, IgA and CD19+ B cells were observed following telitacicept treatment.

Belimumab plus Rituximab

Belimumab provides a modest, durable, therapeutic response in subset of lupus patients. In addition, the increased concentrations of BAFF and the association between higher BAFF concentration and worsening disease after rituximab [49] led to the combined use of anti-CD20 B cell depletion and BAFF. There have now been four studies describing the use of a rituximab and belimumab in combination in LN and non-renal lupus (TABLE 2 and TABLE 3).

TABLE 2. Combined B cell therapies

Study and Author	Number of Patients/ Duration in Weeks	Brief Description	Results
BLISS-BELIEVE Aranow et al. [53]	292 patients/ 104 weeks	Asses co-administration of belimumab and a single cycle of rituximab will optimize treatment with belimumab effective in disease control with a safety profile, administered as subcutaneous and rituximab-placebo or rituximab will be administered by intravenous (i.v) infusions plus standard therapy excluding immunosuppressants, comparing subjects randomized in 3 treatment arms: Arm A. Belimumab SC + placebo (n=72) Arm B. Belimumab SC + rituximab i.v (n=144) Arm C. Belimumab SC + standard therapy (n=76)	**Primary endpoint:** at week 52 not achieved. SLEDAI -2K ≤ 2 without immunosupresants and prednisone ≤ 5 mg/kg/day at week 52. -Disease control n (%): BEL-PBO 12 (16,7%)/BEL-RTX 28 (19,4%)/BEL-ST 12 (25,5%) -Disease control BEL-RTX vs BEL-PBO, observed difference [OR (95% CI)]: 2.78 [1.27 (0.60-2.71)], (p = 0.5342) -Exploratory comparison: BEL-RTX vs BEL-ST, observed difference [OR (95% CI)]: -6.09 [0.71 (0.32–1.54)] **Secondary endpoints,** patients with clinical remission: -Week 64 observed difference [OR (95% CI)] BEL-RTX vs BEL-PBO: 0.69 [1.12 (0.33–3.78)] (p = 0.8582) BEL-RTX vs BEL-ST: −4.39 [0.53 (0.17–1.70)] -Week 104 observed difference [OR (95% CI)] BEL-RTX vs BEL-PBO: 4.17 [1.64 (0.57–4.72)] (p = 0.3613) BEL-RTX vs BEL-ST: −10.17 [0.45 (0.19–1.09)] -Disease control duration by week 52 treatment difference (95% CI) BEL-RTX vs BEL/PBO: 47.0 (8.0–86.0) (p = 0.0188) BEL-RTX vs BEL-ST: 18.2 (−22.3–58.7) -Decrease in anti-dsDNA Ab from BL at week 52, BEL-RTX vs BEL-PBO (p < 0.05) (exact data not available)
BEAT-LUPUS Shipa et al. [52]	52 patients/ 52 weeks	Assess the safety and obtain preliminary evidence for efficacy of belimumab following rituximab therapy. Patients with active SLE received rituximab 1 g (2 weeks apart) and were randomised to either receive 4-8 weeks after their 1st dose of rituximab: -Belimumab (BEL) (n=26): 10 mg/kg i.v at week 0, 2, 4 and then every 4 weeks until week 52. or -Placebo (PBO) (n=26)	**Primary endpoint met:** significant reduction in IgG anti-dsDNA antibody levels in patients with belimumab compared to placebo at week 52 Anti-dsDNA levels, geometric mean (IU/mL) [95% CI], BEL vs. PBO: 47 [25–88] vs. 103 [49–213] (p < 0.001) -Belimumab significantly suppressed B cell repopulation at 52 weeks compared to placebo (p = 0.001), but not total serum IgG

TABLE 3. Combined B cell therapies

Study and Author	Number of Patients/ Duration in Weeks	Brief Description	Results
CALIBRATE Atisha-Fregoso et al. [51]	43 patients/ 96 weeks	Safety of rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis: -RC (n=22): Rituximab 1 g + cyclophosphamide 750 mg IV + solumedrol 100 mg at week 0, 2. - RCB (n=21): Rituximab 1 g + cyclophosphamide 750 mg IV + solumedrol 100 mg at week 0,2 + belimumab 10 mg/kg at weeks 4, 6, 8 and then every 4 weeks through week 48 in addition to prednisone. In both arms prednisone was administered at 40 mg/day for the first 2 weeks, followed by a guided steroid taper to 10 mg/day by Week 12. prednisone was continued through to Week 96 at 10 mg/day, with the potential of a taper to a minimum of 5 mg/day.	**Primary endpoint:** percentage of participants with at least one grade 3 or higher treatment-emergent infectious adverse event by week 0 to 96. RC 27.3 % vs. RCB 9.5 % ($p = 0.15$). **Secondary endpoints:** - Percentage of patients with B cell reconstitution: - At week 60 geometric mean number of B cells, 53 cells/µl [95% CI 26–109] in the RC group versus 11 cells/µl [95% CI 6–20] in the RCB group; ($p = 0.0012$) - At week 48 median IgG level of 1,410.0 mg/dl in the RC group compared to 904.5 mg/dl in the RCB group ($p = 0.022$)
SynBioSe Kraaij et al. [50]	16 patients/ 24 weeks	In refractory SLE patients to assess the immunological consequences (reduction and seroconversion) of pathogenic autoantibodies of a combination treatment with rituximab and belimumab to achieve long-term B-cell depletion and its safety and feasibility. Single arm: -Rituximab 1 g on day 0 and 14 + belimumab 10 mg/kg on day 28, 42, 56. Thereafter patients received belimumab 10 mg/kg every 4 weeks.	**Primary endpoint:** reduction of pathogenic autoantibodies at 24 weeks: Immunological effects of rituximab + belimumab -BlyS decreased to 0.15 ng/mL [0.05–0.4] ($p < 0.01$) -Anti-dsDNA antibodies decreased to 57 IU/mL [10–374] ($p = 0.0004$) -Neutrophil extracellular traps formation reduced to 1.9-fold increase compared to controls [0.4–6.1] ($p = 0.0006$)

