International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
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ARTICLE TITLE	THE USE OF MODIFIED T LYMPHOCYTES (CAR-T AND CAR-Treg) AS A STRATEGY FOR RESTORING IMMUNOLOGICAL TOLERANCE IN SEVERE FORMS OF SYSTEMIC LUPUS ERYTHEMATOSUS AND SYSTEMIC SCLEROSIS – ANALYSIS OF EFFICACY AND SAFETY IN THE LIGHT OF THE LATEST CLINICAL TRIALS - REVIEW
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5498
RECEIVED	09 February 2026
ACCEPTED	11 April 2026
PUBLISHED	17 April 2026
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THE USE OF MODIFIED T LYMPHOCYTES (CAR-T AND CAR-Treg) AS A STRATEGY FOR RESTORING IMMUNOLOGICAL TOLERANCE IN SEVERE FORMS OF SYSTEMIC LUPUS ERYTHEMATOSUS AND SYSTEMIC SCLEROSIS – ANALYSIS OF EFFICACY AND SAFETY IN THE LIGHT OF THE LATEST CLINICAL TRIALS - REVIEW

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ABSTRACT

In recent years, there has been rapid progress in cell therapies based on modified T cells, particularly CAR-T and CAR-Treg technologies, which show promise in the treatment of severe autoimmune diseases. Systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) are diseases characterized by profound dysregulation of the immune system, leading to chronic inflammation and multiorgan damage. Despite the use of conventional immunosuppressive therapies, a significant proportion of patients remain refractory to treatment, justifying the search for new therapeutic strategies.

The aim of this review is to analyze the efficacy and safety of CAR-T and CAR-Treg cells in the context of the latest clinical trials published between 2024 and 2026. Particular attention was paid to the immunological mechanisms underlying the action of these therapies, their ability to "reset" the immune system, and their impact on long-term disease remission.

Available clinical data indicate that B-cell-targeted CAR-T therapy (e.g., CD19) can lead to deep and long-lasting remission in patients with refractory SLE through the elimination of autoreactive cell populations and the restoration of the immune repertoire (Wang et al., 2025; Xu et al., 2025). At the same time, new strategies utilizing CAR-Treg cells are emerging, aimed at restoring immune tolerance without systemic immunosuppression.

Despite promising results, this therapy is associated with potential risks, such as cytokine release syndrome or neurotoxicity, although in recent studies their incidence appears to be limited (Zhou et al., 2024; Wang et al., 2025).

In summary, CAR-T and CAR-Treg therapies represent a breakthrough in the treatment of severe autoimmune diseases; however, their widespread use requires further research on safety, accessibility, and the optimization of therapeutic protocols.

KEYWORDS

CAR-T, CAR-Treg, Systemic Lupus Erythematosus, Systemic Sclerosis, Immunotherapy, Immune Tolerance, Autoimmune Diseases

CITATION

Patrycja Szczygielska, Sylwia Hejna, Weronika Smutkiewicz, Weronika Teterycz, Wiktoria Goździejewska, Łukasz Jaworek, Gabriela Zimka, Krystian Bjorgen, Lilianna Jasińska, Magdalena Roman. (2026) The Use of Modified T Lymphocytes (CAR-T and CAR-Treg) as a Strategy for Restoring Immunological Tolerance in Severe Forms of Systemic Lupus Erythematosus and Systemic Sclerosis – Analysis of Efficacy and Safety in the Light of the Latest Clinical Trials - Review. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5498

1. Introduction

Modern clinical immunology is undergoing a profound transformation, driven by the development of cell therapies capable of precisely modulating the immune response. Genetically modified T cells equipped with chimeric antigen receptors (CARs) have gained particular significance in this context; originally developed as a tool for treating hematologic malignancies, their use in autoimmune diseases is now increasingly being considered.

Systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) are among the most complex autoimmune diseases, in which there is a loss of immune tolerance to self-antigens. Auto-reactive B cells and the production of autoantibodies play a key role in the pathogenesis of these diseases, leading to chronic inflammation and organ damage. Despite the availability of a wide range of therapies, including glucocorticoids, immunosuppressive drugs, and monoclonal antibodies, treatment efficacy remains limited, and a complete cure is still not possible (Zhou et al., 2024).

In recent years, the concept of an "immunological reset" has emerged, which involves the elimination of pathological cell populations and the restoration of the immune system in a more physiological manner. CAR-T therapy, particularly targeting the CD19 antigen, enables the selective removal of B cells responsible for disease progression, leading to a profound remodeling of the immune response and potentially durable remission (Wang et al., 2025).

In parallel, strategies are being developed that utilize CAR-engineered regulatory T cells (Tregs), which, rather than eliminating target cells, act by actively suppressing the autoimmune response and restoring immune tolerance. This approach is part of a broader trend toward seeking therapies that are more selective and less toxic than conventional immunosuppression.

Despite the growing number of preclinical and clinical studies, the application of CAR-T therapy in autoimmune diseases remains in the early stages of development. Most available clinical trials are Phase I studies involving small groups of patients, which limits the ability to unequivocally assess efficacy and safety (Xu et al., 2025).

The aim of this review article is to provide a comprehensive analysis of current data on the use of CAR-T and CAR-Treg cells in the treatment of severe forms of SLE and SSc, with a particular focus on the results of recent clinical trials and the potential implications for the future of autoimmune disease therapy.

2. Methodology

To provide a comprehensive and up-to-date analysis of the therapeutic potential of CAR-T and CAR-Treg cells in the treatment of severe forms of autoimmune diseases, a narrative literature review was conducted in accordance with current standards for evaluating the quality of review articles. The search strategy was designed to include the most recent scientific publications, with a particular focus on clinical and translational studies published between 2024 and 2026.

The database search primarily covered PubMed/MEDLINE, supplemented by Web of Science and Scopus, which allowed for the identification of the most current and peer-reviewed sources. The search strategy employed combinations of keywords and MeSH terms, such as "CAR-T cells," "CAR-Treg," "systemic lupus erythematosus," "systemic sclerosis," "autoimmunity," "immune tolerance," and "clinical trials." Additionally, logical operators (AND, OR) were used to increase the precision of the search results.

The analysis primarily included Phase I and II clinical trials, cohort studies, and high-quality review articles that provided data on the efficacy and safety of the therapies. Particular emphasis was placed on studies involving patients with severe, treatment-resistant forms of SLE and SSc in whom standard therapies had not yielded the expected results. However, publications of limited methodological value, such as single case reports without novel mechanistic insights, were excluded.

Data analysis was conducted qualitatively, taking into account both clinical outcomes and the biological mechanisms underlying the observed therapeutic effects. This approach allows for the integration of knowledge from immunology, molecular biology, and clinical medicine, which is particularly important in the case of complex cell therapies.

3. Mechanisms Of Action of CAR-T And CAR-Treg Therapies in Autoimmune Diseases

Understanding the mechanisms of action of CAR-T and CAR-Treg cells in the context of autoimmune diseases requires a shift away from the classical paradigm of immunosuppression toward the concept of precise modulation of the immune response. Unlike traditional therapies, which lead to a global suppression of the immune system, therapies based on modified T cells allow for selective targeting of key elements of disease pathogenesis.

3.1 Elimination of autoreactive B cells as a mechanism of "immune reset"

One of the best-documented mechanisms of action of CAR-T therapy in autoimmune diseases is the selective elimination of B cells, which play a central role in the pathogenesis of SLE and, to a lesser extent, systemic sclerosis. These lymphocytes are responsible for the production of autoantibodies and antigen presentation, which leads to the activation of autoreactive T cells and the perpetuation of inflammation.

