Review paper

Reumatologia 2026; 64, 4: 322–331
DOI: https://doi.org/10.5114/reum/224664

The role and potential of CD19-targeted chimeric antigen receptor T-cell therapy in systemic sclerosis

Krzysztof Michalak ✉, **Gabriela Chlebowska**, **Oliwia Sędziak**, **Dariusz Woszczyk**

Department of Hematology, Institute of Medical Sciences, University of Opole, Poland

Abstract

Introduction: Systemic sclerosis (SSc) remains a challenge due to high mortality and resistance to treatment. Chimeric antigen receptor T-cell (CAR-T) technology (anti-CD19) may offer an opportunity for an immune system reset and long-term disease remission, eliminating the need for lifelong medication.

Material and methods: This narrative review is based on a literature search in the PubMed and Scopus databases from 2023 to 2026. The main search phrases were: "CAR-T in systemic sclerosis", "CAR-T scleroderma", and "CAR-T SSc."

Results: CD19-targeted CAR-T therapy led to significant clinical improvement across analyzed cases. The median modified Rodnan skin score decreased by 8–13 points within 3–6 months. Disease activity, measured by the European Scleroderma Trials and Research Group Activity Index (EUSTAR-AI), showed a mean improvement ranging from 2.1 to 4.2 points. Pulmonary function remained stable or improved, with forced vital capacity increasing by up to 7% in responders. The safety profile was manageable, primarily consisting of grade 1 cytokine release syndrome in approximately 75–80% of patients.

Conclusions: CD19-targeted CAR-T therapy is a promising investigational option for patients with refractory SSc. Limitations include small study groups and a lack of randomized controlled trials, warranting further validation in ongoing clinical studies.

Key words: immunotherapy, scleroderma, systemic sclerosis.

Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease whose pathogenesis is based on 3 pillars: vasculopathy, immune system dysregulation, and progressive fibrosis of the skin and internal organs [1–3]. Vascular abnormalities initiate the process through endothelial dysfunction and microvascular rarefaction, leading to chronic tissue hypoxia. This environment triggers immune dysregulation, characterized by the activation of both innate and adaptive immunity. B-cells play a pivotal role here, not only by producing specific autoantibodies (e.g., anti-topoisomerase I [anti-Scl-70]) but also by secreting pro-fibrotic cytokines such as interleukin-6 (IL-6) and transforming growth factor-β (TGF-β). This persistent inflammatory signaling drives fibroblast differentiation into myofibroblasts, leading to excessive extracellular matrix deposition and progressive organ fibrosis [1, 3, 4]. Despite the availability of immunosuppressive drugs (such as cyclophosphamide or mycophenolate mofetil), many patients do not achieve sustained remission, and the disease continues to be associated with significant morbidity and mortality [2, 4]. The prognosis in severe forms of the disease remains poor, and traditional treatment rarely leads to long-term remission without the need for continuous drug administration [1].

Autologous hematopoietic stem cell transplantation (HSCT) has become an alternative for patients with severe, treatment-refractory SSc. Studies such as ASTIS and SCOT have demonstrated the superiority of HSCT over cyclophosphamide, showing that it can induce deep and durable remission. Long-term observations confirm that HSCT significantly reduces skin fibrosis and stabilizes organ function, with 5-year overall survival (OS) rates ranging from 79% to 96%. However, this procedure remains associated with a high risk of peri-procedural

Address for correspondence

Krzysztof Michalak, Department of Hematology, Institute of Medical Sciences, University of Opole, 53 Kośnego St., 45-372 Opole, Poland, e-mail: kristofersen55555@gmail.com

Submitted: 28.12.2025; **Accepted:** 16.06.2026; **Published online:** 10.07.2026

toxicity and mortality [4, 5]. Specifically, treatment-related mortality associated with HSCT can reach up to 10% in some cohorts, primarily due to cardiac toxicity or infectious complications. This significant safety concern, alongside the rigorous eligibility criteria, limits its application to a highly selected group of patients. In this context, chimeric antigen receptor (CAR) T-cell technology, originally developed for hematological malignancies, has emerged as a potential therapeutic strategy.

The CAR is a modular synthetic fusion protein designed to redirect T-cell specificity toward a predefined surface antigen [4–6]. The clinical application of autologous CAR-T cells involves a complex "vein-to-vein" manufacturing process, encompassing leukapheresis, *ex vivo* genetic engineering, and a lymphodepletion conditioning regimen (typically comprising fludarabine and cyclophosphamide) to promote CAR-T cell expansion [5, 6]. Therapy with CAR-T targeting the CD19 antigen (CD19-CAR-T) aims at deep B-cell depletion, which may restore immunological tolerance [1, 6]. Recent reports, including case series, indicate that this therapy is feasible and may lead to clinical symptom resolution in SSc patients refractory to standard treatment [1, 7]. In addition to classic autologous CAR-T preparations, allogeneic ("off-the-shelf") products, with genetic modification (e.g., using CRISPR/Cas9), are also being investigated to reduce the risk of rejection, thereby increasing the accessibility of this method [8].

Material and methods

This manuscript is a narrative review without formal quality assessment and aims to provide a comprehensive, clinically relevant synthesis of CAR-T cell therapy approaches in SSc. The literature was reviewed by searching the scientific databases PubMed and Scopus. The materials presented at the most significant international rheumatology congresses, such as the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR), were also analyzed. To ensure retrieval of all relevant literature, the search strategy combined free-text terms with Medical Subject Headings (MeSH). The search terms included the following combinations of keywords: ("CAR-T" OR "CD19-CAR-T" OR "CD19 CAR-T" OR "chimeric antigen receptor" OR "chimeric antigen receptor T-cell" OR "CAR-T cell therapy") AND ("scleroderma" OR "systemic sclerosis" OR "SSc pathogenesis" OR "SSc"). MeSH terms were used to enhance search precision, including "Scleroderma, Systemic" and "Receptors, Chimeric Antigen."

