

CAR-T in systemic lupus erythematosus treatment

Artur Cieślewicz¹ , Wei-Wen Huang²

¹Department of Clinical Pharmacology, Poznan University of Medical Sciences

²Student of the 6-year MD, Poznan University of Medical Sciences

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by immune dysregulation, autoantibody production, and multiorgan involvement. Traditional treatments rely on immunosuppressive agents, but many patients with severe or refractory disease fail to achieve sustained remission. Recent advances in chimeric antigen receptor T-cell (CAR-T) therapy—initially developed for B-cell malignancies—have shown promise in targeting the underlying immune pathology of SLE. By engineering T cells to eliminate CD19⁺ B cells and, in some cases, BCMA⁺ long-lived plasma cells, CAR-T therapy offers a novel approach to reset immune tolerance. Clinical studies have demonstrated rapid, drug-free remission in patients with severe, multiorgan, treatment-resistant SLE, with favorable safety profiles and significant reductions in autoantibodies and inflammatory cytokines. These findings suggest CAR-T therapy could become a novel potential treatment option in autoimmune diseases, though further research is needed to confirm long-term efficacy and optimize therapeutic strategies. (*Farm Współ* 2025; 18: 170-176) doi: 10.53139/FW.20251813

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by aberrant activation of the immune system, leading to sustained inflammation and progressive damage to multiple organs, including the skin, joints, kidneys, central nervous system, and blood vessels [1]. The pathogenesis of SLE involves a complex interplay between the innate and adaptive immune systems, defective clearance of apoptotic debris, and the formation of immune complexes (ICs) that deposit in tissues and provoke inflammatory responses [2].

One of the hallmarks of SLE is B-cell hyperactivity and the production of autoantibodies, particularly anti-double-stranded DNA (anti-dsDNA) antibodies. These antibodies form ICs with nuclear material released from apoptotic cells. Typically, this material should be rapidly cleared by phagocytes, including macrophages and neutrophils. However, in SLE, impaired apoptotic cell clearance results in persistent exposure of autoantigens, amplifying autoreactive B- and T-cell responses [2]. Additionally, plasmacytoid dendritic

cells respond to nucleic acid-containing complexes via Toll-like receptors (TLR7 and TLR9), leading to excessive production of type I interferons (especially IFN- α), which further stimulates autoreactive lymphocytes and perpetuates chronic inflammation [2].

Genetic factors contribute significantly to disease susceptibility. Over 100 genetic loci have been implicated in SLE through genome-wide association studies (GWAS). Notably, polymorphisms in the STAT4 gene are strongly associated with dysregulation of the type I interferon response [3]. Other relevant genes include STAT1, STAT2, and IRF5, which affect the function of B cells, monocytes, and interferon signaling pathways [3]. Complement deficiencies (e.g., C1q, C4A, C4B) further contribute to the defective clearance of ICs and apoptotic material, increasing the risk of autoimmunity [2].

SLE displays marked sex and ethnic disparities. It predominantly affects women, particularly those of childbearing age, with a female-to-male ratio of up to 13:1 in the 15 – 44 age group, which decreases to about 2:1 in children and elderly individuals [1,3]. The higher

incidence among females may be related to estrogen-mediated enhancement of B-cell survival and interferon production [2]. The disease is also more prevalent and severe among African American, Hispanic, and Asian populations. For example, African American women in the United States have a threefold higher prevalence of SLE compared to Caucasian women [1].

Treatment of SLE is individualized and based on disease activity, severity, and organ involvement. Hydroxychloroquine is a cornerstone of therapy due to its immunomodulatory effects and ability to reduce disease flares [3]. Glucocorticoids are used for rapid suppression of inflammation, especially during acute exacerbations, but long-term usage is associated with adverse effects such as osteoporosis, metabolic syndrome, and increased infection risk [3]. Therefore, minimizing steroid exposure is a primary goal of contemporary management strategies.

Immunosuppressive agents, including methotrexate, azathioprine, and mycophenolate mofetil, are used in patients with moderate disease or with involvement of organs such as the kidneys or central nervous system. In recent years, several biologic therapies have emerged, such as:

- Belimumab, a monoclonal antibody against B-cell activating factor (BAFF), was the first biologic explicitly approved for SLE and is effective in reducing disease activity and corticosteroid use [3].
- Rituximab, an anti-CD20 monoclonal antibody, is used off-label for refractory cases, especially lupus nephritis, although results from randomized trials have been mixed [1].
- Anifrolumab, a monoclonal antibody targeting the type I interferon receptor, was approved in 2021 for patients with moderate to severe SLE and has demonstrated efficacy in reducing disease activity and steroid dependency [3].

