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# A COMPREHENSIVE REVIEW OF CAR-T CELL THERAPY ACROSS RHEUMATIC DISEASES

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**ABSTRACT**

**Background:** Autoimmune rheumatic diseases (ARDs) are characterized by a failure of immune tolerance, leading to chronic inflammation, autoantibody production, and progressive organ damage. Conventional therapies often fail to induce long-term, drug-free remission in refractory patients. Chimeric antigen receptor (CAR) T-cell therapy, originally developed for hematological malignancies, has appeared as a promising strategy to achieve the sustained depletion of pathogenic immune cells in rheumatology.
**Objective:** This review critically synthesizes current evidence regarding the pathophysiological mechanisms, molecular designs, clinical efficacy, and toxicity profiles of CAR-T therapy across systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), and adult-onset Still's disease (AOSD).
**Methods:** 77 peer-reviewed sources, including clinical trials, preclinical models, and case series, were analyzed and objectively categorized by target antigens, cellular modifications, and clinical endpoints.
**Results:** CD19-directed CAR-T cells successfully penetrate inflamed tissues and deplete the autoreactive B-cell compartment, resulting in measurable clinical remission in highly refractory SLE, SSc, and IIM cohorts.This enables the complete discontinuation of concurrent immunosuppressive drugs. Due to a complex, hypoxic synovial microenvironment, targeted RA treatment needs advanced approaches, such as fourth-generation CARs and in vivo generation techniques. Therapy-associated toxicities, primarily cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), generally present with significantly lower clinical severity in ARD patients compared to heavily pre-treated oncological cohorts.
**Conclusion:** CAR-T cell therapy represents a fundamental paradigm shift in the management of severe ARD, shifting the objective from chronic immunosuppression to definitive immune reconstitution. Despite logistical, financial, and safety challenges, clinical efficacy in treatment-refractory cases remains exceptionally high.

**KEYWORDS**

CAR-T Cell Therapy, Immunotherapy, Autoimmune Rheumatic Diseases, Systemic Lupus Erythematosus, Rheumatoid Arthritis, Systemic Sclerosis

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**Abbreviations**:
aHSCT:Autologous Hematopoietic Stem Cell Transplantation
AOSD:Adult-Onset Still's Disease
APS:Antiphospholipid Syndrome
ARDs:Autoimmune Rheumatic Diseases
ASS:Antisynthetase Syndrome
BCMA:B-Cell Maturation Antigen
CAR:Chimeric Antigen Receptor
CAR-M:Chimeric Antigen Receptor Macrophages
CAR-Tregs:Regulatory Chimeric Antigen Receptor T cells
CRS:Cytokine Release Syndrome
DM:Dermatomyositis
DMARDs:Disease-Modifying Antirheumatic Drugs
dsDNA:Double-Stranded DNA
FVC:Forced Vital Capacity
GVHD:Graft-Versus-Host Disease
ICANS:Immune Effector Cell-Associated Neurotoxicity Syndrome
IFN:Interferon
IIM:Idiopathic Inflammatory Myopathies

IL:Interleukin
JDM:Juvenile Dermatomyositis
LICATS:Local Immune Effector Cell-Associated Toxicity Syndrome
LNPs:Lipid Nanoparticles
MAS:Macrophage Activation Syndrome
MHC:Major Histocompatibility Complex
MRSS:Modified Rodnan Skin Score
RA:Rheumatoid Arthritis
scFv:Single-Chain Variable Fragment
SLE:Systemic Lupus Erythematosus
SSc:Systemic Sclerosis
TCR:T-Cell Receptor
TGF-beta:Transforming Growth Factor-beta
TNF-alpha:Tumor Necrosis Factor-alpha
TRUCKs:T Cells Redirected for Universal Cytokine-Mediated Killing

**Introduction**

The standardized pharmacological management of autoimmune rheumatic diseases (ARDs) involves the continuous, long-term administration of conventional synthetic, targeted synthetic, and biological disease-modifying antirheumatic drugs (DMARDs) [1, 2]. The underlying pathophysiology of ARDs, encompassing systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), and idiopathic inflammatory myopathies (IIM), is mechanistically driven by the systemic failure of both central and peripheral immunological tolerance mechanisms [3, 4]. This critical tolerance breakdown directly results in the aberrant activation, proliferation, and clonal expansion of autoreactive B and T lymphocyte populations [5]. Following activation, these autoreactive lymphocytes produce highly pathogenic autoantibodies, facilitate the systemic deposition of immune complexes, and mediate the infiltration of mononuclear cells into target solid tissues, including the renal glomeruli, pulmonary interstitium, and synovial membrane [6, 7]. Biological therapies engineered to target specific pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), or specific cellular surface receptors, have statistically improved clinical outcomes across broad patient populations [2, 8]. However, primary non-response and secondary therapeutic resistance occur in a clinically significant percentage of ARD patients [2, 8]. Refractory patient cohorts inevitably present with progressive, irreversible end-organ damage and exhibit statistically increased mortality rates when compared to the matched general population [1, 9].

Prior to the conceptualization and development of advanced cellular therapies, autologous hematopoietic stem cell transplantation (aHSCT) was selectively utilized for severe, highly refractory cases of ARDs [10]. The mechanism of action of aHSCT involves the induction of profound immunoablation utilizing high-dose conditioning chemotherapy regimens, typically incorporating cyclophosphamide and antithymocyte globulin [10, 11]. Following immunoablation, the procedure requires the infusion of autologous hematopoietic progenitor cells to theoretically reconstitute a naive, non-autoreactive immune system [10, 11]. The widespread clinical application of aHSCT is severely limited by high rates of procedure-related morbidity, the emergence of life-threatening opportunistic infections, and clearly documented nonrelapse mortality [10]. The clinical need for focused treatments that achieve complete immunological reconstitution with significantly lower mortality risk has directly led to the investigation of engineered cellular therapies in rheumatology [9, 12, 13].

Chimeric antigen receptor (CAR) T-cell therapy is a highly advanced cellular immunotherapy that was initially developed and approved for the curative treatment of relapsed or refractory B-cell acute lymphoblastic leukemia and aggressive non-Hodgkin lymphomas [14, 15]. The therapy utilizes autologous T lymphocytes that are genetically modified ex vivo using either lentiviral or retroviral vectors to permanently express a synthetic transmembrane receptor [16, 17]. This synthetic receptor allows the engineered T cells to recognize and bind specific target antigens independently of major histocompatibility complex (MHC) presentation pathways [18, 19]. Because B lymphocytes act simultaneously as autoantibody producers and as primary antigen-presenting cells that continuously stimulate T cells in ARDs, researchers are actively investigating the use of CAR-T cells to precisely deplete autoreactive B-cell populations in systemic autoimmune conditions [20, 21, 22]. This comprehensive review critically analyzes molecular construct designs, complex pathophysiological mechanisms, detailed clinical trial outcomes, and specific toxicity profiles associated with CAR-T cell therapy in modern rheumatology.