The SynBioSe 1 [50] combined rituximab-belimumab, with a sustained reduction of pathogenic autoantibodies. After the administration of rituximab, subsequent use of belimumab effectively restrained the rise in circulating BAFF levels identified in patient serum four weeks after the initial rituximab infusion. This intervention corresponded with clinical improvement indicated by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Lupus Low Disease Activity State (LLDAS) indices.

Subsequently, CALIBRATE [51] and BEAT-LUPUS [52] , confirmed that the combination of belimumab and rituximab is safe and achieves relevant immunological and clinical endpoints in refractory SLE and LN patients. These studies showed suppressed B cell repopulation and enhanced negative selection of autoreactive B cells, lower anti-dsDNA levels, and reduced risk of severe flares.

The Bliss-Believe study [53] compared efficacy, safety and tolerability of belimumab combined with a single cycle of rituximab in patients with SLE with belimumab alone, and belimumab plus standard therapy, spanning 104-week. It did not meet its primary efficacy endpoint. Safety findings were consistent with the established safety profiles of belimumab and rituximab.

SynBioSe 2 (NCT03747159) is now planned to study the clinical efficacy of combining belimumab

with rituximab in 70 patients with severe SLE, including LN. The design includes tapering of MMF and prednisolone as maintenance therapy in the intervention group. Patients will be randomized 1:1 to receive standard of care, consisting of prednisolone and MMF as induction and maintenance treatment, or belimumab and rituximab combined with standard of care as induction treatment, followed by prednisolone and belimumab as maintenance. The primary objective is to assess whether combined B cell therapy reduces treatment failure.

Several challenges remain. Post rituximab induced hypogammaglobulinemia was reported in several papers, and infections remain the principal concern. One study [54] emphasized the significance of monitoring immunoglobulin levels in patients before and after rituximab treatment. Second, it may be associated with allergic responses in 13.6 % of patients which limits its use [27]. Although the strategy to reduce immunogenicity of new mAbs could be humanization, evidence indicates clinical immunogenicity does not fully cease to occur in fully humanized mAbs antibodies. There are no data suggesting that the immunogenic risk of mAbs can be predicted although these are being evaluated retrospectively. Multifactorial causes include intrinsic (structural changes) and extrinsic factors (route of administration or dosage) have been described as one of the highest risk factors for immunogenicity. The exact causes are still not fully understood [55].

Rituximab is effective in treating many aspects of SLE; however, it is not a cure and some patients who respond initially may not do so subsequently. This is referred to as secondary non-depletion and non-response including patients who developed an infusion reaction during a further cycle of treatment, resulting in a failure to deplete CD20+ naïve and memory B-cells. This failure may be linked to the development of anti-rituximab antibodies.

Whether this problem will be overcome by using fully humanised anti-CD20 mAbs [56–58] should be answered soon [3].

Fully humanized anti-CD20

One randomised trial of ocrelizumab in patients with LN (BELONG) failed to show a difference versus placebo (endpoint being complete renal response (CRR)) when added to standard-of-care immunosuppression. It was terminated due to a higher incidence of infections in patients with severe LN who received ocrelizumab [59,60].

Ofatumumab, was studied in SLE/LN patients who were rituximab intolerant due to severe infuse reactions. In 14/16 patients treated with ofatumumab it was well-tolerated, safe and effective [61]. Four patients with LN who had developed an infusion reaction to rituximab were treated with ofatumumab. It was well tolerated in 3/4, and a reduction of proteinuria was seen in all cases [62].

Ofatumumab might be an option in SLE-associated autoimmune haemolytic anaemia refractory to multiple treatment modalities including rituximab. It was used in a case of a 20-year-old patient, who had a severe reaction during a second rituximab course. After 6 infusions of ofatumumab, complete B cell depletion associated with remission of both anaemia and SLE (SLEDAI = 0) [63]. To date, there are no active formal clinical trials in SLE with ofatumumab.

Obinutuzumab was evaluated in the NOBILITY phase II trial [64]. It recruited SLE patients with class III/IV active/chronic LN. 125 patients were randomised and received blinded infusions (63 obinutuzumab/62 placebo) and followed until week 104. The primary endpoint at week 52 was the proportion of patients who achieved CRR. The trial met its primary endpoint and was greater with obinutuzumab (22 (35%) vs 14 (23%) placebo; 12% (95% CI −3.4% to 28%; p=0.115, alpha level 0.2) and at week 104 (26 (41%) vs 14 (23%); p=0.026). Improvements in serologies, eGFR and proteinuria were greater with obinutuzumab.