An interesting direction includes chimeric antigen receptor T-cell (CAR-T) treatments targeting CD19-positive B cells. Preliminary results suggest that such approaches may induce long-term remission in patients with refractory autoimmune disease, including SLE, by deeply depleting autoreactive B-cell clones and resetting immune tolerance [2].

Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

Chimeric antigen receptor T-cell therapy is an innovative form of immunotherapy that redirects the cytotoxic activity of T lymphocytes to target cancer cells in a precise and potent manner. The therapy involves the *ex vivo* genetic modification of a patient's T cells to express synthetic receptors – CARs – that recognize tumor-associated antigens independently of major histocompatibility complex (MHC) presentation [4].

A CAR is a modular construct composed of three essential components: an extracellular antigen recognition domain (typically a single-chain variable fragment – scFv – derived from a monoclonal antibody), a transmembrane domain, and one or more intracellular signaling domains, such as CD28, 4-1BB, and CD3 ζ (figure 1) [5,6]. The scFv binds directly to surface antigens expressed on tumor cells, most commonly CD19 in B-cell malignancies [6]. Upon antigen binding, the intracellular domains, which usually include the CD3 ζ signaling chain and one or more costimulatory motifs such as CD28 or 4-1BB, initiate T-cell activation, proliferation, cytokine secretion, and cytotoxic activity [7].

Unlike native T-cell receptors (TCRs), which require antigen presentation via MHC molecules, CARs are not MHC-restricted. This allows CAR-T cells to recognize and kill tumor cells even in cases where MHC expression is downregulated – a common immune evasion strategy employed by cancer cells [4].

The CAR-T therapy process begins with leukapheresis, during which T cells are collected from the patient. These cells are then transduced using an integrating vector (typically based on a lentiviral or retroviral genome) to express the CAR construct. After *ex vivo* expansion, the engineered T cells are infused back into the patient following a lymphodepleting chemotherapy regimen. Once in circulation, CAR-T cells seek out and bind to tumor cells expressing the target antigen, triggering their activation and leading to tumor cell lysis through perforin and granzyme release, as well as induction of apoptosis [8].

CAR-T cells can also engage in a positive feedback loop by secreting cytokines such as IL-2, IFN- γ , and TNF- α , which enhance T-cell expansion and further recruit immune system elements. However, this hyperactivation can also contribute to treatment-associated toxicities such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome [9].