**Mechanistic Foundations of CAR-T in Autoimmunity**

The biological function and targeted cytolytic capacity of CAR-T cells depend strictly on their synthetic molecular architecture [23, 24]. A standard, first-generation CAR construct consists of an extracellular single-chain variable fragment (scFv), which is typically derived from a murine or humanized monoclonal antibody and is responsible for specific antigen recognition [16, 25]. This extracellular domain is linked via a structural hinge region to a robust transmembrane domain, which is subsequently attached to an intracellular CD3-zeta signaling domain necessary for the initiation of the primary T-cell activation cascade [16, 25]. Second-generation CAR constructs obligatorily include additional intracellular costimulatory endodomains, most typically derived from the CD28 or 4-1BB (CD137) surface receptors [13, 24]. The inclusion of these costimulatory domains is physiologically required to enhance cellular proliferation, alter metabolic profiles toward oxidative phosphorylation or glycolysis, and support prolonged in vivo cellular persistence [13, 24].

In the targeted treatment of B-cell mediated ARDs, the CD19 glycoprotein is the most frequently used target antigen [26, 27]. CD19 is a transmembrane glycoprotein expressed continuously throughout B-cell development, from the early pro-B cell stage in the bone marrow to mature, circulating memory B cells [25, 28]. A critical biological limitation of targeting the CD19 antigen exclusively is that long-lived plasma cells, which reside within specific protective niches in the bone marrow and continuously secrete autoantibodies, often exhibit significant downregulation or the complete absence of CD19 surface expression [29]. To effectively address this immunological evasion mechanism, researchers have engineered compound CAR-T cells designed to simultaneously target both CD19 and B-cell maturation antigen (BCMA) [30, 31]. BCMA is highly and specifically expressed on the surface of mature plasma cells [29, 30]. This dual-targeting methodology permits comprehensive depletion of both the precursor memory B-cell pool and the terminally differentiated, autoantibody-producing plasma cell compartment [29, 30].

CAR-T cells show unique, highly dynamic pharmacokinetic properties compared with conventional monoclonal antibodies [25, 32]. Monoclonal antibodies, such as the anti-CD20 agent rituximab, demonstrate limited tissue penetration due to their large molecular size and do not effectively deplete tissue-resident memory B cells located deep within secondary lymphoid organs or inflamed solid tissues [6, 28]. Conversely, CAR-T cells operate as living drugs capable of active migration across the vascular endothelium and subsequent diapedesis into solid tissues [25, 32]. Histological data and tissue biopsies confirm that CD19-directed CAR-T cells induce deep tissue depletion of B cells and actively dismantle ectopic tertiary lymphoid structures that are frequently present in chronic autoimmune lesions [25, 28].

Concurrent research is also focused on the development and optimization of regulatory CAR-T cells (CAR-Tregs) designed specifically to restore systemic immune homeostasis [18, 33]. In rigorously controlled preclinical murine models of SLE, CAR-Tregs engineered to target the CD19 antigen migrated directly to secondary lymphoid organs [18, 33]. Upon encountering the specific CD19 antigen on target cells, these CAR-Tregs secreted high local concentrations of suppressive cytokines, primarily including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-beta) [24, 33]. The localized secretion of these cytokines effectively inhibited the activation and proliferation of autoreactive B cells without causing the systemic B-cell aplasia that is universally associated with cytotoxic CD8+ CAR-T cell interventions [24, 33]. Modulating the specific costimulatory domains of CAR-Tregs is critical for maintaining the lineage stability of FoxP3 expression and preventing their pathogenic conversion into an effector T-cell phenotype in highly inflammatory environments [24, 34].

**Safety, Toxicities, and Clinical Management**

The systemic administration of CAR-T cells is inextricably associated with a specific, highly complex toxicity profile that requires specialized hematological monitoring and intensive care infrastructure [35, 36]. Cytokine release syndrome (CRS) is the most common acute adverse event recorded following CAR-T cell infusion [9, 35]. The pathophysiology of CRS is initiated by the rapid, synchronous activation of CAR-T cells upon target antigen engagement, leading to the systemic release of pro-inflammatory cytokines such as IL-6, IL-1, and interferon-gamma [35, 37]. These primary cytokines subsequently activate host bystander macrophages, which further amplify the systemic inflammatory cascade [35, 37]. Clinical manifestations of severe CRS routinely include high-grade fever, systemic hypotension, tachycardia, and potentially life-threatening tissue hypoxia [35, 38]. Observational data derived from early autoimmune clinical trials consistently indicate that CRS in ARD patients is typically classified as low-grade, specifically Grade 1 or Grade 2, according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria [27, 39]. The significantly lower severity of CRS observed in autoimmune patients compared

to oncology patients is directly attributed to a much lower baseline total body burden of target CD19-positive cells [9, 40]. The standard pharmacological treatment for symptomatic CRS is the prompt intravenous administration of tocilizumab, an IL-6 receptor antagonist [35, 37]. Tocilizumab effectively reduces systemic inflammation and reverses hypotension without preventing the necessary in vivo expansion or cytolytic efficacy of the infused CAR-T cells [35, 37].

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a severe neurological complication characterized by widespread endothelial activation and increased permeability of the blood-brain barrier [35, 37]. The structural breakdown of the blood-brain barrier allows high concentrations of circulating cytokines and activated T lymphocytes to physically enter the central nervous system parenchyma [9, 35]. Because the large monoclonal antibody tocilizumab does not efficiently penetrate the central nervous system, the clinical management of ICANS strictly requires the administration of highly penetrant systemic corticosteroids, most frequently dexamethasone [35, 37]. Immune effector cell-associated haematotoxicity frequently manifests as delayed, biphasic, or highly prolonged cytopenias, primarily including severe neutropenia and thrombocytopenia [36]. This hematological condition results from the combined toxicity of lymphodepleting conditioning regimens, which typically use specific doses of fludarabine and cyclophosphamide, and the persistent cytokine-mediated suppression of early hematopoietic progenitor cells in the bone marrow [36]. Consequently, these severe and prolonged cytopenias drastically increase the risk of fatal opportunistic infections, representing a major driver of nonrelapse mortality following CAR-T cell therapy [41]. Retrospective clinical analyses also indicate a statistically increased incidence of cardiovascular events, including dangerous arrhythmias and transient left ventricular dysfunction, occurring during the peak of systemic inflammation following CAR-T therapy [42]. Rigorous pre-infusion cardiological screening and continuous hemodynamic monitoring are absolutely required due to the elevated baseline cardiovascular risk inherently present in patients with chronic ARDs [21, 42].