Recent clinical trials have demonstrated that the use of CAR-T cells targeting the CD19 antigen leads to nearly complete depletion of the B-cell population, resulting in a rapid decline in autoantibody levels and improvement in clinical parameters. Importantly, this effect is not limited to merely transient suppression of the immune system but leads to a profound reorganization of the immune repertoire (Wang et al., 2025; Mougiakakos et al., 2025).

Further analyses indicate that following the elimination of pathological B-cell clones, these cells are gradually reconstituted from hematopoietic precursors, enabling the emergence of a "new" immune system devoid of autoreactivity. This process is referred to as an "immunological reset" and constitutes one of the most important concepts in modern immunotherapy (Xu et al., 2025; Mackensen et al., 2026).

3.2 Modulation of the immune response by CAR-Tregs and restoration of tolerance

In parallel with elimination strategies, approaches based on the use of regulatory T cells (Tregs), which play a key role in maintaining immune tolerance, are being developed. Under physiological conditions, Tregs suppress excessive activation of the immune system; however, in autoimmune diseases, their function is often impaired.

The use of CAR technology allows Treg cells to be directed against specific antigens associated with the autoimmune process, which significantly increases their efficacy. Preclinical studies and early-phase clinical trials have demonstrated that CAR-Treg cells are capable of locally suppressing the inflammatory response, limiting the activation of effector T cells, and modulating the function of antigen-presenting cells (Zhang et al., 2025; Ferreira et al., 2019).

Importantly, unlike CAR-T therapies, which act by eliminating target cells, CAR-Tregs promote the restoration of immune tolerance through active suppressive mechanisms, such as the secretion of anti-inflammatory cytokines (e.g., IL-10, TGF-β) and direct interaction with effector cells. This approach has the potential to reduce the risk of adverse effects associated with profound immunosuppression (Rosado-Sánchez et al., 2025; Raffin et al., 2026).

3.3 Functional Differences Between CAR-T and CAR-Treg – Therapeutic Implications

Although both CAR-T and CAR-Treg utilize similar genetic engineering technologies, their biological mechanisms and potential clinical applications differ significantly. CAR-T therapies are highly effective at eliminating specific cell populations, making them particularly useful in situations where rapid suppression of disease activity is necessary.

In contrast, CAR-Treg offers a more nuanced therapeutic approach, aimed at long-term stabilization of the immune response. In the context of diseases such as SSc, where fibrotic processes are associated with chronic immune activation, CAR-Treg-based strategies may prove particularly promising (Ferreira et al., 2019; Zhang et al., 2025).

Recent data also suggest the possibility of combining both approaches within sequential or combination therapies, which may allow for both rapid clinical effects and sustained disease remission. Such strategies are currently the subject of intensive translational research and may represent the next stage in the development of immunotherapy for autoimmune diseases (Mackensen et al., 2026; Rosado-Sánchez et al., 2025).

4. Efficacy of CAR-T and CAR-Treg Therapies – an Analysis of The Latest Clinical Trials (2024–2026)

4.1 Efficacy of CAR-T therapy in systemic lupus erythematosus (SLE)

In recent years, groundbreaking reports have emerged regarding the use of CAR-T cells in the treatment of patients with severe, treatment-resistant forms of SLE. Of particular significance are clinical trials utilizing CAR-T cells targeting the CD19 antigen, which is widely expressed on the surface of B cells involved in the autoimmune process.

The analyzed studies demonstrated that the administration of autologous CAR-T cells leads to rapid and profound depletion of B cells, which correlates with a significant reduction in disease activity as assessed using standard clinical scales. In most patients, clinical remission was achieved within a relatively short time after therapy administration, often within a few weeks of infusion (Mackensen et al., 2025; Wang et al., 2025).

Importantly, recent studies emphasize the durability of the therapeutic effects achieved. Even after the gradual recovery of the B-cell population, patients maintained disease remission, suggesting that CAR-T therapy may lead to a lasting change in immune system function rather than merely its temporary suppression (Xu et al., 2025; Mougiakakos et al., 2025).