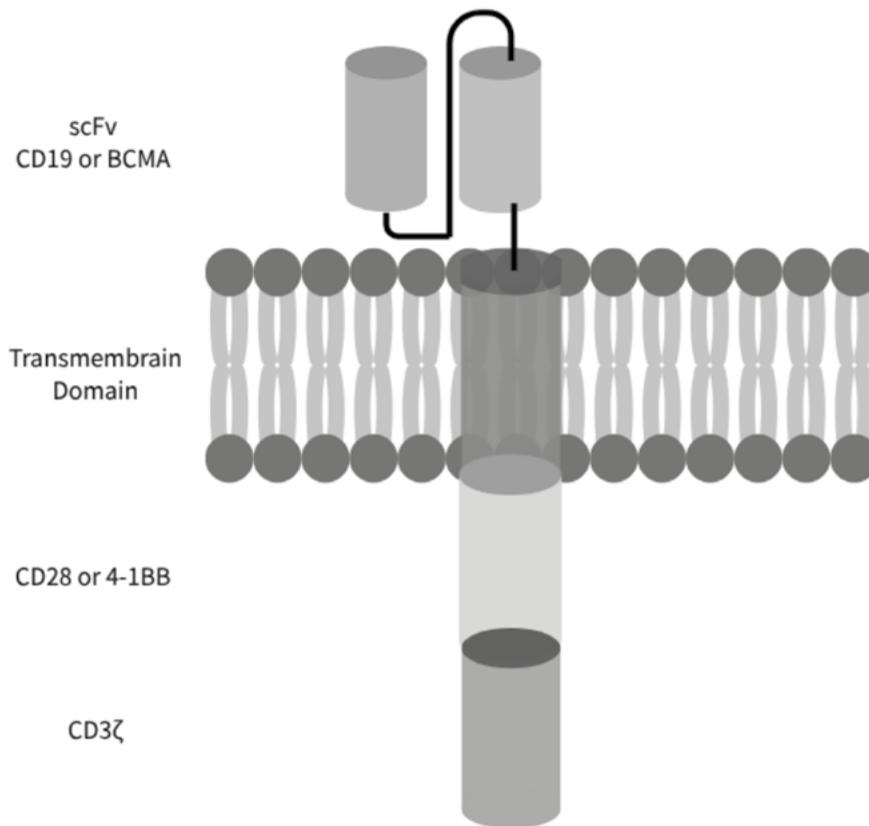


Figure 1. Structure of chimeric antigen receptor (CAR). Based on [5]

It is worth noticing that CAR-T cell therapy leads to profound and sustained B-cell depletion and impaired humoral immunity [10,11]. This iatrogenic hypogammaglobulinemia, often considered an adverse effect in oncology, highlights the capacity of CAR-T therapy to reset dysregulated immune responses. As such, it opens new therapeutic options in the treatment of antibody-mediated autoimmune diseases, including systemic lupus erythematosus (SLE), where pathological B cells play a central role [12,13].

CAR-T in systemic lupus erythematosus CD19 CAR-T cell

CD19 is a type I transmembrane protein involved in early B-cell heavy chain gene rearrangement and remains active until plasma cells are formed. It plays a significant role in antigen-independent maturation and survival via B-cell receptor (BCR) signaling [14,15]. In antigen-dependent activation, CD19 amplifies BCR

signals upon antigen binding through phosphorylation [15].

CAR-T therapy in SLE targets CD19 on B cells. A groundbreaking case study published in *The New England Journal of Medicine* reported the successful use of autologous CD19-targeted CAR-T cell therapy in a 20-year-old woman with severe, treatment-refractory SLE [12]. The patient had active lupus nephritis (WHO class IIIA), nephrotic syndrome, pericarditis, arthritis, and a history of Libman–Sacks endocarditis, and had failed multiple immunosuppressive and B-cell-targeted therapies, including rituximab and belimumab. Following lymphodepletion with fludarabine and cyclophosphamide, a single infusion of CD19 CAR-T cells led to rapid in vivo expansion, sustained depletion of circulating B cells, and a marked reduction of anti-dsDNA antibodies, from over 5000 U/mL to just 4 U/mL within five weeks. Notably, the patient experienced no CAR-T-related toxicities such as cytokine release

syndrome or neurotoxicity. Clinical remission was achieved, as evidenced by normalization of complement levels, resolution of proteinuria, and a reduction in SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) score from 16 to 0. This case demonstrated for the first time that CD19 CAR-T cell therapy can induce rapid and durable remission in refractory SLE, highlighting its potential to reset immune dysregulation in autoimmune disease.

Mackensen et al. provided further details on CD19 CAR-T therapy in five young adults with severe, multiorgan, treatment-refractory SLE [13]. All patients received a single infusion of autologous CD19 CAR-T cells following lymphodepletion with fludarabine and cyclophosphamide. The results showed robust CAR-T cell expansion in all patients, peaking on day 9, and complete depletion of CD19+ B cells starting from day 2 post-infusion. Following successful immune reconstitution, anti-dsDNA antibodies were undetectable at the three-month follow-up. Other autoantibodies also significantly decreased, except for anti-nucleosome and anti-SS-A/Ro60 antibodies in one patient. Despite the persistence of these antibodies, no SLE relapse occurred in that patient. Naïve B cells expressing IgM and IgD BCRs predominated after immune reconstitution, while CD11+CD21^{lo} activated memory B cells, associated with SLE, were absent. All five patients achieved drug-free remission, fulfilling the DORIS (Definition of Remission in SLE) remission criteria three months post-CAR-T treatment. The therapy was well tolerated, with only mild cytokine release syndrome and no neurotoxicity. This study demonstrated that CD19 CAR-T-cell therapy can induce deep and sustained immune reset in SLE, offering a potential path to long-term remission without ongoing immunosuppression.