Local immune effector cell-associated toxicity syndrome (LICATS) has been specifically identified and documented in rheumatological patients receiving CAR-T therapy [43]. The clinical presentation of LICATS is characterized by acute inflammatory flares strictly localized to pre-existing target tissues, such as the synovial membrane in patients with RA or the dermis in patients with SSc [32, 43]. These highly localized flares correlate directly with the active tissue infiltration, localized expansion, and cytotoxic activity of CAR-T cells [32, 43]. Importantly, LICATS occurs temporally just prior to the deep depletion of tissue-resident B cells and the subsequent induction of clinical disease remission [32, 43].

**Systemic Lupus Erythematosus (SLE)**

SLE is a highly complex systemic autoimmune disease fundamentally characterized by a complete loss of B-cell tolerance and the continuous production of multiple pathogenic autoantibodies, including anti-double-stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm) antibodies [3, 4]. The systemic circulation and subsequent tissue deposition of these autoantibody-antigen immune complexes lead to local complement activation and severe end-organ damage, which frequently presents clinically as life-threatening lupus nephritis [6, 7]. Preclinical murine models rigorously demonstrated the high efficacy of CD19-targeted CAR-T cells in treating lupus-like pathology [44, 45]. In genetically prone NZB/W F1 murine models, the administration of CD19-directed CAR-T cell therapy significantly reduced proteinuria, structurally improved renal histopathology, and statistically increased overall animal survival [33, 45]. Furthermore, detailed transcriptomic analyses indicated that CD19 CAR-T cell therapy durably suppresses the type I interferon signature, which is a critical molecular pathway heavily involved in the sustained pathogenesis of SLE [28].

The groundbreaking phase 1/2 CASTLE basket trial systematically evaluated the safety and clinical efficacy of CD19-targeted CAR-T cells in patients with refractory SLE [27]. Patients presenting with severe, multi-organ SLE who had definitively not responded to multiple lines of standard DMARDs received a carefully calibrated single infusion of autologous CD19-directed CAR-T cells following standard lymphodepletion [26, 27]. The clinical evaluations demonstrated a rapid and profound reduction in systemic disease activity, the absolute normalization of previously depleted C3 and C4 complement levels, and the complete serological clearance of anti-dsDNA autoantibodies from the peripheral blood [6, 26].

The remarkable clinical response observed in these initial trials strictly met the established criteria for drug-free remission, allowing for the complete and safe discontinuation of all prior immunosuppressive medications [26, 39]. Long-term follow-up data indicated that upon the physiological repopulation of the B-cell compartment months later, the newly generated B cells consistently exhibited a naive phenotype. Concurrently, the pathogenic, autoreactive memory B-cell clones remained completely undetectable via high-

sensitivity flow cytometry [39]. In specific patients presenting with SLE and concomitant severe antiphospholipid syndrome (APS), CAR-T cell therapy led to sustained, complete disappearance of antiphospholipid antibodies [46, 47]. This critical observation suggests that CD19 CAR-T cell therapy effectively and permanently depletes the specific autoreactive B-cell subpopulations responsible for producing highly thrombogenic autoantibodies [46, 47]. To preemptively address the theoretical potential for disease relapse originating from CD19-negative plasma cells, clinical trials evaluating dual-targeted BCMA-CD19 compound CAR T cells for SLE have been officially initiated [30, 31].

**Rheumatoid Arthritis (RA)**

RA is a chronic, highly destructive inflammatory joint disease, characterized by profound synovial hyperplasia, dense infiltration of diverse immune cells, and progressive, irreversible destruction of articular cartilage and subchondral bone [22, 48].

The hyperplastic synovial pannus constitutes an exceptionally complex, hypoxic microenvironment containing aggressive fibroblast-like synoviocytes, activated macrophages, and interacting T and B lymphocytes [48, 49]. Because broad B-cell depletion utilizing the monoclonal antibody rituximab produces highly heterogeneous and often inadequate clinical responses in RA, the use of standard CD19 CAR-T cells is severely limited by poor synovial tissue penetrance and localized microenvironmental immunosuppression [48, 49]. To mechanistically address these severe limitations, researchers are actively developing fourth-generation CAR-T therapies, frequently referred to in the literature as TRUCKs (T cells redirected for universal cytokine-mediated killing) [17, 49]. TRUCKs are genetically engineered to conditionally express transgenic pro-inflammatory or regulatory cytokines that actively modulate the fibrotic synovial stroma and enhance local immune regulation within the joint [17, 49].

Sophisticated in vitro mechanistic studies demonstrate the high efficacy of universal chimeric antigen receptor T cells in recognizing and eliminating autoreactive B cells directly isolated from RA patients [50, 51]. These universal CAR platforms utilize proprietary soluble adapter molecules to target multiple, distinct cell surface antigens, thereby significantly reducing the probability of cellular antigen escape [5, 51]. Experimental models also rigorously evaluate engineered CD8+ T cells expressing an HLA-DR1 CAR that is specifically designed to target and eliminate pathogenic autoimmune CD4+ T cells [52, 53]. This highly precise, antigen-specific targeting aims to definitively inhibit the upstream autoimmune response without inducing the severe risks associated with broad, systemic immunosuppression [52, 53].

Translational research is rapidly progressing toward the in vivo generation of CAR-T cells to entirely avoid the logistical and financial burdens of ex vivo cellular manufacturing [54, 55]. These experimental methods utilize highly specialized T-cell-targeted fusogenic nanovesicles or engineered lipid nanoparticles (LNPs) to deliver CAR-encoding mRNA directly into circulating host T lymphocytes [54, 55]. This revolutionary approach has the distinct potential to eliminate the clinical need for patient leukapheresis and highly toxic lymphodepleting chemotherapy [54, 56]. Historically, clinical observations of CAR-T efficacy in human RA were derived primarily from detailed case reports of patients treated for concomitant hematological malignancies [57, 58]. However, recent breakthrough studies utilizing fourth-generation CAR-T platforms have now demonstrated direct tolerability and clinical efficacy specifically in patients with treatment-resistant RA [49]. Complete, drug-free remission of RA symptoms was definitively documented in a patient who received tandem CD20-CD19-directed CAR-T cell therapy indicated for a diffuse large B-cell lymphoma [57, 59]. Furthermore, profound autoantibody seroconversion and significant clinical improvement were rigorously observed in an RA patient suffering from coexisting myasthenia gravis following the successful administration of autologous CD19-CAR T cells [58, 60].