The inclusion criteria were as follows:

- original scientific articles (clinical trials and observational studies) on the efficacy or safety of CAR-T cell therapy in SSc,
- studies published between January 2023 and January 2026.

The exclusion criteria included studies that:

- lacked full text,
- were non-English publications,
- described the use of CAR-natural killer (NK) cell therapy.

The initial stage of the process involved selecting articles based on their titles. In the second stage, the importance of the abstract was considered, and finally, the full texts were examined. The reference lists of the included studies and relevant reviews were also screened to identify any additional records. Two independent reviewers screened the articles for relevance to the review's objectives following a database search. This review included 21 patients with SSc who had undergone CAR-T cell therapy. Auth et al. [7] reported a case series involving 6 patients with diffuse SSc (dSSc). Notably, this series incorporated preliminary data from 2 patients with SSc enrolled in the CASTLE study (NCT06347718), a phase 1/2a basket trial evaluating the safety and efficacy of zorpocabtagene autoleucel. Consequently, the present review considers 4 patients described by Auth et al. [7] and 9 patients from the CASTLE study. Additionally, 5 patients from the study by Pecher et al. [9] were included. The remaining 3 patients were identified from case reports.

Discussion

Mechanistic rationale for CD19-targeted chimeric antigen receptor T-cell therapy in systemic sclerosis

The application of cellular therapy in SSc stems from the fundamental role of B lymphocytes in the initiation and perpetuation of the disease process, which is confirmed by numerous studies on SSc pathogenesis [7, 10]. B lymphocytes in SSc exhibit features of constitutive hyperreactivity, which manifests, among other things, as approximately 20% increased expression of the signaling molecule CD19 compared to healthy individuals. This CD19 overexpression lowers the activation threshold of B cells, leading to excessive stimulation and disruption of homeostasis, as manifested by the expansion of naive B lymphocytes alongside a decrease in the number of memory cells [10]. A consequence of this dysregulation is the differentiation of B lymphocytes into plasma cells that produce autoantibodies strictly correlated with the clinical phenotype, such as anti-Scl-70 and anti-RNA polymerase III (ARPA), whose titers are linked to disease activity and prognosis [7, 8]. Importantly, the pathogenicity of B lymphocytes in SSc extends beyond the production of classic nuclear autoantibodies; functional agonist autoantibodies have also been identified, directed, for example, against the platelet-derived growth

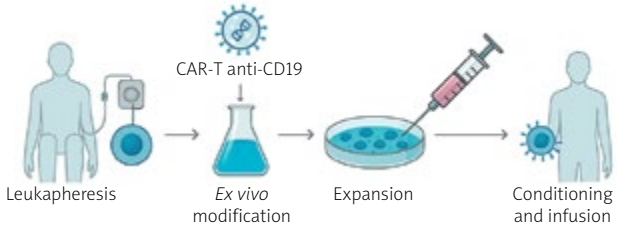

Fig. 1. Production and administration process of autologous anti-CD19 CAR-T cell therapy.

Anti-CD19 – anti-cluster of differentiation 19, CAR-T – chimeric antigen receptor T cells.

factor receptor (PDGF) or the angiotensin II type 1 receptor. These antibodies can directly stimulate fibroblasts to produce collagen and promote vascular changes, thus forming a direct link between autoimmunity and fibrosis [10]. Furthermore, activated B lymphocytes perform crucial effector functions, secreting pro-inflammatory and pro-fibrotic cytokines, such as IL-6 and TGF-β, and acting as antigen-presenting cells, which stimulate T lymphocytes and drive chronic inflammation [7, 9].

Although B-lymphocyte depletion strategies using anti-CD20 monoclonal antibodies, such as rituximab (RTX), have demonstrated some clinical efficacy in improving skin conditions, their potential in SSc is limited by the incomplete elimination of pathogenic clones [6, 10, 11]. Rituximab often fails to achieve complete B-lymphocyte depletion in deep tissue compartments, such as fibrotic skin or lymph nodes, where these cells can survive and perpetuate the disease process [1, 6]. CAR-T anti-CD19 therapy offers a mechanistic advantage due to its broader target range and distinct mode of action. The CD19 antigen is expressed on a broader spectrum of the B-lymphocyte lineage than CD20, covering stages from pro-B lymphocytes through mature cells up to plasmablasts and early plasma cells [1, 12]. Plasmablasts, a key source of autoantibodies, often lack CD20 expression, rendering them resistant to RTX treatment, but they remain susceptible to anti-CD19 CAR-T therapy [1, 6, 10]. Furthermore, as a "living drug," CAR-T cells are capable of active migration from the bloodstream into inflamed tissues, allowing for effective elimination of residual B lymphocytes inaccessible to passively acting antibodies [1, 10] (Fig. 1).