The results from NOBILITY support prior reports correlating the degree and duration of B-cell depletion to clinical responses in LN [65,66]. Obinutuzumab was associated with an increased prevalence of low IgM but not low IgG, compared with baseline, and encouragingly it was not associated with reductions in concentrations of pre-existing protective antibodies.

Obinutuzumab lead to a more rapid and potent depletion of peripheral B cells than rituximab, without an increase of serious adverse events or death compared with placebo [64].

The use of obinutuzumab in proliferative LN is being further evaluated in a global phase III study (REGENCY, NCT04221477). Participants will be randomized into 2 groups, one receiving obinutuzumab 1g at baseline and weeks 2, 24, 26, 50, and 52 plus MMF and tapered prednisone. Group 2, will receive the same doses of Obinutuzumab plus MMF and prednisone in the same weeks, and placebo at week 50. Those adequate responders at week 76 will receive blinded obinutuzumab infusions every 6 months

from week 80, those non responders at week 76 may be eligible for open-label obinutuzumab starting at week 80. The primary outcome will be the percentage of participants with CRR at week 76.
In the ALLEGORY trial (NCT04963296), 300 active autoantibody-positive SLE patients will be included, treated with standard-of-care therapy, and will evaluate efficacy and safety of obinutuzumab versus placebo. The experimental group will receive obinutuzumab 1g infusions on day 1 and at weeks 2, 24 and 26. The primary outcome will be the percentage of participants who achieve SLE SRI 4 [67] at week 52.

Another phase III trial (OBILUP, NCT04702256) will explore the efficacy of obinutuzumab in proliferative LN (class III or IV) with induction therapy for LN with no added oral steroids, comparing oral corticosteroids plus MMF versus obinutuzumab and MMF. The primary objective is to demonstrate that a regimen free of additional oral corticosteroids (obinutuzumab and MMF) is non-inferior to a regimen based on oral corticosteroids and MMF in achieving the primary outcome of complete renal response at week 52 without receiving corticosteroids above a prespecified dose.

Chimeric antigen-receptor T cell therapy

Although autoreactive B cells play a key role in the pathogenesis of SLE, antibody-mediated B cell depletion does not cure SLE.

A barrier to long-term remissions with CD20-targeting B cells therapies has been attributed to the inaccessibility and persistence of autoreactive immunologic memory B cells within lymphatic organs and inflamed tissues [68] or the pathologic role of CD20-negative plasma cells, which may contribute to the production of autoantibodies in SLE patients [69].

One approach to overcome these issues is the use of CAR – modified T cells (CAR-T cells), engineered molecules capable of redirecting the specific T-cells towards specific target antigen by expressing a vector construct [70] . This approach has been approved for the treatment of patients with relapsed or refractory B-cell malignancies [71] showing highly effective depletion of target cells [72,73], due to their ability to exert their effector function directly onto the B cell niches in tissues, enabling them to kill the target cells efficiently [74].

This advancement in technology, coupled with compelling findings from preclinical lupus models [74], has provided a rationale for the use of CAR-T cells therapy as a potential treatment in SLE patients. Thus, achieving a major depletion of CD19+ B cells and plasmablasts in tissues has the potential to initiate an 'immune reset' which could result in the discontinuation of the need for immunosuppressive treatments.
The process of generating CAR-T cells is complex and costly. First, leukapheresis is performed and 1×10^8 T cells are used as the starting population, activated and transduced with a lentiviral vector containing the sequence for a single-chain variable fragment derived from an antihuman CD19 hybridoma clone (FMC63). Cells are expanded for 12 days until the infusion. Treatment is stopped in all patients except for low dose prednisolone. To facilitate homeostatic expansion of CAR-T cells, all patients undergo a lymphodepleting chemotherapy regimen (25mg/m^2/d of fludarabine for three days and one dose of 1g/m^2/d of cyclophosphamide three days before the infusion of CAR-T cells). CAR-T cells are administered to patients as a single infusion at a fixed dose of 1×10^6/g. Following the infusion, patients are hospitalized for ten days to monitor toxicity closely [75].

Mougiakakos et al. [11] reported the first attempt to use anti-CD19 CAR-T cells in a 20-year-old woman with severe and refractory SLE. Prior to the CAR-T cells infusion, all other treatment was discontinued, apart from low-dose prednisolone. The patient did not experience any adverse events related to CAR-T cells therapy. The results showed serologic and clinical remission. SLEDAI score decreased from 16 at baseline to 0 up to 44 days.