**Systemic Sclerosis (SSc)**

SSc is a highly lethal connective tissue disease defined pathophysiologically by widespread microvascular dysfunction, systemic autoimmunity, and massive extracellular matrix deposition resulting in severe fibrosis of the skin and internal organs [61, 62]. Pathogenic B cells contribute heavily to SSc pathogenesis by continuously secreting specific autoantibodies, such as anti-topoisomerase I (anti-Scl70), and by producing high levels of pro-fibrotic cytokines, including TGF-beta and IL-6 [9, 25]. These secreted cytokines directly and persistently stimulate local dermal and pulmonary fibroblasts to synthesize excessive, pathological amounts of collagen [61, 63]. Rigorous preclinical studies utilizing a validated murine model of SSc demonstrated that deep B-cell depletion achieved via CD19-targeted CAR-T cells significantly reduced both dermal and pulmonary fibrosis [63]. These promising in vivo results are highly consistent with recent

clinical observations in human patients, where CAR-T cell therapy reversed dermal thickening and stabilized pulmonary function [62].

In nascent clinical applications, systemic administration of CD19-targeted CAR-T cells to patients with severe, rapidly progressive diffuse SSc resulted in highly measurable and significant clinical improvements [9, 61]. Detailed clinical case reports and series reported statistically significant, rapid reductions in the Modified Rodnan Skin Score (MRSS), which objectively indicates decreased skin thickness and improved dermal elasticity [61, 62]. The application of CAR-T cell therapy also contributed significantly to the structural stabilization of internal organ disease, particularly regarding life-threatening interstitial lung disease [61, 62]. Serial pulmonary function tests consistently showed the stabilization of forced vital capacity (FVC) in the treated patient cohorts [61, 62]. Complex pharmacodynamic studies emphasize that the initial physical penetration of CAR-T cells into dense fibrotic tissues transiently induces localized inflammation (LICATS) before long-term clinical improvements in skin elasticity are observed [32, 43]. The careful clinical management of this localized toxicity is absolutely required during the acute phase of in vivo cellular expansion [32, 43].

**Idiopathic Inflammatory Myopathies (IIM)**

The diverse IIM spectrum clinically includes polymyositis, dermatomyositis (DM), and antisynthetase syndrome (ASS), all of which present with debilitating proximal muscle weakness and an exceptionally high incidence of rapidly progressive interstitial lung disease [64, 65]. The complex pathophysiology involves severe complement-mediated microangiopathy, direct cellular infiltration into muscle tissue, and the continuous production of highly specific myositis-associated autoantibodies, such as anti-Jo-1 [29, 66]. Clinical evaluations indicate that CD19-targeted CAR-T cells are highly effective in treating refractory myositis and ASS-associated interstitial lung disease [64, 67].

CD19 CAR-T cell therapy has been successfully utilized as a critical salvage treatment in severely ill ASS patients who had previously failed multiple lines of therapy with conventional anti-CD20 monoclonal antibodies [64, 68]. Within the specialized field of pediatric rheumatology, autologous CD19-targeted CAR-T cells were successfully administered to a pediatric patient diagnosed with highly refractory juvenile dermatomyositis [15, 65]. This advanced cellular treatment resulted in the rapid normalization of elevated muscle enzymes, significant improvement in objective muscle strength, and the safe, complete discontinuation of all systemic corticosteroids [65].

The established pathological role of terminal plasma cells in IIM pathology heavily contributes to the high risk of disease relapse observed following isolated CD19-directed therapy [29, 69]. A detailed clinical report described a specific patient with relapsing IIM who experienced a severe recurrence of disease activity shortly after an initially successful response to CD19 CAR-T cells [69]. This patient subsequently achieved deep clinical remission following a second infusion utilizing BCMA-directed CAR-T cells [67, 69]. This critical case indicates that targeting the BCMA antigen is essential to completely deplete the plasma cell lineage and maintain durable remission in specific, highly refractory IIM subtypes [29, 69].

**Adult-Onset Still's Disease (AOSD)**

AOSD is a severe, systemic autoinflammatory disorder clinically characterized by daily spiking fevers, an evanescent salmon-colored rash, inflammatory polyarthritis, and extreme hyperferritinemia [70, 71]. The pathophysiology of AOSD differs markedly from that of classical autoantibody-mediated ARDs and is driven exclusively by massive dysregulation and hyperactivation of the innate immune system [70, 71]. The uncontrolled hyperactivation of macrophages and neutrophils directly leads to excessive systemic production of highly inflammatory cytokines, primarily IL-1, IL-6, and IL-18 [70, 72]. Conventional, evidence-based biological therapies for AOSD strictly involve the continuous use of specific IL-1 and IL-6 receptor antagonists [70, 71].

Highly refractory cases of AOSD carry an extreme risk of rapidly progressing to macrophage activation syndrome (MAS), a fulminant condition characterized by profound bone marrow hemophagocytosis, severe coagulopathy, and rapid organ failure [70, 73]. Because CD19 and BCMA are exclusive markers of the B-cell lineage, standard, commercially available CAR-T therapies targeting these specific antigens are completely inapplicable to the targeted treatment of AOSD and MAS [71, 72].

Advanced preclinical research is currently investigating alternative cellular therapies that specifically target the innate immune system based on the detailed transcriptomic profiling of MAS [73, 74]. Experimental therapeutic approaches include the bioengineering of Chimeric Antigen Receptor Macrophages (CAR-M) and

highly specialized CAR-Tregs, which are genetically programmed to bind strictly to activated myeloid cells [24, 75]. Upon target cellular engagement, these engineered cells secrete high local concentrations of suppressive cytokines, such as IL-10, to rapidly and effectively inhibit the inflammatory cytokine cascade [24]. These theoretical, highly advanced applications currently remain sequestered in the preclinical, in vitro stage of scientific development [24, 75].

**Current Barriers and Future Perspectives**

The widespread clinical application of CAR-T cell therapy in routine rheumatology is currently limited by severe logistical challenges, astronomical financial costs, and significant biological toxicities [76, 77]. The standard autologous manufacturing process strictly requires patient leukapheresis, complex ex vivo viral transduction, and prolonged cellular expansion within certified Good Manufacturing Practice (GMP) facilities [76, 77]. This rigid process is inextricably associated with exceptionally high manufacturing costs and severe production delays that negatively impact patients experiencing active, life-threatening disease flares [76, 77].

The mandatory administration of pre-conditioning lymphodepleting chemotherapy, typically utilizing specific weight-based doses of fludarabine and cyclophosphamide, causes profound, prolonged bone marrow suppression [36, 76]. This induced lymphodepletion drastically increases the clinical risk of opportunistic bacterial, viral, and fungal infections in patients with severe pre-existing immunosuppression [36, 41]. The rapid scientific advancement of novel CAR technologies is absolutely required to systematically address these major clinical barriers [55, 75].