Support for this mechanism comes from histopathological studies showing extensive elimination of B lymphocytes from the skin of SSc patients following CAR-T cell infusion [10]. The complete depletion of B lymphocytes at both the peripheral and tissue levels by CAR-T cells may promote immune system reconstitution, a phenomenon commonly referred to as an "immunological reset" [1, 7]. Available clinical observations indicate that after a period of B-lymphocyte aplasia, lasting on average approximately 112 days, the B-cell population undergoes reconstitution characterized predominantly by naïve cells with a newly formed receptor repertoire lacking autoreactive clones [1, 10]. This process may interrupt pathological immunological memory and contribute to treatment-free remission in selected cases [1, 5]. However, the mechanism of action of CAR-T in SSc extends beyond the adaptive immune response, also affecting innate immunity. It has been demonstrated that the elimination of autoantibodies and circulating immune complexes after CAR-T therapy leads to the phenotypic "rejuvenation" of NK cells. In the active phase of the disease, immune complexes activate NK cells via the CD16 receptor, contributing to tissue damage; the cessation of this stimulus after CAR-T therapy restores the normal, less activated NK cell phenotype [11]. The potential clinical reflection of these molecular processes may be the regression of fibrotic changes observed in some studies, which were previously considered irreversible [1, 7, 8]. In patients treated with both autologous and allogeneic CAR-T products, stabilization as well as improvement in imaging parameters, including lung computed tomography and cardiac magnetic resonance imaging, were observed. In addition, a significant reduction in the modified Rodnan skin score (mRSS) was noted [7, 8, 10]. This suggests that the precise removal of the driving factor, which is autoreactive B lymphocytes, allows for the activation of endogenous tissue repair mechanisms even in advanced stages of the disease, although this hypothesis remains to be substantiated in larger prospective studies [7, 10, 13].

Characteristics of patients treated with CAR-T cell therapy for SSc are shown in Table I [7–9, 14, 15].

Primary and secondary endpoints

The primary objective of most studies was to evaluate the safety of CAR-T cell therapy in SSc. Key secondary outcomes included changes in the mRSS (with higher scores indicating worse skin fibrosis), imaging (which is a component of the assessment of lung fibrosis), anti-nuclear antibody (ANA) levels, ARPA levels (specifically the RP11 and RP155 subunits), and anti-DNA topoisomerase I (ATA) levels (which were assessed by immunoblot and ELISA). Changes in the lungs were assessed using forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO), whereas heart function was assessed by measuring left ventricular ejection fraction, pulmonary artery systolic pressure (PASP), and *N*-terminal pro-B-type natriuretic peptide (NT-proBNP). Other outcomes included changes in the European Scleroderma Trials and Research Group Activity Index (EUSTAR-AI) and the American College of Rheumatology Composite Response Index in Systemic Sclerosis (ACR-CRISS) score, which is a weighted score

that includes the following 5 core set measures: mRSS, FVC as a percentage of the predicted value, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and patient and clinician global assessments [16].

Efficacy of chimeric antigen receptor T-cell therapy in systemic sclerosis

The median age among the 21 SSc patients who underwent CAR-T therapy was 43 years. Women accounted for 12 of 21 (57%), and men for 9 of 21 (43%); however, the sex distribution varied across studies [7–9, 14, 15]. In the study by Pecher et al. [9], women accounted for 4 out of 5 (80%), whereas in other case series, the population consisted exclusively of men. The average disease duration was 3.2 years, and the follow-up period was 11.2 months. Nevertheless, the follow-up period was very short in some cases, so the results should be interpreted with appropriate caution. Auth et al. [7] observed a tenfold decrease in the average ANA titer after 3 months. In one patient, ARPA was the predominant autoantibody type, and it was completely eliminated following treatment. However, starting on day 618, ARPA became detectable again. In contrast, ATA concentrations decreased steadily over the observation period, reaching a maximum decrease of more than 90% relative to baseline. Müller et al. [15] also observed a 66% decrease in ATA levels after 6 months.

Lung function, as assessed by FVC and DLCO, improved significantly in most cases [7–9, 14, 15]. Among 9 patients in the CASTLE study, FVC increased significantly from a median of 2.83 to 3.23 l (+14.1%), while DLCO increased significantly from a median of 4.23 mmol/ml/kPa to 5.48 mmol/ml/kPa (+29.5%) [15]. Despite treatment, 3 patients showed progression of pulmonary fibrosis following the diagnosis of interstitial lung disease (ILD) associated with SSc. A reduction in ground-glass opacities, which are associated with ILD activity related to SSc, was observed in the lungs. Meanwhile, the severity of the reticular pattern, which reflects visible fibrous tissue remodeling, remained stable. Cardiac function was assessed only by Auth et al. [7]. Left ventricular ejection fraction remained stable in all patients during follow-up (55–60%). One patient had an NT-proBNP level of 7.202 pg/ml, which normalized during CAR-T therapy.

Skin lesions showed significant improvement, with an average reduction of 11.2 points on the mRSS scale across all patients. Müller et al. [15] reported a reduction in median mRSS scores from 26 to 12 points, whereas Auth et al. [7] observed improved skin condition in all patients, with a median decrease of 8 points over 100 days. This improvement was either maintained or further reduced during the 12-month follow-up.