Additional immunological analyses indicate that, following therapy, the B-cell repertoire is reconstituted with cells that are more “naive” and less autoreactive. At the same time, normalization of autoantibody levels and improvement in serological parameters, such as complement levels, are observed, which provides further confirmation of the therapy’s efficacy (Wang et al., 2025; Mackensen et al., 2026).

4.2 The Use of CAR-T Therapy in Systemic Sclerosis (SSc)

Compared to SLE, the number of clinical trials investigating the use of CAR-T therapy in systemic sclerosis is currently more limited; however, available data suggest the growing potential of this therapeutic approach. Systemic sclerosis is characterized not only by an autoimmune component but also by progressive tissue fibrosis, which poses an additional therapeutic challenge.

Early pilot studies have shown that the elimination of B cells using CAR-T can lead to a reduction in inflammatory activity and a slowing of fibrotic processes. Improvements in clinical parameters, such as skin elasticity and internal organ function, were observed, although these effects were more variable than in SLE (Zhou et al., 2024; Wang et al., 2025).

Some studies suggest that the efficacy of CAR-T therapy in SSc may depend on the disease stage and the predominant pathogenic mechanism. In more inflammatory phases, the therapy appears to yield greater benefits, whereas in advanced stages of fibrosis, its effectiveness may be limited (Xu et al., 2025; Ferreira et al., 2019).

4.3 The Therapeutic Potential of CAR-Treg – New Directions in Clinical Research

Although most of the available clinical data pertains to CAR-T therapy, there is a growing number of studies exploring the use of CAR-Treg cells as an alternative or complementary therapeutic strategy. This approach is based on enhancing natural mechanisms of immune tolerance rather than eliminating specific cell populations.

Early-phase studies have shown that the administration of CAR-Treg cells can lead to a significant reduction in disease activity by inhibiting the inflammatory response and modulating the function of effector cells. These effects were particularly evident in models of diseases with chronic inflammatory courses, where long-term regulation of the immune system is of key importance (Zhang et al., 2025; Rosado-Sánchez et al., 2025).

Despite promising results, it should be emphasized that CAR-Treg therapy is still in the early stages of clinical development. The available data come mainly from preclinical studies and small pilot trials, which limits the ability to unequivocally assess its efficacy compared to CAR-T therapy (Raffin et al., 2026; Ferreira et al., 2019).

5. Safety of CAR-T and CAR-Treg Therapies

5.1 Cytokine Release Syndrome (CRS)

One of the most commonly reported adverse effects associated with CAR-T therapy is cytokine release syndrome (CRS), resulting from the rapid activation of the immune system and massive release of inflammatory mediators. Symptoms of CRS include fever, hypotension, and organ dysfunction, and their severity can vary.

In the context of autoimmune diseases, however, the course of CRS is typically milder than in the case of oncological therapies. In most of the analyzed clinical trials, CRS was mild to moderate in nature and was effectively controlled with standard treatment, including IL-6 receptor antagonists (Mackensen et al., 2025; Wang et al., 2025).

It has been suggested that the lower severity of CRS in autoimmune diseases may result from a lower antigenic load compared to hematologic malignancies, leading to less intense activation of CAR-T cells (Zhou et al., 2024; Xu et al., 2025).

5.2 Neurotoxicity (ICANS)

Another potential adverse effect is neurotoxicity associated with CAR-T therapy, referred to as ICANS (immune effector cell-associated neurotoxicity syndrome). Symptoms may include altered consciousness, seizures, and other neurological symptoms.

In the analyzed studies on SLE and SSc, the incidence of neurotoxicity was relatively low, and the observed cases were typically mild and transient. In most cases, symptoms resolved spontaneously or following supportive treatment (Wang et al., 2025; Mougiakakos et al., 2025).

These data suggest that the safety profile of CAR-T therapy in autoimmune diseases may be more favorable than in oncology, although long-term monitoring of patients remains necessary (Xu et al., 2025; Mackensen et al., 2026).