The ongoing development of allogeneic, off-the-shelf CAR-T cells critically involves the use of CRISPR/Cas9 gene-editing technology to permanently delete the endogenous T-cell receptor (TCR) to prevent lethal graft-versus-host disease (GVHD) [55, 75]. Additionally, prominent researchers are rigorously investigating in vivo cellular programming using specifically targeted lipid nanoparticles (LNPs) or fusogenic nanovesicles [54, 75]. The successful clinical application of in vivo programming would eliminate the logistical need for ex vivo cellular manufacturing and highly toxic pre-conditioning lymphodepletion [54, 55].

**Conclusions**

The clinical application of CAR-T cell therapy radically changes the established therapeutic approach to treating severe, refractory autoimmune rheumatic diseases [9, 15]. Objective clinical data demonstrate that the intravenous administration of CD19 and BCMA-targeted CAR-T cells successfully induces deep B-cell depletion and sustained, drug-free remission in specific patients with treatment-refractory SLE, SSc, and IIM [26, 61]. The extensive evaluation of cellular therapies clearly indicates a major paradigm shift from chronically managing clinical symptoms with standard DMARDs to achieving definitive, sustained immune reconstitution [9, 15].

The ongoing development of universal CAR adapters, specific CAR-Tregs, and in vivo delivery platforms aims to address the biological limitations of conventional CAR-T cells in treating compartmentalized diseases such as RA and innate autoinflammatory disorders [49, 54]. The long-term optimization of CAR-T cell therapy strictly requires the implementation of standardized clinical protocols for the management of CRS and hematotoxicity, as well as necessary modifications to scale the manufacturing process [35, 36]. Future, large-scale randomized clinical trials will definitively determine the long-term safety profile and the exact placement of CAR-T cell therapy within established rheumatological treatment algorithms [9, 15].

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All authors have read and agreed to the published version of the manuscript.
**Conflict of interest**: No conflicts of interest to declare.

## REFERENCES


1. Lyu, X., Gupta, L., Tholouli, E., & Chinoy, H. (2023). Chimeric antigen receptor T cell therapy: A new emerging landscape in autoimmune rheumatic diseases. *Rheumatology, 63*(5), 1206–1216. https://doi.org/10.1093/rheumatology/kead616
2. Li, Y., & Chen, Z. (2022). Cell-based therapies for rheumatoid arthritis: Opportunities and challenges. *Therapeutic Advances in Musculoskeletal Disease, 14*. https://doi.org/10.1177/1759720X221100294
3. Li, Y. R., Lyu, Z., Chen, Y., Fang, Y., & Yang, L. (2024). Frontiers in CAR-T cell therapy for autoimmune diseases. *Trends in Pharmacological Sciences, 45*(9), 839–857. https://doi.org/10.1016/j.tips.2024.07.005
4. Zhou, J., Lei, B., Shi, F., Luo, X., Wu, K., Xu, Y., Zhang, Y., Liu, R., Wang, H., Zhou, J., & He, X. (2024). CAR T-cell therapy for systemic lupus erythematosus: Current status and future perspectives. *Frontiers in Immunology, 15*, Article 1476859. https://doi.org/10.3389/fimmu.2024.1476859
5. Liu, J., Zhao, Y., & Zhao, H. (2024). Chimeric antigen receptor T-cell therapy in autoimmune diseases. *Frontiers in Immunology, 15*. https://doi.org/10.3389/fimmu.2024.1492552
6. Taubmann, J., Müller, F., Yalcin Mutlu, M., Völkl, S., Aigner, M., Bozec, A., Mackensen, A., Grieshaber-Bouyer, R., & Schett, G. (2024). CD19 chimeric antigen receptor T cell treatment: Unraveling the role of B cells in systemic lupus erythematosus. *Arthritis & Rheumatology, 76*(4), 497–504. https://doi.org/10.1002/art.42784
7. Saegusa, K., Tsuchida, Y., Komai, T., Tsuchiya, H., & Fujio, K. (2025). Advances in targeted therapy for systemic lupus erythematosus: Current treatments and novel approaches. *International Journal of Molecular Sciences, 26*(3), Article 929. https://doi.org/10.3390/ijms26030929
8. Nie, W., Yang, X., Ma, M., Xu, X., & Hou, J. (2025). Chimeric antigen receptor T cell therapy for autoimmune diseases. *Current Opinion in Immunology, 95*, 102596. https://doi.org/10.1016/j.coi.2025.102596
9. Schett, G., Müller, F., Taubmann, J., Mackensen, A., Wang, W., Furie, R., Gold, R., Haghikia, A., Merkel, P., Caricchio, R., D'Agostino, M., Locatelli, F., June, C., & Mougiakakos, D. (2024). Advancements and challenges in CAR T cell therapy in autoimmune diseases. *Nature Reviews Rheumatology, 20*(9), 531–544. https://doi.org/10.1038/s41584-024-01139-z
10. Alexander, T., & Greco, R. (2022). Hematopoietic stem cell transplantation and cellular therapies for autoimmune diseases: Overview and future considerations from the Autoimmune Diseases Working Party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplantation, 57*(7), 1055–1062. https://doi.org/10.1038/s41409-022-01702-w
11. Rangel-Peláez, C., Martínez-Gutiérrez, L., Tristán-Manzano, M., Callejas, J., Ortego-Centeno, N., Martín, F., & Martín, J. (2024). CD19 CAR-T cell therapy: A new dawn for autoimmune rheumatic diseases? *Frontiers in Immunology, 15*. https://doi.org/10.3389/fimmu.2024.1502712
12. Anyfanti, P., Evangelidis, P., Kotsiou, N., Papakonstantinou, A., Eftychidis, I., Sakellari, I., Dimitroulas, T., & Gavriilaki, E. (2025). Chimeric antigen receptor T cell immunotherapy for autoimmune rheumatic disorders: Where are we now? *Cells, 14*. https://doi.org/10.3390/cells14161242
13. Wu, D., Xu-Monette, Z., Zhou, J., Yang, K., Wang, X., Fan, Y., & Young, K. (2025). CAR T-cell therapy in autoimmune diseases: A promising frontier on the horizon. *Frontiers in Immunology, 16*. https://doi.org/10.3389/fimmu.2025.1613878
14. Kuipers, M. T., & Kersten, M. J. (2025). CD19-directed chimeric antigen receptor T-cell therapy: What can we learn from the haematologist? *Lupus Science & Medicine, 12*(1), Article e001157. https://doi.org/10.1136/lupus-2024-001157
15. Schett, G., Mackensen, A., & Mougiakakos, D. (2023). CAR T-cell therapy in autoimmune diseases. *The Lancet*. https://doi.org/10.1016/S0140-6736(23)01126-1
16. Alnefaie, A., Albogami, S., Asiri, Y., Ahmad, T., Alotaibi, S. S., Al-Sanea, M. M., & Althobaiti, H. (2022). Chimeric antigen receptor T-cells: An overview of concepts, applications, limitations, and proposed solutions. *Frontiers in Bioengineering and Biotechnology, 10*, Article 797440. https://doi.org/10.3389/fbioe.2022.797440
17. Patel, K. K., Tariveranmoshabad, M., Kadu, S., Shobaki, N., & June, C. (2025). From concept to cure: The evolution of CAR-T cell therapy. *Molecular Therapy, 33*(5), 2123–2140. https://doi.org/10.1016/j.ymthe.2025.03.005
18. Doglio, M., Alexander, T., Del Papa, N., Snowden, J., & Greco, R. (2022). New insights in systemic lupus erythematosus: From regulatory T cells to CAR-T-cell strategies. *The Journal of Allergy and Clinical Immunology, 150*(5), 1019–1021. https://doi.org/10.1016/j.jaci.2022.08.003
19. Kalliolias, G., Basdra, E., & Papavassiliou, A. (2025). Chimeric antigen receptor (CAR) therapies for precise eradication of pathogenic cells in autoimmunity. *Arthritis Research & Therapy, 28*. https://doi.org/10.1186/s13075-025-03711-8