Table I. Characteristics of patients treated with CAR-T cell therapy for SSc

Patient sex/ age [years]	Previous treatment	Lymphodepletion	Intervention	CAR-T cell dose cells/kg body weight	Follow-up duration [months]	Median disease duration [years]	Reference
M/60	MMF, MTX	FLU, CYC	Autologous CD19-targeted CAR T cells	1×10^6	18	2	[7]
M/36	MMF, HCQ, GCS	FLU, CYC	Autologous CD19-targeted CAR T cells	1×10^6	14	2.5	[7]
F/37	MMF, MTX, TCZ, RTX	FLU, CYC	Autologous CD19-targeted CAR T cells	1×10^6	12	1.3	[7]
M/47	MMF, CYC, NIN	FLU, CYC	Autologous CD19-targeted CAR T cells	1×10^6	8	11.2	[7]
M/45	CYC, MMF, HCQ, BEL, TEL	FLU, CYC	Allogeneic CD19-targeted CAR T cells	1×10^6	6	3	[8]
M/56	CYC, MMF, TAC	FLU, CYC	Allogeneic CD19-targeted CAR T cells	1×10^6	6	1	[8]
F/32	MTX, HCQ, AZA, TCZ, GCS, NIN, SIL, NIFE, Iloprost	FLU, CYC	Allogeneic CD19-targeted CAR T cells	1×10^6	6	6	[16]
F/51	CYC, MMF, NIN	FLU, CYC	Autologous CD19-targeted CAR T cells	1×10^6	12.7	2.5	[17]
F/42	MTX, MMF, CSA, CYC, NIN, RTX, HCQ	FLU, CYC	Autologous CD19-targeted CAR T cells	1×10^6	12.7	5.7	[17]
M/48	MTX, MMF, CSA, CYC, TCZ, RTX, HSCT	FLU, CYC	Autologous CD19-targeted CAR T cells	1×10^6	8	3	[17]
F/68	MTX, RTX, MMF, TCZ	FLU, CYC	Autologous CD19-targeted CAR T cells	1×10^6	1	3	[17]
F/59	MTX, TCZ, MMF, RTX	FLU, CYC	Autologous CD19-targeted CAR T cells	1×10^6	5	3	[17]
9 patients, median age 36	MTX, MMF, RTX, NIN, AZA, GCS	FLU, CYC	Autologous CD19-targeted CAR T cells	2.0×10^9	13	2.5	[18]

AZA – azathioprine, BEL – belimumab, CAR-T – chimeric antigen receptor T-cells, CD19 – cluster of differentiation, CSA – cyclosporine A, CYC – cyclophosphamide, F – female, FLU – fludarabine, GCS – glucocorticoids, HCQ – hydroxychloroquine, HSCT – hematopoietic stem cell transplantation, M – male, MMF – mycophenolate mofetil, MTX – methotrexate, NIFE – nifedipine, NIN – nintedanib, RTX – rituximab, SIL – sildenafil, SSc – systemic sclerosis, TAC – tacrolimus, TCZ – tocilizumab, TEL – telitacicept.

The average improvement in the EUSTAR-AI index was 4.2 points [7–9, 14, 15]. According to a study by Auth et al. [7], the mean EUSTAR-AI score was 5.7 before the start of CAR-T therapy and decreased by an average of 3.4 points in 4 patients at the last follow-up. In their case report, Albach et al. [14] observed a 5-point improvement on the EUSTAR-AI scale. The remaining studies used the ACR-CRISS criteria, except for 5 patients described by Pecher et al. [9], who did not use EUSTAR-AI or ACR-CRISS. In the CASTLE trial, all patients met the ACR CRISS 25 response criteria; 8 out of 9 met the CRISS 50 (2 out of 5 items) criteria, and 7 out of 9 met the CRISS 50 (3 out of 5 items) criteria.

Assessment of skin changes, general activity, and adverse events (AEs) during CAR-T cell therapy are shown in Table II [7–9, 14, 15].

Cytokine release syndrome

Cytokine release syndrome is characterized as a systemic inflammatory response resulting from the rapid activation of CAR-T cells and subsequent cytokine release, particularly IL-6. The primary associated symptom is fever, which may be accompanied by hypotension, tachycardia, and an altered emotional state [17, 18]. Cytokine release syndrome is the most prevalent AE associated with CAR-T cell therapy. The severity of CRS is typically assessed using the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria. These criteria are based on established guidelines and include factors such as fever and the need for supplemental oxygen or vasopressor support [17]. In cases of mild CRS, the recommended approach is threefold: observation,

Table II. Assessment of skin changes, disease activity, and AEs during CAR-T therapy in individuals with SSc

Patient sex/age [years]	mRSS baseline	mRSS 6 months	EUSTAR-AI baseline	EUSTAR AI after CAR-T	CRS or ICANS	AEs	References
M/60	24	17	4.75	2.2	CRS (grade 1)	URTI (*Haemophilus influenzae*)	[7]
M/36	27	17	9	2.5	CRS (grade 1)	Cellulitis, herpes zoster	[7]
F/37	32	15	5.25	2.5	CRS (grade 1)	mild SARS-CoV-2 infection, URTI without antibiotics	[7]
M/47	17	12	3.93	2.1	None	URTI without antibiotics, influenza A with bacterial superinfection	[7]
M/45	26	6	-	CRISS 75 (3/5 items)	None	None	[8]
M/56	39	19	-	CRISS 50 (3/5 items)	None	None	[8]
F/32	9	4	9	4	CRS (grade 2)	Neutropenia grade 3, transient liver enzyme elevation	[16]
F/51	7	3	NA	NA	CRS (grade 1)	None	[17]
F/42	17	8	NA	NA	None	None	[17]
M/48	30	10	NA	NA	CRS (grade 1)	None	[17]
F/68	32	30	NA	NA	Initially CRS (grade 1)	HLH, prolonged neutropenia, fatal outcome on day 74	[17]
F/59	32	31	NA	NA	CRS (grade 1)	None	[17]
9 patients, median age 36	26	12	NA	CRISS 25 (5/5 items) 9/9 CRISS 50 (2/5 items) 8/9 CRISS 50 (3/5 items) 7/9	CRS (grade 1) 5/9 (56%) CRS (grade 2) 1/9 (11%)	Early ICAHT (any grade) 3/9 (33%) Late ICAHT (any grade) 1/9 (11%) LICATS (any grade) 6/9 (66%)	[18]

AEs – adverse events, CAR-T – chimeric antigen receptor T-cells, CRISS – composite response index in systemic sclerosis, CRS – cytokine release syndrome, EUSTAR-AI – European Scleroderma Trials And Research Group Activity Index, F – female, HLH – hemophagocytic lymphohistiocytosis, ICAHT – immune effector cell-associated hematotoxicity, ICANS – immune effector cell-associated neurotoxicity syndrome, LICATS – local immune effector cell-associated toxicity, M – male, mRSS – modified Rodnan skin score, NA – not applicable, SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2, SSc – systemic sclerosis, URTI – upper respiratory tract infection.

symptomatic treatment, and exclusion of infection. In contrast, the prevailing therapeutic approach for CRS ≥ 2 requires prompt administration of tocilizumab, often in combination with intravenous glucocorticoids (GCs) if the patient's condition does not improve [18]. Refractory or severe CRS necessitates the administration of GCs, most commonly dexamethasone [19].