In another study by Schett et al. [76], four patients with severe and refractory SLE, including LN, undergo treatment with CAR-T cells therapy after failing standard therapy. All SLE treatment, except a low-dose prednisolone, was stopped. It was well tolerated, with only mild fever reported in all cases without evidence of infection or severe side effects, such as immune effector cell-associated neurotoxicity syndrome (ICANS) or cytokine-release syndrome (CRS). All patients achieved the LLDAS and remarkably all SLE-specific medication, including glucocorticoids, was stopped with no SLE flare observed up to 10 months past treatment. The patients experienced a complete loss of antinuclear antibodies and anti-dsDNA despite reappearance of B cells. In an update [75], five patients with active-refractory SLE with multiorgan involvement enrolled a compassionate-use CAR-T cells. CAR-T cells were administered resulting in deep depletion of B cells and improvement in clinical symptoms. Disappearance of anti-dsDNA antibodies was observed and remission of SLE according to DORIS criteria [77] was achieved. After three months, the

median SLEDAI score was 0. Only mild CRS was reported, and no infection occurred in short-term follow-up and during the phase of B cell aplasia. Remarkably, drug-free remission was maintained during extended follow-up, even after the reappearance of B cells, with no SLE relapse. Overall IgG levels did not experience significant decline following CAR-T cells therapy. This, along with the absence of regular immunoglobulin substitution and the stability of anti-vaccination responses, suggests the majority of long-lived plasma cells are not affected by this approach. Instead, the eradication of activated B cells and plasmablasts appears sufficient to achieve clinical and immunologic remission, in at least some of the SLE patients [75].

Side effects of CAR-T cells are variable depending upon multiple factors, including CAR design, and can be solved using specific strategies [78].

CRS and ICANS are frequently observed toxicities after CAR-T cell therapy in patients with hematologic malignancies [79]. CRS results from a rapid expansion of activated CAR-T cells. It induces systemic inflammation by recruiting myeloid cells that release pro-inflammatory cytokines. Rapid expansion of CAR-T cells and high tumor burden is associated with risk of severe toxicity. These patients require close monitoring, and intensive care treatment [79]. Encouragingly, to date higher-grade CRS was not observed in SLE patients treated with CAR-T cells [11,75,76], probably due to the considerably lower B cell burden in SLE compared to those with active B cell malignancies. No cases of ICANS have occurred in patients with SLE to date [75] however, the number of SLE patients studied is very small.

B-cell aplasia is a well-established consequence of CAR-T cells, which can persist until T cells regain functionality [80]. Re-assuringly, Schett et al. found no evidence of prolonged cytopenia [76]. In other studies, besides B cell depletion, no severe infection occurred in the short-term follow-up and during the phase of B aplasia [11,75].

Another concern in generating CAR-T cells from autoimmune patients is that the quality of autologous T-cells could be diminished by the disease and multiple long term immunosuppressive therapies, which are crucial for managing autoimmune conditions and cannot be easily discontinued in these patients. Thus, the process of obtaining an adequate number of functional T-cells, successfully transducing them with the CAR gene, and expanding them ex-vivo may be hindered in autoimmune patients [81]. It is essentially a cautious approach that effectively reduces immunosuppressants before apheresis. This step is as vital as it allows for successful CAR-T cell generation while also avoiding the risk of exposing the patient to uncontrolled autoimmune flares. Kretschamann et al. [81] showed in 6 patients with severe SLE, who tapered immunosuppression before leukapheresis with glucocorticoid doses reduced to a maximum of 10 mg/day, that sufficient numbers of T-cells can be obtained which could be effectively transduced with a CD19 CAR-encoding construct and expanded ex-vivo to gain adequate amounts of viable autologous CAR-T cells needed for treatment.

Assessing the safety and durability of responses during B-cell repopulation will require much long-term follow up and a large cohort of patients. Also, the ideal patient profiling is yet to be established and not every patient may respond. The limited studies done so far have focused on patients with multiorgan involvement, but limited organ damage, without neuropsychiatric lupus, resistant to conventional treatments [11,75,76].

Finally, the main drawback to the use of engineered cells is the substantial cost of the procedure probably limiting its applicability to highly selected patients [82]. However, the availability and cost of manufacturing facilities should improve, making this therapeutic option more affordable [83,84].

The application of CAR technology has been extended to regulatory T-cells (Tregs) therapies using Tregs engineered with CAR (CAR-Tregs). Tregs form a heterogeneous population found in secondary lymphoid organs and tissues, endowed with immune-suppressive functions [85]. In laboratory models, CAR-Tregs have shown great potential for treating various diseases, such as type 1 diabetes [86], and inflammatory bowel disease [87]. CAR-Treg therapy holds significant advantages due to their intrinsic properties, including the ability to suppress T-cells with different antigen specificity through bystander suppression and induce endogenous tolerogenic cells through infectious tolerance [88]. Despite several preclinical studies, this approach has not yet been used in SLE patients.

Conclusions

Despite many setbacks, SLE treatment is now rapidly evolving with new approaches under investigation. Enhanced knowledge of the pathologic mechanisms and technical advances in manufacturing engineered antibodies have led to the development of specific therapies to modify relevant cellular interactions and improve clinical outcomes. The exact role of novel cellular therapies

in the future treatment approach for SLE remains to be determined.

Autoreactive B cells have long been targeted SLE. Despite providing clinical benefits, anti-CD20 mAbs on their own failed to achieve the primary end points in randomized controlled trials [27,28]. Some clinical trials suggests that belimumab after rituximab will provide a useful clinical outcome. However, attaining drug-free remission and seroconversion in SLE remains challenging [76].

A key challenge following CD20-targeted B cell-depletion antibody treatment is the incomplete removal of tissue B cells [74]. CAR-T cells represent an interesting and promising approach for SLE treatment which may lead to more robust B-cell depletion, with significant reduction of memory B cells and plasmasblasts. This treatment results in a rapid and sustained breakdown of the B cell-mediated autoimmune response, leading to drug-free remission of refractory SLE [75]. This is an important advantage of CAR-T cells, which may off set the high cost of this approach which threatens its widespread adoption.