20. Chasov, V., Zmievskaya, E., Ganeeva, I., Gilyazova, E., Davletshin, D., Khaliulin, M., Kabwe, E., Davidyuk, Y. N., Valiullina, A., Rizvanov, A., & Bulatov, E. (2024). Immunotherapy strategy for systemic autoimmune diseases: Betting on CAR-T cells and antibodies. *Antibodies, 13*(1), Article 10. https://doi.org/10.3390/antib13010010
21. Franco-Fuquen, P., Figueroa-Aguirre, J., Martínez, D., Moreno-Cortes, E., Garcia-Robledo, J., Vargas-Cely, F., Castro-Martínez, D., Almaini, M., & Castro, J. (2024). Cellular therapies in rheumatic and musculoskeletal diseases. *Journal of Translational Autoimmunity, 10*, Article 100264. https://doi.org/10.1016/j.jtauto.2024.100264
22. Freeley, M. (2025). CAR T cell therapy for rheumatoid arthritis. *Clinical Reviews in Allergy & Immunology, 68*. https://doi.org/10.1007/s12016-025-09113-7
23. Ellebrecht, C., Bhoj, V., Nace, A., Choi, E., Mao, X., Cho, M., Di Zenzo, G., Lanzavecchia, A., Seykora, J., Cotsarelis, G., Milone, M., & Payne, A. (2016). Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. *Science, 353*(6295), 179–184. https://doi.org/10.1126/science.aaf6756
24. Boroughs, A., Larson, R., Choi, B., Bouffard, A., Riley, L., Schiferle, E., Kulkarni, A., Cetrulo, C., Ting, D., Blazar, B., Demehri, S., & Maus, M. (2019). Chimeric antigen receptor costimulation domains modulate human regulatory T cell function. *JCI Insight, 5*(8). https://doi.org/10.1172/jci.insight.126194
25. Tur, C., Eckstein, M., Velden, J., Rauber, S., Bergmann, C., Auth, J., Bucci, L., Corte, G., Hagen, M., Wirsching, A., Grieshaber-Bouyer, R., Reis, P., Kittan, N., Wacker, J., Rius Rigau, A., Ramming, A., D'Agostino, M. A., Hartmann, A., . . . Raimondo, M. G. (2025). CD19-CAR T-cell therapy induces deep tissue depletion of B cells. *Annals of the Rheumatic Diseases, 84*(1), 106–114. https://doi.org/10.1136/ard-2024-226142
26. Mougiakakos, D., Krönke, G., Völkl, S., Kretschmann, S., Aigner, M., Kharboutli, S., Böltz, S., Manger, B., Mackensen, A., & Schett, G. (2021). CD19-targeted CAR T cells in refractory systemic lupus erythematosus. *The New England Journal of Medicine, 385*(6), 567–569. https://doi.org/10.1056/NEJMc2107725
27. Müller, F., Hagen, M., Wirsching, A., et al. (2026). CD19 CAR-T cells for treatment-refractory autoimmune diseases: The phase 1/2 CASTLE basket trial. *Nature Medicine, 32*, 1142–1150. https://doi.org/10.1038/s41591-025-04185-6
28. Wilhelm, A., Chambers, D., Müller, F., Bozec, A., Grieshaber-Bouyer, R., Winkler, T., Mougiakakos, D., Mackensen, A., Schett, G., & Krönke, G. (2024). Selective CAR T cell–mediated B cell depletion suppresses IFN signature in SLE. *JCI Insight, 9*(12). https://doi.org/10.1172/jci.insight.179433
29. Groener, M., & Paik, J. J. (2025). Emerging B and plasma cell-targeting immune therapies in idiopathic inflammatory myopathies. *Frontiers in Immunology, 16*, Article 1581323. https://doi.org/10.3389/fimmu.2025.1581323
30. Wang, W., He, S., Zhang, W., Zhang, H., DeStefano, V. M., Wada, M., Pinz, K., Deener, G., Shah, D., Hagag, N., Wang, M., Hong, M., Zeng, R., Lan, T., Ma, Y., Li, F., Liang, Y., Guo, Z., Zou, C., . . . Yuan, Y. (2024). BCMA-CD19 compound CAR T cells for systemic lupus erythematosus: A phase 1 open-label clinical trial. *Annals of the Rheumatic Diseases, 83*(10), 1304–1314. https://doi.org/10.1136/ard-2024-225785
31. Dao, L., Vũ, T., Nguyen, Q., Hoang, V., & Nguyen, T. (2024). Current cell therapies for systemic lupus erythematosus. *Stem Cells Translational Medicine, 13*(9), 859–872. https://doi.org/10.1093/stcltm/szae044
32. Dingfelder, J., Taubmann, J., Von Heydebrand, F., Aigner, M., Bergmann, C., Knitza, J., Park, S., Cheng, J., Van Blarcom, T., Schett, G., Mackensen, A., & Lutzny-Geier, G. (2025). Exploring CAR T-cell dynamics: Balancing potent cytotoxicity and controlled inflammation in CAR T-cells derived from systemic sclerosis and myositis patients. *International Journal of Molecular Sciences, 26*(2), Article 467. https://doi.org/10.3390/ijms26020467
33. Doglio, M., Ugolini, A., Bercher-Brayer, C., Camisa, B., Toma, C., Norata, R., Del Rosso, S., Greco, R., Ciceri, F., Sanvito, F., Casucci, M., Manfredi, A. A., & Bonini, C. (2024). Regulatory T cells expressing CD19-targeted chimeric antigen receptor restore homeostasis in systemic lupus erythematosus. *Nature Communications, 15*(1), Article 2542. https://doi.org/10.1038/s41467-024-46448-9
34. Legato, L., Bisio, M., Fasano, F., Benevolo Savelli, C., Secreto, C., Dellacasa, C. M., Botto, B., Busca, A., Cerrano, M., Freilone, R., & Novo, M. (2025). Mechanisms of resistance to CAR T-cells and how to overcome them. *Methods and Protocols, 8*(5), 108. https://doi.org/10.3390/mps8050108
35. Brudno, J. N., & Kochenderfer, J. N. (2024). Current understanding and management of CAR T cell-associated toxicities. *Nature Reviews Clinical Oncology, 21*(7), 501–521. https://doi.org/10.1038/s41571-024-00903-0
36. Rejeski, K., Jain, M. D., Shah, N. N., Perales, M. A., & Subklewe, M. (2024). Immune effector cell-associated haematotoxicity after CAR T-cell therapy: From mechanism to management. *The Lancet Haematology, 11*(6), e459–e470. https://doi.org/10.1016/S2352-3026(24)00077-2
37. Schubert, M. L., Schmitt, M., Wang, L., Ramos, C. A., Jordan, K., Müller-Tidow, C., & Dreger, P. (2021). Side-effect management of chimeric antigen receptor (CAR) T-cell therapy. *Annals of Oncology, 32*(1), 34–48. https://doi.org/10.1016/j.annonc.2020.10.478
38. Gómez-Puerta, J., Monegal, A., Ponce, A., Peris, P., Martínez-Cibrian, N., Sarmiento-Monroy, J., Ortiz-Maldonado, V., Triguero, A., De Larrea, C., Delgado, J., García-Herrera, A., Albero-González, R., Bosch-Amate, X., Español-Rego, M., González, A., Sanmartí, R., & Juan, M. (2024). Rheumatologic complications of CAR-T cell therapy: Experience of a single center. *Seminars in Arthritis and Rheumatism, 71*, Article 152610. https://doi.org/10.1016/j.semarthrit.2024.152610