Immune effector cell-associated neurotoxicity syndrome

Immune effector cell-associated neurotoxicity syndrome (ICANS) is presented as a manifestation of neurological complications following chimeric antigen receptor CAR-T cell therapy. The pathophysiology of ICANS is based on neuroinflammatory mechanisms and damage to the blood-brain barrier [20]. As outlined in the clinical findings, the manifestation of symptoms includes convulsive seizures, ataxia, and confusion. Conversely, cerebral edema may be a consequence of severe ICANS [19]. The standard treatment for ICANS entails the intravenous administration of GCs (particularly dexamethasone) and anticonvulsants. Anakinra, an IL-1 receptor antagonist, is recommended for treating GC-refractory ICANS [21]. Moreover, in instances where toxic effects on the nervous system coexist with significant CRS, tocilizumab is the therapeutic agent of choice in such circumstances [18].

Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome during chimeric antigen receptor T-cell therapy for the treatment of systemic sclerosis

Recent scientific reports have focused on evaluating the efficacy and safety of CD19 CAR-T therapy in the treatment of SSc. Grade 1 CRS was observed in 12 of 21 patients (57%), while grade 2 CRS occurred in 2 of 21 patients (10%) who received CAR-T therapy. No cases of CRS above grade 2 were reported [7–9, 14, 15]. In the CASTLE study, the median time to onset of CRS was 1 day, and the median duration of CRS was 2 days [15]. In most cases of CAR-T therapy use in SSc, conservative treatment of grade 1 CRS proved sufficient. Müller et al. [15] administered tocilizumab to 5 of 9 patients (56%) and GCs to 1 patient. Current scientific reports on SSc suggest a favorable early neurological profile for ICANS treatment in this patient cohort. This assertion is bolstered by the absence of clinically significant ICANS among SSc patients who underwent the treatment model presented [7–9, 14, 15]. However, the current sample size of treated patients is insufficient to rule out the possibility of rare or delayed neurotoxicity.

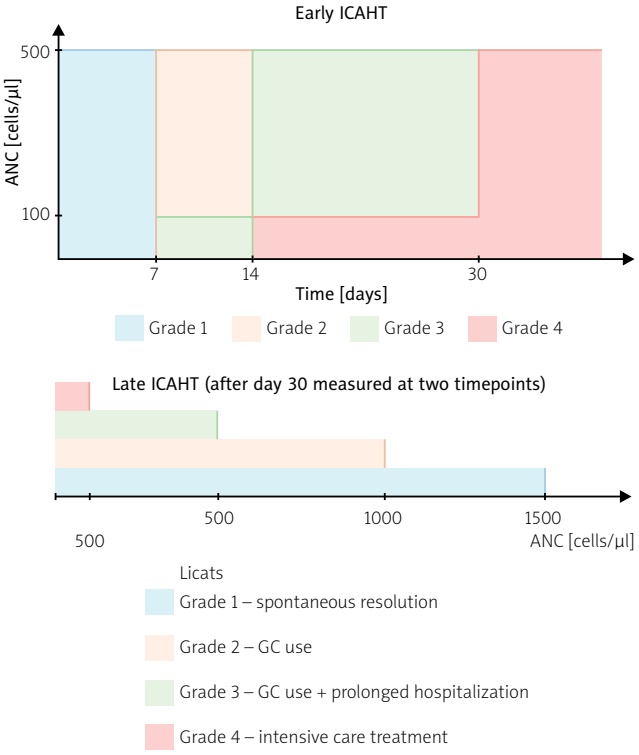

Fig. 2. Criteria for bone marrow suppression associated with lymphodepletion therapy.

ANC – absolute neutrophil count, GC – glucocorticosteroid, ICAHT – immune effector cell-associated hematotoxicity, LICATS – local immune effector cell-associated toxicity.

Compared with hematologic malignancies, SSc appears to be associated with a lower incidence and reduced severity of treatment-related toxicity. This phenomenon can be attributed to the lower degree of "burden" on target cells in patients with autoimmune diseases [17, 18, 22, 23]. Criteria for bone marrow suppression associated with lymphodepletion therapy are shown in Figure 2.

Other adverse reactions

Potential AEs of CAR-T therapy in SSc, in addition to the previously mentioned CRS and ICANS, encompass prolonged cytopenia [24]. Müller et al. [15] attempted to standardize criteria for reporting myelotoxicity associated with lymphodepletion therapy using immune effector cell-associated hematotoxicity (ICAHT) and local immune effector cell-associated toxicity (LICATS). Late ICATS occurred in 6/9 (66%) patients, early ICAHT in 3/9 (33%), and late ICAHT in 1/9 (11%) [15]. These criteria require wider dissemination and further validation, but they may prove useful for reporting this type of AE. Dahunsi et al. [25] posited that the administration of granulocyte-colony stimulating factor and blood transfusions is