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References

1. Tsokos GC. Autoimmunity and organ damage in systemic lupus erythematosus. *Nat Immunol*. 2020;21(6):605-14. doi:10.1038/s41590-020-0677-6
2. Ponticelli C, Moroni G. Monoclonal antibodies for systemic lupus erythematosus (SLE). *Pharmaceuticals*. 2010;3(1):300-22. doi:10.3390/ph3010300
3. Bag-Ozbek A, Hui-Yuen JS. Emerging b-cell therapies in systemic lupus erythematosus. *Ther Clin Risk Manag*. 2021;17:39-54. doi:10.2147/TCRM.S252592
4. Lee DSW, Rojas OL, Gommerman JL. B cell depletion therapies in autoimmune disease: advances and mechanistic insights. *Nat Rev Drug Discov*. 2021;20(3):179-99. doi:10.1038/s41573-020-00092-2
5. Hahn BH, McMahon MA, Wilkinson A, et al. American college of rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. 2012;64(6):797-808. doi:10.1002/acr.21664
6. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the joint european league against rheumatism and european renal association-european dialysis and transplant association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis*. 2020;79(6):713-23. doi:10.1136/annrheumdis-2020-216924
7. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9767):721-31. doi:10.1016/S0140-6736(10)61354-2
8. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71(11):1833-8. doi:10.1136/annrheumdis-2011-200831
9. Iaccarino L, Andreoli L, Bocci EB, et al. Clinical predictors of response and discontinuation of belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study. *J Autoimmun*. 2018;86:1-8. doi:10.1016/j.jaut.2017.09.004
10. van Vollenhoven RF, Petri MA, Cervera R, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. *Ann Rheum Dis*. 2012;71(8):1343-9. doi:10.1136/annrheumdis-2011-200937
11. Mougiakakos D, Krönke G, Völkl S, et al. CD19-Targeted CAR T Cells in refractory systemic lupus erythematosus. *New Eng J Med*. 2021;385(6):567-9. doi:10.1056/nejmc2107725
12. Wang X, Xia Y. Anti-double stranded DNA antibodies: origin, pathogenicity, and targeted therapies. *Front Immunol*. 2019;10:1667. doi:10.3389/fimmu.2019.01667
13. Dema B, Charles N. Autoantibodies in SLE: specificities, isotypes and receptors. *Antibodies (Basel)*. 2016;5(1):2. doi:10.3390/antib5010002
14. Meyer S, Evers M, Jansen JHM, et al. New insights in type I and II CD20 antibody mechanisms-of-action with a panel of novel CD20 antibodies. *Br J Haematol*. 2018;180(6):808-20. doi:10.1111/bjh.15132
15. Wood C, McKay G, Fisher M. Rituximab. *Practical Diab*. 2017;34(7):258-9a. doi: org/10.1002/pdi.2132
16. Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2011;70(6):909-20. doi:10.1136/ard.2010.144998
17. Edwards JCW, Szczepanski S, Szechinski S, et al. Efficacy of B-cell–targeted therapy with rituximab in patients with rheumatoid arthritis. *New Eng J Med*. 2004;350(25):2572-81. doi:10.1056/NEJMoa032534
18. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79(6):685-99. doi:10.1136/annrheumdis-2019-216655
19. Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update [published online ahead of print, 2023 Mar 16]. *Ann Rheum Dis*. 2023;ard-2022-223764. doi:10.1136/ard-2022-223764
20. Chavarot N, Verhelst D, Pardon A, et al. Rituximab alone as induction therapy for membranous lupus nephritis: a multicenter retrospective study. *Medicine (Baltimore)*. 2017;96(27):e7429. doi:10.1097/MD.0000000000007429
21. Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus

erythematosus. *Arthritis Rheum*. 2002;46(10):2673-7. doi:10.1002/art.10541
22. Thatayatikom A, White AJ. Rituximab: a promising therapy in systemic lupus erythematosus. *Autoimmun Rev*. 2006;5(1):18-24. doi:10.1016/j.autrev.2005.05.006
23. Melander C, Sallée M, Trolliet P, et al. Rituximab in severe lupus nephritis: early B-cell depletion affects long-term renal outcome. *Clin J Am Soc Nephrol*. 2009;4(3):579-87. doi:10.2215/CJN.04030808
24. Catapano F, Chaudhry AN, Jones RB, Smith KGC, Jayne DW. Long-term efficacy and safety of rituximab in refractory and relapsing systemic lupus erythematosus. *Nephrol Dial Transplant*. 2010;25(11):3586-92. doi:10.1093/ndt/gfq256
25. Pepper R, Griffith M, Kirwan C, et al. Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids. *Nephrol Dial Transplant*. 2009;24(12):3717-23. doi:10.1093/ndt/gfp336
26. Roccatello D, Sciascia S, Rossi D, et al. Intensive short-term treatment with rituximab, cyclophosphamide and methylprednisolone pulses induces remission in severe cases of SLE with nephritis and avoids further immunosuppressive maintenance therapy. *Nephrol Dial Transplant*. 2011;26(12):3987-92. 2011;26(12):3987-3992. doi:10.1093/ndt/gfr109
27. Merrill JT, Neuwelt CM, Wallace DJ, 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*. 2010;62(1):222-33. doi:10.1002/art.27233
28. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. *Arthritis Rheum*. 2012;64(4):1215-26. doi:10.1002/art.34359
29. Turner-Stokes T, Lu TY, Ehrenstein MR, Giles I, Rahman A, Isenberg DA. The efficacy of repeated treatment with B-cell depletion therapy in systemic lupus erythematosus: an evaluation. *Rheumatology (Oxford)*. 2011;50(8):1401-8. doi:10.1093/rheumatology/ker018
30. Murphy G, Isenberg DA. Biologic therapies for systemic lupus erythematosus- where are we now?. *Curr Opin Rheumatol*. 2020;32(6):597-608. doi:10.1097/BOR.0000000000000736
31. Chen X, Shi X, Xue H, et al. Rituximab as maintenance therapy following remission induction in relapsing or refractory systemic lupus erythematosus. *Rheumatology (Oxford)*. 2023;62(3):1145-52. doi:10.1093/rheumatology/keac471
32. Maningding E, Dall'Era M, Trupin L, Murphy LB, Yazdany J. Racial and ethnic differences in the prevalence and time to onset of manifestations of systemic lupus erythematosus: the California lupus surveillance project. *Arthritis Care Res (Hoboken)*. 2020;72(5):622-9. doi:10.1002/acr.23887
33. Dooley MA, Hogan S, Jennette C, Falk R. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. *Kidney Int*. 1997;51(4):1188-95. doi:10.1038/ki.1997.162
34. Litwic A, Sriranganathan K M, Edwards J C. Race and the response to therapies for lupus: how strong is the evidence?. *Int J Clin Rheumtol*. 2013;8(4):471-81. doi:10.2217/ijr.13.41
35. Sans-Pola C, Danés I, Bosch JÀ, Marrero-Álvarez P, Cortés J, Agustí A. Off-label use of rituximab in patients with systemic lupus erythematosus with extrarenal disease activity: a retrospective study and literature review. *Front Med (Lausanne)*. 2023;10:1159794. doi:10.3389/fmed.2023.1159794
36. Wiesik-Szewczyk E, Olesinska M. B-cell targeted therapy in systemic lupus erythematosus: potential of rituximab. *Biologics*. 2012;6:347-54. doi:10.2147/BTT.S25407
37. Adler M, Chambers S, Edwards C, Neild G, Isenberg D. An assessment of renal failure in an SLE cohort with special reference to ethnicity, over a 25-year period. *Rheumatology (Oxford)*. 2006;45(9):1144-7. doi:10.1093/rheumatology/kel039
38. Huang W, Quach TD, Dascalu C, et al. Belimumab promotes negative selection of activated autoreactive B cells in systemic lupus erythematosus patients. *JCI Insight*. 2018;3(17):e122525. doi:10.1172/jci.insight.122525
39. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *New Eng J Med*. 2020;383(12):1117-28. doi:10.1056/nejmoa2001180
40. Harvey PR, Gordon C. B-cell targeted therapies in systemic lupus erythematosus: successes and challenges. *BioDrugs*. 2013;27(2):85-95. doi:10.1007/s40259-013-0015-8
41. Isenberg D, Gordon C, Licu D, Copt S, Rossi CP, Wofsy D. 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) [published correction appears in Ann Rheum Dis. 2016 May;75(5):946]. *Ann Rheum Dis*. 2015;74(11):2006-15. doi:10.1136/annrheumdis-2013-205067