A subsequent study by Taubman et al., involving seven patients with severe, treatment-resistant SLE, revealed that a single infusion of autologous CD19-directed CAR-T cells led to rapid and sustained clinical remission [16]. All participants, who previously exhibited active multi-organ involvement and had failed a median of seven prior treatments, achieved drug-free remission within three months post-treatment, as assessed by DORIS criteria and lupus low disease activity state (LLDAS). The therapy was well tolerated, with no neurotoxicity and only mild cytokine release syndrome. Notably, CAR-T cell expansion coincided with complete B cell depletion and seroconversion, including the loss of pathogenic autoantibodies. These

results once again underscore the potential of CD19 CAR-T cell therapy to induce long-lasting, treatment-free remission by fundamentally disrupting autoreactive immune processes in SLE.

Krickau et al. described the use of CD19-targeted CAR-T-cell therapy in a 15-year-old female patient with rapidly progressive, treatment-refractory SLE and severe class IV lupus nephritis requiring haemodialysis [17]. Despite multiple immunosuppressive therapies – including hydroxychloroquine, mycophenolate mofetil, azathioprine, belimumab, high-dose corticosteroids, and cyclophosphamide – her renal function deteriorated rapidly, culminating in end-stage kidney disease. Following lymphodepletion with dose-adjusted fludarabine and cyclophosphamide, the patient received an infusion of autologous CD19 CAR-T cells. The therapy was well tolerated, with only transient grade 4 granulocytopenia and mild cytokine release syndrome. Strikingly, the patient achieved a dialysis-free state within 17 days post-infusion. Complement levels normalized, anti-dsDNA antibodies became undetectable, and the SLEDAI score decreased from 23 to 0. At six months, CAR-T cells remained detectable, and B-cell aplasia persisted. Despite residual proteinuria, the patient's renal function significantly improved, and she returned to full daily activity and school. This case, the first to document CD19 CAR-T use in a pediatric lupus patient, illustrated the feasibility and efficacy of this approach even in the context of severe organ involvement and supported early intervention in juvenile-onset SLE.

To better understand the immunologic impact of anti-CD19 CAR-T-cell therapy in SLE, Nunez et al. analyzed serum cytokine and antibody profiles in six patients before and three months after CAR-T-cell infusion [18]. Clinically, all patients achieved drug-free remission, but the underlying immune modulation was also notable. The study revealed a significant decrease in inflammatory cytokines such as IL-6, IL-10, and TNF- α , indicating reduced systemic inflammation post-therapy. Conversely, levels of IL-7 and BAFF – both associated with B-cell homeostasis – increased, likely reflecting the transient CD19+ B-cell aplasia induced by CAR-T-cell treatment. In five of six patients, the serological analysis also showed a profound reduction in SLE-associated autoantibodies, including anti-dsDNA, anti-nucleosome, and anti-histone antibodies. Importantly, pre-existing humoral immunity to infectious agents and vaccines remained largely intact,

underscoring the selective nature of CAR-T-cell-mediated immune modulation. These findings highlighted that anti-CD19 CAR-T-cell therapy induced clinical remission and reshaped the inflammatory and auto-reactive landscape in SLE, supporting its potential to provide a durable immune reset without broadly compromising protective immunity.

A recent study by Yang et al. reported the first clinical application of allogeneic CD19-targeted CAR-T cells (TyU19) in patients with refractory SLE, demonstrating both safety and substantial clinical efficacy [19]. Four young women with severe, multiorgan SLE, including histories of lupus cerebritis, received TyU19 cells following reduced-intensity lymphodepletion. The allogeneic CAR-T product was genetically modified using CRISPR/Cas9 (Clustered Regularly-Interspaced Short Palindromic Repeats) to eliminate T-cell receptor and major histocompatibility complex expression, minimizing the risk of graft-versus-host disease (GVHD) and immune rejection. All patients achieved clinical remission, with SELENA-SLEDAI scores dropping to zero, and normalization of complement levels and proteinuria within three months. Peripheral B cells were fully depleted and later reconstituted as primarily naïve B cells, while autoantibody levels, including anti-dsDNA and anti-Sm (anti-Smith antibodies), markedly declined. Interestingly, despite the presence of CD19-negative, BCMA-positive plasma cells before infusion, these populations also decreased post-treatment, suggesting that TyU19 may influence long-lived autoantibody-producing cells. No patients experienced neurotoxicity or GVHD; only mild, transient cytokine release syndrome (grade 1) was observed. Notably, one patient achieved sustained drug-free remission, and others were weaned to low-dose corticosteroids. This study highlighted the potential of off-the-shelf, genome-edited allogeneic CAR-T cells as a scalable, effective, and well-tolerated therapy for refractory SLE, paving the way for broader application in autoimmune diseases.