5.3 Risk of Infection and Immunosuppression

Due to the mechanism of action of CAR-T therapy, which involves extensive depletion of B cells, there is a potential risk of increased susceptibility to infections. However, in the studies analyzed, the incidence of severe infections was relatively low, and most infections were mild.

An important aspect of clinical management is monitoring immunoglobulin levels and administering replacement therapy as needed. In many cases, immune system function gradually normalizes as the B-cell population recovers (Mackensen et al., 2025; Wang et al., 2025).

5.4 Safety of CAR-Treg Therapy

For CAR-Treg therapy, the safety profile appears to be potentially more favorable, which stems from the different mechanism of action of these cells. Instead of inducing a strong cytotoxic response, CAR-Tregs act by suppressing the immune response, which reduces the risk of CRS and neurotoxicity.

To date, studies indicate that this therapy is well tolerated; however, its long-term safety remains under investigation. Of particular importance is the assessment of the risk of excessive immunosuppression and the potential impact on the development of infections and neoplasms (Raffin et al., 2026; Rosado-Sánchez et al., 2025).

6. Clinical Implications

Advances in CAR-T and CAR-Treg cell-based therapies may significantly reshape treatment strategies for severe autoimmune diseases, such as systemic lupus erythematosus and systemic sclerosis. Results from existing studies suggest that the use of CAR-T therapy in patients resistant to standard treatment may lead to deep clinical remission, offering a potential alternative to long-term immunosuppression (Mackensen et al., 2025; Wang et al., 2025).

From a clinical perspective, the ability of these therapies to induce lasting changes in immune system function is particularly significant, as this may translate into a reduction in disease recurrence rates and a decrease in the need for chronic use of broad-spectrum immunosuppressive drugs (Xu et al., 2025; Mougiakakos et al., 2025). At the same time, it is suggested that the optimal timing of therapy initiation may be critical for its efficacy, especially in diseases characterized by irreversible organ damage, such as systemic sclerosis (Ferreira et al., 2019).

The introduction of CAR-Treg therapy into clinical practice may further enable a more selective and physiological restoration of immune tolerance, which is potentially associated with a lower risk of adverse effects compared to conventional treatment methods (Raffin et al., 2026; Rosado-Sánchez et al., 2025).

Despite promising prospects, the implementation of these therapies in routine clinical practice remains limited by high costs, the complexity of the manufacturing process, and the need to administer treatment at specialized centers. Additionally, further research is still needed to assess long-term safety and the durability of the therapeutic effects achieved (Wang et al., 2025; Mackensen et al., 2026).

7. Discussion

The rapid development of therapies based on modified T cells represents one of the most groundbreaking trends in modern clinical immunology. The results of recent studies suggest that the use of CAR-T cells in autoimmune diseases, such as systemic lupus erythematosus, may lead to therapeutic effects that go beyond the classical understanding of immunosuppression. Unlike standard treatments, which merely suppress immune system activity, CAR-T therapy appears to enable a profound remodeling of the immune system, leading to sustained disease remission (Mackensen et al., 2025; Wang et al., 2025).

One of the most important conclusions drawn from the analysis of available studies is the confirmation of the concept of an "immunological reset." The elimination of autoreactive B lymphocytes, followed by their reconstitution from hematopoietic precursors, leads to the formation of a more tolerogenic immune repertoire. Importantly, the observed effects persist even after the immune system has been recolonized, indicating a lasting change in its function rather than merely a transient therapeutic effect (Xu et al., 2025; Mougiakakos et al., 2025).

Despite these promising results, attention must be paid to the significant limitations of the available data. Most clinical trials were conducted on small groups of patients, often as part of early-phase studies, which limits the ability to generalize the results to a broader patient population. Furthermore, there is a lack of long-term observational data that would allow for a definitive assessment of remission durability and potential long-term adverse effects (Zhou et al., 2024; Mackensen et al., 2026).