Table III. Advantages and disadvantages of CAR-T vs. HSCT therapies in SSc

Characteristic	CAR-T therapy	Autologous HSCT
Administration	Single infusion	Single infusion
First application	2023	~2011
The duration of follow-up across studies	~10.5 months, short-term observation	12 months – 15 years, long-term observation
Lymphodepletion/ conditioning	Lymphodepletion (FLU, CYC)	Conditioning (MAC, TBI)
Geographic availability	Only at specialized, accredited centers (potentially not only transplant centers)	Only at specialized, accredited centers
Viral vector	Viral vector integration into the host genome increases the risk of transgene-positive T-cell lymphomas or other transgene-positive tumors	Not associated
Patients' median age across studies	43.2 years	35 years
OS	No data are available on 5-year OS	Available data on 5-year OS (79–96%)
mRSS	Significant improvement (average improvement of 11.63 points)	Significant improvement (heterogeneous data across studies)
CRS	This is more common and generally of a milder grade (grade 1 or 2)	Not associated
ICANS	No such cases have been observed in SSc to date	Not associated
SPM	Data on the incidence of SPM as a result of treatment for SSc are not available	Data on the incidence of SPM as a result of treatment for SSc are not available
TRM	No treatment-related deaths or severe immune complications reported	~6–10%, infections, cytopenia, cardiotoxicity, and amenorrhea

The data on CAR-T therapy are taken from studies included in our review, whereas the data on HSCT are taken from systematic reviews [27, 28]. Auto-HSCT – autologous hematopoietic stem cell transplantation, CAR-T – chimeric antigen receptor T-cells, CRS – cytokine release syndrome, CYC – cyclophosphamide, FLU – fludarabine, HSCT – hematopoietic stem cell transplantation, ICANS – immune effector cell-associated neurotoxicity syndrome, MAC – myeloablative conditioning, mRSS – modified Rodnan skin score, OS – overall survival, SPM – second primary malignancy, SSc – systemic sclerosis, TBI – total body irradiation, TRM – treatment-related mortality.

a recommended course of action. Furthermore, in cases of refractory thrombocytopenia, thrombopoietin agonists are recommended. As demonstrated in the existing body of research, delayed infections are among the most significant late complications, necessitating antiviral prophylaxis and immunoglobulins. The pathomechanism of this phenomenon has been determined to result from prolonged B-cell aplasia and hypogammaglobulinemia. In addition, a potential AE associated with the treatment is the risk of secondary malignancies, particularly myeloid malignancies, although the incidence remains low [26]. Pecher et al. [9] reported a case of a patient who developed fatal secondary hemophagocytic lymphohistiocytosis, which was probably caused by a herpes simplex virus infection.

Having considered both the clinical efficacy outcomes and the distinct toxicity profiles of CD19-targeted CAR-T cell therapy, a comprehensive synthesis of the advantages and disadvantages of this emerging modality compared to the current gold standard, autologous HSCT, is provided in Table III [27, 28].

Limitations of chimeric antigen receptor T-cell therapy in systemic sclerosis

Notwithstanding early encouraging observations of CAR-T therapy in the treatment of autoimmune diseases, the therapeutic modality is also associated with numerous significant limitations. Primarily, these limitations pertain to small patient cohorts and limited databases, with many conclusions based on analyses of individual cases. The consequence is difficulty in monitoring the therapy's effectiveness in a wider group of recipients, which creates challenges in future assessments of its effectiveness and safety [29]. Another important aspect is the lack of available randomized studies. Contemporary scientific reports indicate that the limited duration of observation constitutes a significant challenge. This limitation adversely impacts the capacity to ascertain data about the durability of remission and to estimate the likelihood of subsequent AEs [30]. A further challenge lies in the divergence of protocols, the absence of a clearly delineated standard of care, and the heterogeneity

of methodologies across studies, rendering comparisons of results across centers a formidable task. This circumstance creates considerable challenges in identifying the key elements that contribute to achieving the intended therapeutic outcome [30, 31]. This treatment method necessitates substantial financial expenditures and the establishment of specialized infrastructure, factors that consequently restrict its accessibility [32].

Future directions for the development of chimeric antigen receptor T-cell therapy in systemic sclerosis

Recent perspectives on the treatment of SSc using CAR-T cell therapy emphasize the need for prospective studies with standardized protocols and long-term monitoring. This is significant because such observations facilitate analysis of remission in terms of durability and enable evaluation of a comprehensive safety profile [14, 29, 33, 34]. The authors likewise underscore the need to leverage inflammatory response markers to facilitate optimal patient selection. Moreover, this approach enables us to determine whether early intervention in patients with an aggressive phenotype has a lasting impact on disease progression [14, 29, 33]. A significant avenue for advancement lies in implementing readily available allogeneic formulations that reduce qualification waiting periods and minimize costs. Additional genetic manipulations remain crucial to ensure the safety and efficacy of these "off-the-shelf products." These include the use of CRISPR/Cas9 technology. Gene editing primarily leads to the elimination of endogenous T-cell receptor (TCR) expression. Consequently, allogeneic CAR-T cells become undetectable to the immune system, reducing the risk of graft-versus-host disease (GvHD). To prevent the immune system from rejecting therapeutic cells, molecules such as human leukocyte antigens (HLA) or CD52 are eliminated in most cases. Another significant aspect, apart from gene editing, is the appropriate selection of the cell source, which can influence the incidence of GvHD. For example, using regulatory T cells (Tregs) or NK cells as the basis for CAR modification may reduce the risk of GvHD compared to conventional T cells. CARs can be synthesized on the surface of conventional T cells, Tregs, NK cells, or macrophages, thereby enabling these cells to acquire distinct functional characteristics. In addition, important challenges remain in CAR-based allogeneic therapy, and solutions are still pending. Nonetheless, several preparations using universal platforms have entered clinical trials. A case study demonstrating the feasibility of achieving deep remission and regression of fibrotic changes while ensuring safety is provided by an analysis employing TyU19 (which uses CRISPR/Cas9 to achieve these exact gene knockouts) in 2 patients with dSSc. This finding reinforces the prospect of future observations regarding the universality of products obtained using CRISPR [8, 33–35]. Concurrently, alternative methods of deep B-cell depletion are being promoted; these may either compete with or coexist with standard CD19-CAR-T. Numerous scientific reports on rheumatic diseases and SSc underscore the distinctive role of bispecific antibodies, exemplified by blinatumomab. These antibodies effectively facilitate the targeting of autologous T cells against CD19+, eliminating the need for viral vectors and enhanced conditioning [30, 33, 36]. The future of CAR-T therapy for SSc holds enormous potential, but it remains in its early stages of development. Several trials are underway to further assess the efficacy and safety of CAR-T cells in SSc.