42. Richez C, Truchetet ME, Schaeverbeke T, Bannwarth B. Atacicept as an investigated therapy for rheumatoid arthritis. *Expert Opin Investig Drugs*. 2014;23(9):1285-94. doi:10.1517/13543784.2014.943835
43. Dillon SR, Gross JA, Ansell SM, Novak AJ. An APRIL to remember: novel TNF ligands as therapeutic targets. *Nat Rev Drug Discov*. 2006;5(3):235-46. doi:10.1038/nrd1982
44. Stohl W. Biologic differences between various inhibitors of the BLyS/ BAFF pathway: should we expect differences between belimumab and other inhibitors in development?. *Curr Rheumatol Rep*. 2012;14(4):303-9. doi:10.1007/s11926-012-0254-6
45. Ginzler EM, Wax S, Rajeswaran A, et al. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. *Arthritis Res Ther*. 2012;14(1):R33. doi:10.1186/ar3738
46. Isenberg DA. Meryl Streep and the problems of clinical trials. *Arthritis Res Ther*. 2012;14(2):113. doi:10.1186/ar3751
47. Merrill JT, Wallace DJ, Wax S, 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 [published correction appears in Arthritis Rheumatol. 2018 Mar;70(3):467] [published correction appears in Arthritis Rheumatol. 2021 Nov;73(11):2043]. *Arthritis Rheumatol*. 2018;70(2):266-76. doi:10.1002/art.40360
48. Wang L, Li J, Fang J, Vollenhoven Van R, Zhang F. OP0137 Efficacy and safety of telitacicept, a novel BlyS/APRIL dual inhibitor, in patients with systemic lupus eryhtematosus: a phase 3, randomized, placebo-controlled 52-week study. *Ann Rheum Dis*. 2023;82:90-1. doi:10.1136/annrheumdis-2023-eular.4709
49. Carter LM, Isenberg DA, Ehrenstein MR. 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*. 2013;65(10):2672-9. doi:10.1002/art.38074
50. Kraaij T, Kamerling SWA, de Rooij ENM, et al. The NET-effect of combining rituximab with belimumab in severe systemic lupus erythematosus. *J Autoimmun*. 2018;91:45-54. doi:10.1016/j.jaut.2018.03.003
51. Atisha-Fregoso Y, Malkiel S, Harris KM, et al. Phase II randomized trial of rituximab plus cyclophosphamide followed by belimumab for the treatment of lupus nephritis [published correction appears in Arthritis Rheumatol. 2021 Dec;73(12):2356]. *Arthritis Rheumatol*. 2021;73(1):121-31. doi:10.1002/art.41466
52. Shipa M, Embleton-Thirsk A, Parvaz M, et al. Effectiveness of belimumab after rituximab in systemic lupus erythematosus: a randomized controlled trial. *Ann Intern Med*. 2021;174(12):1647-57. doi:10.7326/M21-2078
53. Aranow C, Allaart C, Amoura Z, et al. Efficacy and safety of subcutaneous belimumab (BEL) and rituximab (RTX) sequential therapy in patients with systemic lupus erythematosus: the phase 3, randomized, placebo-controlled BLISS-BELIEVE study [abstract]. *Arthritis Rheumatol*. 2021;73(suppl 9). https://acrabstracts.org/abstract/efficacy-and-safety-of-subcutaneous-belimumab-bel-and-rituximab-rtx-sequential-therapy-in-patients-with-systemic-lupus-erythematosus-the-phase-3-randomized-placebo-controlled-bliss-believe-stud/.
54. Barmettler S, Ong MS, Farmer JR, Choi H, Walter J. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. *JAMA Netw Open*. 2018;1(7):e184169. doi:10.1001/jamanetworkopen.2018.4169
55. Mayrhofer P, Kunert R. Nomenclature of humanized mAbs: early concepts, current challenges and future perspectives. *Hum Antibodies*. 2018;27(1):37-51. doi:10.3233/HAB-180347
56. Arnold J, Dass S, Twigg S, et al. Efficacy and safety of obinutuzumab in systemic lupus erythematosus patients with secondary non-response to rituximab. *Rheumatology (Oxford)*. 2022;61(12):4905-9. doi:10.1093/rheumatology/keac150
57. Md Yusof MY, Shaw D, El-Sherbiny YM, et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. *Ann Rheum Dis*. 2017;76(11):1829-36. doi:10.1136/annrheumdis-2017-211191
58. Vallejo-Yagüe E, Keystone EC, Kandhasamy S, Micheroli R, Finckh A, Burden AM. Primary and secondary non-response: in need of operational definitions in observational studies. *Ann Rheum Dis*. 2021;80(8):961-4. doi:10.1136/annrheumdis-2021-220202
59. Gregersen JW, Jayne DRW. B-cell depletion in the treatment of lupus nephritis. *Nat Rev*