39. Müller, F., Taubmann, J., Bucci, L., Wilhelm, A., Bergmann, C., Völkl, S., Aigner, M., Rothe, T., Minopoulou, I., Tur, C., Knitza, J., Kharboutli, S., Kretschmann, S., Vasova, I., Spoerl, S., Reimann, H., Munoz, L., Gerlach, R. G., Schäfer, S., . . . Schett, G. (2024). CD19 CAR T-cell therapy in autoimmune disease: A case series with follow-up. *The New England Journal of Medicine, 390*(8), 687–700. https://doi.org/10.1056/NEJMoa2308917
40. Kattamuri, L., Lal, B., Vojjala, N., Jain, M., Sharma, K., Jain, S., & Hadidi, S. (2025). Safety and efficacy of CAR-T cell therapy in patients with autoimmune diseases: A systematic review. *Rheumatology International, 45*. https://doi.org/10.1007/s00296-024-05772-5
41. Cordas Dos Santos, D. M., Tix, T., Shouval, R., Gafter-Gvili, A., Alberge, J. B., Cliff, E. R. S., Theurich, S., von Bergwelt-Baildon, M., Ghobrial, I. M., Subklewe, M., Perales, M. A., & Rejeski, K. (2024). A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy. *Nature Medicine, 30*(9), 2667–2678. https://doi.org/10.1038/s41591-024-03084-6
42. Lefebvre, B., Kang, Y., Smith, A. M., Frey, N. V., Carver, J. R., & Scherrer-Crosbie, M. (2020). Cardiovascular effects of CAR T cell therapy: A retrospective study. *JACC: CardioOncology, 2*(2), 193–203. https://doi.org/10.1016/j.jaccao.2020.04.012
43. Hagen, M., Müller, F., Wirsching, A., Kharboutli, S., Spoerl, S., Düsing, C., Krickau, T., Metzler, M., Völkl, S., Aigner, M., Kretschmann, S., Vasova, I., Saake, M., Schliep, S., Kubacki, T., Hunzelmann, N., Bucci, L., Taubmann, J., Bergmann, C., . . . Schett, G. (2023). Local immune effector cell-associated toxicity syndrome in CAR T-cell treated patients with autoimmune disease: An observational study. *The Lancet Rheumatology*. https://doi.org/10.1016/S2665-9913(25)00091-8
44. Jin, X., Xu, Q., Pu, C., Zhu, K., Lu, C., Jiang, Y., Xiao, L., Han, Y., & Lu, L. (2021). Therapeutic efficacy of anti-CD19 CAR-T cells in a mouse model of systemic lupus erythematosus. *Cellular & Molecular Immunology, 18*(8), 1896–1903. https://doi.org/10.1038/s41423-020-0472-1
45. Kansal, R., Richardson, N., Neeli, I., Khawaja, S., Chamberlain, D., Ghani, M., Ghani, Q. U., Balazs, L., Beranova-Giorgianni, S., Giorgianni, F., Kochenderfer, J. N., Marion, T., Albritton, L. M., & Radic, M. (2019). Sustained B cell depletion by CD19-targeted CAR T cells is a highly effective treatment for murine lupus. *Science Translational Medicine, 11*(482), Article eaav1648. https://doi.org/10.1126/scitranslmed.aav1648
46. Friedberg, E., Wohlfarth, P., Schiefer, A., Skrabs, C., Pickl, W., Worel, N., Staber, P., Jäger, U., & Ay, C. (2024). Disappearance of antiphospholipid antibodies after anti-CD19 CAR T-cell therapy of B-cell lymphoma in a patient with systemic lupus erythematosus and antiphospholipid syndrome. *Journal of Thrombosis and Haemostasis*. https://doi.org/10.1016/j.jtha.2024.09.024
47. Meroni, P., Capobianco, E., & Tedesco, F. (2025). Can we cure antiphospholipid syndrome? *Current Opinion in Immunology, 96*, Article 102610. https://doi.org/10.1016/j.coi.2025.102610
48. Blagov, A. V., Pleshko, E. M., Maltseva, O. N., Asoyan, A. Z., Ravani, A. L., & Orekhov, A. N. (2025). CAR-T cell therapy for rheumatoid arthritis: Current status and molecular insights. *Cellular and Molecular Biology, 71*(6), 80–88. https://doi.org/10.14715/cmb/2025.71.6.11
49. Li, Y., Li, S., Zhao, X., Sheng, J., Xue, L., Schett, G., Shi, C., Hu, B., Wang, X., & Chen, Z. (2025). Fourth-generation chimeric antigen receptor T-cell therapy is tolerable and efficacious in treatment-resistant rheumatoid arthritis. *Cell Research, 35*(3), 220–223. https://doi.org/10.1038/s41422-024-01068-2
50. Avouac, J., & Scherlinger, M. (2024). CAR T-cell therapy for rheumatic diseases: What does the future hold? *BioDrugs, 39*, 5–19. https://doi.org/10.1007/s40259-024-00692-z
51. Zhang, B., Wang, Y., Yuan, Y., Sun, J., Liu, L., Huang, D., Hu, J., Wang, M., Li, S., Song, W., Chen, H., Zhou, D., & Zhang, X. (2020). In vitro elimination of autoreactive B cells from rheumatoid arthritis patients by universal chimeric antigen receptor T cells. *Annals of the Rheumatic Diseases, 80*(2), 176–184. https://doi.org/10.1136/annrheumdis-2020-217844
52. Whittington, K., Prislovsky, A., Beaty, J., Albritton, L., Radic, M., & Rosloniec, E. (2022). CD8+ T cells expressing an HLA-DR1 chimeric antigen receptor target autoimmune CD4+ T cells in an antigen-specific manner and inhibit the development of autoimmune arthritis. *The Journal of Immunology, 208*(1), 16–26. https://doi.org/10.4049/jimmunol.2100643
53. Orvain, C., Boulch, M., Bousso, P., Allanore, Y., & Avouac, J. (2021). Is there a place for chimeric antigen receptor–T cells in the treatment of chronic autoimmune rheumatic diseases? *Arthritis & Rheumatology, 73*. https://doi.org/10.1002/art.41812
54. Liang, S., Zhou, S., Zeng, Y., Chen, Y., Sun, Y., Xiao, Z., Zhao, G., Xu, C., & Lai, P. (2026). T-cell-targeted fusogenic nanovesicles generate CAR-T cells in vivo for rheumatoid arthritis therapy. *Biomarker Research, 14*. https://doi.org/10.1186/s40364-026-00905-3
55. Liang, Z., Xie, H., & Wu, D. (2025). Immune mediated inflammatory diseases: Moving from targeted biologic therapy, stem cell therapy to targeted cell therapy. *Frontiers in Immunology, 16*. https://doi.org/10.3389/fimmu.2025.1520063
56. Segovia, M., Landoni, D., Defranchi, Y., Jofré, R., Olivares, C., & Keppeke, G. (2025). A new therapeutic pathway in autoimmune diseases: Chimeric antigen receptor T cells (CAR-T) targeting specific cell subtypes or antigen-specific B lymphocytes—a brief review. *Exploration of Immunology*. https://doi.org/10.37349/ei.2025.1003185