An overview of CAR-T therapy in the treatment of SSc is presented in Supplementary Table I.

Conclusions

CD19-targeted CAR-T therapy currently represents an early proof of concept in patients with treatment-refractory SSc, with promising initial clinical responses, including reductions in skin fibrosis and stabilization of organ involvement. The early safety profile appears favorable, characterized primarily by low-grade CRS and a notable absence of severe neurotoxicity, which compares positively to procedures such as HSCT. Despite these promising results, the available evidence is largely based on individual case reports and heterogeneous groups, with limited observation periods. Consequently, the long-term safety and durability of remission remain unproven. Further validation through long-term randomized controlled trials is therefore essential. Advances in allogeneic "off-the-shelf" products and bispecific antibodies may help to standardize and expand clinical access to this new therapeutic strategy.

Disclosures

Conflicts of interest: The authors declare no conflicts of interest.
Funding: No external funding.
Ethics approval: Not applicable.
Availability of data and material: Not applicable.

References

1. Müller F, Taubmann J, Bucci L, et al. CD19 CAR T-Cell Therapy in Autoimmune Disease – A Case Series with Follow-up. N Engl J Med 2024; 390: 687–700, DOI: 10.1056/NEJMoa2308917.
2. Chen L, Huang R, Huang C, et al. Cell therapy for scleroderma: progress in mesenchymal stem cells and CAR-T