Nephrol. 2012;8(9):505-14. doi:10.1038/nrneph.2012.141

60. Mysler EF, Spindler AJ, Guzman R, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. *Arthritis Rheum*. 2013;65(9):2368-79. doi:10.1002/art.38037
61. Masoud S, McAdoo SP, Bedi R, Cairns TD, Lightstone L. Ofatumumab for B cell depletion in patients with systemic lupus erythematosus who are allergic to rituximab. *Rheumatology (Oxford)*. 2018;57(7):1156-61. doi:10.1093/rheumatology/key042
62. Haarhaus ML, Svenungsson E, Gunnarsson I. Ofatumumab treatment in lupus nephritis patients. *Clin Kidney J*. 2016;9(4):552-5. doi:10.1093/ckj/sfw022
63. Karageorgas T, Zomas A, Kazakou P, Katsimbri P, Mantzourani M, Boumpas D. Successful treatment of life-threatening autoimmune haemolytic anaemia with ofatumumab in a patient with systemic lupus erythematosus. *Rheumatology (Oxford)*. 2016;55(11):2085-7. doi:10.1093/rheumatology/kew267
64. Furie RA, Aroca G, Cascino MD, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2022;81(1):100-7. doi:10.1136/annrheumdis-2021-220920
65. Vital EM, Dass S, Buch MH, et al. B cell biomarkers of rituximab responses in systemic lupus erythematosus. *Arthritis Rheum*. 2011;63(10):3038-47. doi:10.1002/art.30466
66. Mendez LMG, Cascino MD, Garg J, et al. Peripheral blood B cell depletion after rituximab and complete response in lupus nephritis [published correction appears in Clin J Am Soc Nephrol. 2019 Jan 7;14(1):111]. *Clin J Am Soc Nephrol*. 2018;13(10):1502-9. doi:10.2215/CJN.01070118
67. Luijten KM, Tekstra J, Bijlsma JW, Bijl M. The systemic lupus erythematosus responder index (SRI); a new SLE disease activity assessment. *Autoimmun Rev*. 2012;11(5):326-9. doi:10.1016/j.autrev.2011.06.011
68. Kamburova EG, Koenen HJPM, Borgman KJE, Ten Berge IJ, Joosten I, Hilbrands LB. A single dose of rituximab does not deplete B cells in secondary lymphoid organs but alters phenotype and function. *Am J Transplant*. 2013;13(6):1503-11. doi:10.1002/ajt.12220
69. Hiepe F, Dörner T, Hauser AE, Hoyer BF, Mei H, Radbruch A. Long-lived autoreactive plasma cells drive persistent autoimmune inflammation. *Nat Rev Rheumatol*. 2011;7(3):170-8. doi:10.1038/nrrheum.2011.1
70. Kalos M, Levine BL, Porter DL, et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. *Sci Transl Med*. 2011;3(95):95ra73. doi:10.1126/scitranslmed.3002842
71. Hayden PJ, Roddie C, Bader P, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the european society for blood and marrow transplantation (EBMT) and the joint accreditation committee of ISCT and EBMT (JACIE) and the european haematology association (EHA). *Ann Oncol*. 2022;33(3):259-75. doi:10.1016/j.annonc.2021.12.003
72. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *New Eng J Med*. 2017;377(26):2545-54. doi:10.1056/nejmoa1708566
73. June CH, Sadelain M. Chimeric antigen receptor therapy. *New Eng J Med*. 2018;379(1):64-73. doi:10.1056/NEJMra1706169
74. Kansal R, Richardson N, Neeli I, et al. Sustained B cell depletion by CD19-targeted CAR T cells is a highly effective treatment for murine lupus. *Sci Transl Med*. 2019;11(482):eaav1648. doi:10.1126/scitranslmed.aav1648
75. Mackensen A, Müller F, Mougiakakos D, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus [published correction appears in Nat Med. 2022 Nov 3;:]. *Nat Med*. 2022;28(10):2124-32. doi:10.1038/s41591-022-02017-5
76. Schett G, Boeltz S, Müller F, et al. CAR-T cell treatment of refractory systemic lupus erythematosus - safety and preliminary efficacy data from the first four patients. *Ann Rheum Dis*. 2022;81(suppl 1):185. doi:10.1136/annrheumdis-2022-eular.1120
77. van Vollenhoven RF, Bertsias G, Doria A, et al. 2021 DORIS definition of remission in SLE: final recommendations from an international task force [published correction appears in Lupus Sci Med. 2022 Feb;9(1):]. *Lupus Sci Med*. 2021;8(1):e000538. doi:10.1136/lupus-2021-000538
78. Brudno JN, Lam N, Vanasse D, et al. Safety and feasibility of anti-CD19 CAR T cells with fully human binding domains in patients with B-cell lymphoma [published correction appears in Nat Med. 2020 May;26(5):803]. *Nat Med*. 2020;26(2):270-80. doi:10.1038/s41591-019-0737-3.Epub

79. Schubert ML, Schmitt M, Wang L, et al. Side-effect management of chimeric antigen receptor (CAR) T-cell therapy. *Ann Oncol*. 2021;32(1):34-48. doi:10.1016/j.annonc.2020.10.478
80. Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. *Haematologica*. 2021;106(4):978-86. doi:10.3324/haematol.2019.238634
81. Kretschmann S, Völkl S, Reimann H, et al. Successful generation of CD19 chimeric antigen receptor T cells from patients with advanced systemic lupus erythematosus. *Transplant Cell Ther*. 2023;29(1):27-33. doi:10.1016/j.jtct.2022.10.004
82. Lyman GH, Nguyen A, Snyder S, Gitlin M, Chung KC. Economic evaluation of chimeric antigen receptor T-cell therapy by site of care among patients with relapsed or refractory large B-cell lymphoma [published correction appears in JAMA Netw Open. 2020 Apr 1;3(4):e208117]. *JAMA Netw Open*. 2020;3(4):e202072. doi:10.1001/jamanetworkopen.2020.2072
83. Ran T, Eichmüller SB, Schmidt P, Schlander M. Cost of decentralized CAR T-cell production in an academic nonprofit setting. *Int J Cancer*. 2020;147(12):3438-45. doi:10.1002/ijc.33156
84. Lam C, Meinert E, Yang A, Cui Z. Comparison between centralized and decentralized supply chains of autologous chimeric antigen receptor T-cell therapies: a UK case study based on discrete event simulation. *Cytotherapy*. 2021;23(5):433-51. doi:10.1016/j.jcyt.2020.08.007
85. Göschl L, Scheinecker C, Bonelli M. Treg cells in autoimmunity: from identification to Treg-based therapies. *Semin Immunopathol*. 2019;41(3):301-14. doi:10.1007/s00281-019-00741-8.Epub
86. Tenspolde M, Zimmermann K, Weber LC, et al. Regulatory T cells engineered with a novel insulin-specific chimeric antigen receptor as a candidate immunotherapy for type 1 diabetes. *J Autoimmun*. 2019;103:102289. doi:10.1016/j.jaut.2019.05.017
87. Boardman DA, Wong MQ, Rees WD, et al. Flagellin-specific human CAR Tregs for immune regulation in IBD. *J Autoimmun*. 2023;134:102961. doi:10.1016/j.jaut.2022.102961
88. Arjomandnejad M, Kopec AL, Keeler AM. CAR-T regulatory (CAR-Treg) cells: engineering and applications. *Biomedicines*. 2022;10(2):287. doi:10.3390/biomedicines10020287