In the context of systemic sclerosis, interpreting the results is even more complex. This disease is characterized not only by an immunological component but also by advanced fibrotic processes, which may be less amenable to reversal even after the successful elimination of autoreactive cells. Consequently, the efficacy of CAR-T therapy in SSc may depend significantly on the timing of its administration and the dominant pathogenic mechanisms (Ferreira et al., 2019; Xu et al., 2025).

An important area of development remains the use of CAR-Treg cells, which represent a more physiological approach to restoring immune balance. Unlike eliminative therapies, CAR-Tregs act by actively suppressing the autoimmune response and supporting tolerance mechanisms. This approach may be particularly beneficial in chronic diseases, where long-term regulation of the immune system is crucial (Raffin et al., 2026; Rosado-Sánchez et al., 2025).

However, the development of CAR-Treg therapy also presents significant challenges. One of the main issues is the stability of the cells' regulatory phenotype after they are administered to the patient. There are concerns that under conditions of strong inflammatory stimulation, these cells may lose their suppressive properties or even transform into effector cells, which could potentially exacerbate the autoimmune process (Zhang et al., 2025; Ferreira et al., 2019).

Another important aspect is the safety of the therapy. Although the adverse event profile appears more favorable than in oncological applications, there remains a risk of complications such as cytokine release syndrome or neurotoxicity. Although the course of these complications was generally mild in the analyzed studies, it is necessary to develop standardized protocols for monitoring and treating them (Wang et al., 2025; Mougiakakos et al., 2025).

The practical aspects of implementing CAR-T therapy into routine clinical practice must also not be overlooked. The cell manufacturing process is complex, time-consuming, and costly, which significantly limits the availability of this treatment method. Additionally, it requires highly specialized infrastructure and close collaboration between clinical centers and cell engineering laboratories (Mackensen et al., 2026; Rosado-Sánchez et al., 2025).

It is also worth noting the potential of combination therapies. Increasingly, researchers are considering the possibility of combining eliminative strategies (CAR-T) with regulatory approaches (CAR-Treg), which could lead to both rapid clinical response and long-term disease stabilization. This approach may prove

particularly important in the treatment of complex autoimmune diseases with heterogeneous courses (Ferreira et al., 2019; Mackensen et al., 2026).

In summary, CAR-T and CAR-Treg therapies open new perspectives in the treatment of severe autoimmune diseases; however, their clinical application requires further research. Future randomized trials and long-term follow-up studies will be crucial for a better understanding of both the efficacy and safety of these innovative therapeutic strategies.

8. Conclusions

An analysis of the latest clinical trials indicates that therapies based on modified T cells, particularly CAR-T cells, represent a breakthrough approach in the treatment of severe, refractory forms of autoimmune diseases, especially systemic lupus erythematosus. Their efficacy stems primarily from the ability to selectively eliminate autoreactive B cells and the subsequent restoration of the immune system, leading to the permanent restoration of immune tolerance and the maintenance of clinical remission even after the regeneration of cell populations.

In the case of systemic sclerosis, therapeutic effects are more varied, likely due to the complex pathogenesis of the disease and the significant role of fibrotic processes, which may limit the efficacy of therapy, particularly in advanced stages. At the same time, the development of CAR-Treg cell-based therapies opens new treatment prospects through a more selective and physiological restoration of immune balance, although this approach is still in the early stages of clinical trials and requires further validation.

Available data suggest that the safety profile of CAR-T therapy in autoimmune diseases is more favorable than in oncological applications; however, there remains a need to monitor potential adverse effects, such as cytokine release syndrome, neurotoxicity, and an increased risk of infection. Organizational and economic factors also remain significant limitations, including the high cost of therapy and its limited availability due to the complexity of the manufacturing process.

In summary, CAR-T and CAR-Treg therapies represent a promising direction for the development of personalized medicine in the treatment of autoimmune diseases; however, their widespread clinical application requires further research, particularly randomized controlled trials and long-term follow-up studies, which will allow for a comprehensive assessment of their efficacy, safety, and optimal role in therapeutic strategy.

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