treatment. Front Med 2025; 11: 1530887, DOI: 10.3389/fmed.2024.1530887.
3. Asano Y. The Pathogenesis of Systemic Sclerosis: An Understanding Based on a Common Pathologic Cascade across Multiple Organs and Additional Organ-Specific Pathologies. JCM 2020; 9: 2687, DOI: 10.3390/jcm9092687.
4. Ramalingam S, Shah A. Stem Cell Therapy as a Treatment for Autoimmune Disease-Updates in Lupus, Scleroderma, and Multiple Sclerosis. Curr Allergy Asthma Rep 2021; 21: 22, DOI: 10.1007/s11882-021-00996-y.
5. Cras A, Farge D, Carmoi T, et al. Update on mesenchymal stem cell-based therapy in lupus and scleroderma. Arthritis Res Ther 2015; 17: 301, DOI: 10.1186/s13075-015-0819-7.
6. Hagen M, Wirsching A, Bohr D, et al. CAR T-cell therapy in rheumatology-What we know so far? Z Rheumatol 2024; 83: 485–491, DOI: 10.1007/s00393-024-01514-x [Article in German].
7. Auth J, Müller F, Völkl S, et al. CD19-targeting CAR T-cell therapy in patients with diffuse systemic sclerosis: a case series. Lancet Rheumatol 2025; 7: e83–93, DOI: 10.1016/S2665-9913(24)00282-0.
8. Wang X, Wu X, Tan B, et al. Allogeneic CD19-targeted CAR-T therapy in patients with severe myositis and systemic sclerosis. Cell 2024; 187: 4890–4904.e9, DOI: 10.1016/j.cell.2024.06.027.
9. Pecher A-C, Hensen L, Schairer R, et al. CD19-targeting CAR T cell therapy in five patients with systemic sclerosis unsuitable for autologous stem cell transplantation. EULAR Rheumatology Open 2025; S3050708125000084, DOI: 10.1016/j.ero.2025.03.005
10. Yoshizaki A, Fukasawa T, Ebata S, et al. Involvement of B cells in the development of systemic sclerosis. Front Immunol 2022; 13: 938785, DOI: 10.3389/fimmu.2022.938785.
11. Claus M, Freitag M, Ewald M, et al. Immunological effects of CD19.CAR-T cell therapy in systemic sclerosis: an extended case study. Arthritis Res Ther 2024; 26: 211, DOI: 10.1186/s13075-024-03451-1.
12. Garantziotis P, Auth J, Schett G, Bergmann C. CAR T-cell therapy in systemic sclerosis: the next frontier in immune modulation. Curr Opin Rheumatol 2026; 38: 60–68, DOI: 10.1097/BOR.0000000000001133.
13. Zhao K, Kong C, Shi N, et al. Potential angiogenic, immunomodulatory, and antifibrotic effects of mesenchymal stem cell-derived extracellular vesicles in systemic sclerosis. Front Immunol 2023; 14: 1125257, DOI: 10.3389/fimmu.2023.1125257.
14. Albach FN, Minopoulou I, Wilhelm A, et al. Targeting autoimmunity with CD19-CAR T-cell therapy: efficacy and seroconversion in diffuse systemic sclerosis and rheumatoid arthritis. Rheumatology 2025; 64: 4075–4077, DOI: 10.1093/rheumatology/keaf077.
15. Müller F, Hagen M, Wirsching A, et al. CD19 CAR-T cells for treatment-refractory autoimmune diseases: the phase 1/2 CASTLE basket trial. Nat Med 2026; 32: 1142–1151, DOI: 10.1038/s41591-025-04185-6.
16. Bergmann C, Müller F, Distler JHW, et al. Treatment of a patient with severe systemic sclerosis (SSc) using CD19-targeted CAR T cells. Ann Rheum Dis 2023; 82: 1117–20, DOI: 10.1136/ard-2023-223952.
17. Berry CT, Frazee CS, Herman PJ, et al. Current advancements in cellular immunotherapy for autoimmune disease. Semin Immunopathol 2025; 47: 7, DOI: 10.1007/s00281-024-01034-5
18. Wu Y, Han L, Wang Y, et al. CAR-T therapy: pioneering a new era in the treatment of autoimmune diseases. Front Immunol 2025; 16: 1625166, DOI: 10.3389/fimmu.2025.1625166
19. Arvanitis P, Tziotis A, Papadimatos S, et al. Pathogenesis, Diagnosis, and Management of Cytokine Release Syndrome in Patients with Cancer: Focus on Infectious Disease Considerations. Curr Oncol 2025; 32: 198, DOI:10.3390/curroncol32040198
20. Sterner RC, Sterner RM. Immune effector cell associated neurotoxicity syndrome in chimeric antigen receptor-T cell therapy. Front Immunol 2022; 13: 879608, DOI: 10.3389/fimmu.2022.879608.
21. Wehrli M, Gallagher K, Chen YB, et al. Single-center experience using anakinra for steroid-refractory immune effector cell-associated neurotoxicity syndrome (ICANS). J Immunother Cancer 2022; 10: e003847, DOI: 10.1136/jitc-2021-003847.
22. Sakkas LI, Katsiari C, Syrmou V, Chikanza IC. CAR-T cells in systemic sclerosis. Clin Rheumatol 2026; 45: 651–656, DOI: 10.1007/s10067-025-07554-1.
23. Lee BW, Kwon EJ, Ju JH. Chimeric Antigen Receptor T-cell therapy in systemic autoimmune rheumatic diseases: current insights and future prospects. J Rheum Dis 2025; 32: 154–165, DOI: 10.4078/jrd.2024.0122.
24. Bishop MR. Late complications and long-term care of adult CAR T-cell patients. Hematology Am Soc Hematol Educ Program 2024; 2024: 109–115, DOI: 10.1182/hematology.2024000534.
25. Dahunsi D, Eleanya C, Akintunde A, et al. Prolonged Cytopenia with CAR-T Cell Therapy and Management Recommendations. Clin Hematol Int 2025; 7: 47–54, DOI: 10.46989/001c.126463.
26. Testa U, Castelli G, Pelosi E, et al. Toxicities Associated with CAR-T Cell Therapies. Mediterr J Hematol Infect Dis 2025; 17: e2025039, DOI: 10.4084/MJHID.2025.039. eCollection 2025.
27. Bakirova S, Baigenzhin A, Tuganbekova S, et al. Comparative Efficacy of Autologous Hematopoietic and Mesenchymal Stem Cell Transplantation in Patients with Systemic Sclerosis: A Systematic Review. J Clin Med 2025; 15: 261, DOI: 10.3390/jcm15010261.
28. Sullivan KM. Hematopoietic stem cell transplant, chimeric antigen receptor T-cells, and other cellular therapies as stepping stones toward long-term improvement in severe scleroderma and other autoimmune diseases. Semin Arthritis Rheum 2025; 72S: 152676, DOI: 10.1016/j.semarthrit.2025.152676.
29. Sieiro Santos C, Del Galdo F. New horizons in systemic sclerosis treatment: advances and emerging therapies in 2025. RMD Open 2025; 11: e005776, DOI: 10.1136/rmdopen-2025-005776.
30. Conforti A, Cifuentes-González C, Ariani A, et al. CAR-T Cell Therapy in Autoimmune Diseases: Promise, Progress, and Pitfalls. Rheumato 2025; 5: 15, DOI: 10.3390/rheumato5040015.
31. Xu X, Su SH. CAR-T cell therapies in autoimmune rheumatic diseases: a brief report on the clinical trial landscape, current status, and future perspectives. Front Immunol 2025; 16: 1630569, DOI: 10.3389/fimmu.2025.1630569.
32. Li YR, Lyu Z, Chen Y, et al. Frontiers in CAR-T cell therapy for autoimmune diseases. Trends Pharmacol Sci 2024; 45: 839-857, DOI: 10.1016/j.tips.2024.07.005.

33. Anyfanti P, Evangelidis P, Kotsiou N, et al. Chimeric Antigen Receptor T Cell Immunotherapy for Autoimmune Rheumatic Disorders: Where Are We Now? Cells 2025; 14: 1242, DOI: 10.3390/cells14161242.
34. Wu D, Xu-Monette ZY, Zhou J, et al. CAR T-cell therapy in autoimmune diseases: a promising frontier on the horizon. Front Immunol 2025; 16: 1613878, DOI: 10.3389/fimmu.2025.1613878.
35. Lyu X, Gupta L, Tholouli E, et al. Chimeric antigen receptor T cell therapy: a new emerging landscape in autoimmune rheumatic diseases. Rheumatology (Oxford) 2024; 63: 1206–1216, DOI: 10.1093/rheumatology/kead616.
36. Subklewe M, Magno G, Gebhardt C, et al. Application of blinatumomab, a bispecific anti-CD3/CD19 T-cell engager, in treating severe systemic sclerosis: A case study. Eur J Cancer 2024; 204: 114071, DOI: 10.1016/j.ejca.2024.114071.