CD19/BCMA CAR-T cell

The survival of long-lived plasma cells (PCs) in the bone marrow is a key factor sustaining chronic autoantibody production in SLE, and evidence points to B-cell maturation antigen (BCMA), a member of the TNF receptor superfamily, as a critical regulator of this process [20,21]. It mediates survival signals from BLyS (B Lymphocyte Stimulator) and APRIL (A prolifera-

tion-inducing ligand), two key cytokines in humoral immunity, and is essential for the maintenance, not formation, of long-lived PCs. Since long-lived PCs do not express CD19, a combination therapy targeting both CD19 and BCMA seems rational, as it aims not only to eliminate autoreactive B cells but also to deplete the long-lived plasma cell reservoir that conventional CD19-directed therapies leave untouched [20,21].

Feng et al. conducted a Phase I clinical study investigating the safety and efficacy of dual-targeted CD19/BCMA CAR-T therapy in 12 patients with severe, treatment-refractory SLE [22]. Following lymphodepleting chemotherapy, patients received a single infusion of both CD19 and BCMA CAR-T cells. Mild (grade 1) cytokine release syndrome was observed, with no neurotoxicity reported. Hematologic toxicity was common (grade 3–4 in all patients). Clinically, all patients achieved LLDAS and discontinued all SLE-specific medications, including corticosteroids. Disease activity, measured by SLEDAI-2K scores, dropped significantly from an average of 18.3 to 1.5, and no disease flares were observed during the follow-up period. Importantly, dual CAR-T therapy achieved broad B-cell depletion and led to seroconversion of anti-dsDNA and antinuclear antibodies, with partial reconstitution of peripheral B cells around three months post-infusion. These findings suggest that targeting both CD19 and BCMA can achieve a deeper immunologic reset than CD19 targeting alone, offering a promising path toward durable drug-free remission in refractory SLE.

A recent phase 1 open-label clinical trial led by Wang et al. explored the safety and efficacy of a novel compound CAR-T cell therapy (cCAR) targeting both CD19 and BCMA in patients with SLE, particularly those with lupus nephritis refractory to standard treatments [23]. The cCAR-Therapy combines dual-targeting of B cells and long-lived plasma cells—key drivers of autoantibody production in SLE—thereby aiming for a complete immune reset. In this study, 13 patients received a single infusion of 3×10^6 cCAR cells/kg following lymphodepleting conditioning, with one receiving a lower dose due to lymphopenia. Within three months, 12 patients achieved LLDAS, and nine reached complete remission per DORIS criteria. The treatment induced rapid depletion of peripheral B cells and autoantibodies, including anti-dsDNA, antinuclear, and anti-SSA/Ro antibodies, with B cell reconstitution occurring within 2–6 months. The therapy showed a favorable safety profile, with only

mild cytokine release syndrome and no neurotoxicity or severe infections. The results demonstrate that cCAR-therapy can achieve medication-free remission in refractory SLE patients by effectively targeting both CD19⁺ B and CD19⁻ long-lived plasma cells.

Conclusion

Chimeric antigen receptor (CAR)-T cell therapy, particularly CD19- and CD19/BCMA-directed approaches, represents an interesting novel direction in the treatment of refractory SLE. By depleting autoreactive B cells and long-lived plasma cells, CAR-T therapy can reset immune tolerance and induce durable, drug-free remission. Early clinical studies have shown remarkable efficacy with manageable safety profiles across both autologous and allogeneic platforms. While long-term

data and larger trials are needed, CAR-T therapy holds significant promise as a potential paradigm shift in managing severe, treatment-resistant autoimmune disease.

Conflict of interest

None

Correspondence address

✉ Artur Cieślęwicz

Department of Clinical Pharmacology, Poznan University of Medical Sciences

Św. Marii Magdaleny 14 Str., 61-861 Poznań

☎ (+48 61) 668 78 21

✉ artcies@ump.edu.pl

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