57. Szabo, D., Balogh, A., Gopcsa, L., Giba-Kiss, L., Lakatos, G., Paksi, M., Réti, M., Takács, P., Heteren, P., Zadoyan, G., Holtkamp, S., Overstijns, T., Miltenyi, S., Remenyi, P., & Nagy, G. (2024). Sustained drug-free remission in rheumatoid arthritis associated with diffuse large B-cell lymphoma following tandem CD20-CD19-directed non-cryopreserved CAR-T cell therapy using zamtocabtagene autoleucel. *RMD Open, 10*. https://doi.org/10.1136/rmdopen-2024-004727
58. Haghikia, A., Hegelmaier, T., Wolleschak, D., Böttcher, M., Pappa, V., Motte, J., Borie, D., Gold, R., Feist, E., Schett, G., & Mougiakakos, D. (2024). Clinical efficacy and autoantibody seroconversion with CD19-CAR T cell therapy in a patient with rheumatoid arthritis and coexisting myasthenia gravis. *Annals of the Rheumatic Diseases, 83*, 1597–1598. https://doi.org/10.1136/ard-2024-226017
59. Zulfiqar, F., Shahzad, M., Amin, M., Vyas, A., Sarfraz, Z., Zainab, A., Qasim, H., Kaur, D., Khavandgar, N., Lutfi, F., Hematti, P., Mcguirk, J., & Mushtaq, M. (2024). Outcomes with chimeric antigen receptor T-cell therapy in rheumatological disorders: A systematic review. *Transplant Immunology*, 102137. https://doi.org/10.1016/j.trim.2024.102137
60. Patil, H., Bharadwaj, R., Dutta, N., Subramanian, R., Prasad, S., & Mamadapur, M. (2025). CAR-T cell therapy in rheumatic diseases: A review article. *Clinical Rheumatology*. https://doi.org/10.1007/s10067-025-07451-7
61. Bergmann, C., Müller, F., Distler, J. H. W., Györfi, A. H., Völkl, S., Aigner, M., Kretschmann, S., Reimann, H., Harrer, T., Bayerl, N., Boeltz, S., Wirsching, A., Taubmann, J., Rösler, W., Spriewald, B., Wacker, J., Atzinger, A., Uder, M., Kuwert, T., . . . Schett, G. (2023). Treatment of a patient with severe systemic sclerosis (SSc) using CD19-targeted CAR T cells. *Annals of the Rheumatic Diseases, 82*(8), 1117–1120. https://doi.org/10.1136/ard-2023-223952
62. Auth, J., Müller, F., Völkl, S., Bayerl, N., Distler, J., Tur, C., Raimondo, M., Fakhouri, C., Atzinger, A., Coppers, B., Eckstein, M., Liphardt, A., Bäuerle, T., Tascilar, K., Aigner, M., Kretschmann, S., Wirsching, A., Taubmann, J., Hagen, M., . . . Bergmann, C. (2024). CD19-targeting CAR T-cell therapy in patients with diffuse systemic sclerosis: A case series. *The Lancet Rheumatology*. https://doi.org/10.1016/S2665-9913(24)00282-0
63. Avouac, J., Cauvet, A., Orvain, C., Boulch, M., Tilotta, F., Tu, L., Thuillet, R., Ottaviani, M., Guignabert, C., Bousso, P., & Allanore, Y. (2023). Effects of B cell depletion by CD19-targeted chimeric antigen receptor T cells in a murine model of systemic sclerosis. *Arthritis & Rheumatology, 76*. https://doi.org/10.1002/art.42677
64. Pecher, A. C., Hensen, L., Klein, R., Schairer, R., Lutz, K., Atar, D., Seitz, C., Stanger, A., Schneider, J., Braun, C., Schmidt, M., Horger, M., Bornemann, A., Faul, C., Bethge, W., Henes, J., & Lengerke, C. (2023). CD19-targeting CAR T cells for myositis and interstitial lung disease associated with antisynthetase syndrome. *JAMA, 329*(24), 2154–2162. https://doi.org/10.1001/jama.2023.8753
65. Nicolai, R., Merli, P., Moran Alvarez, P., Bracaglia, C., Del Bufalo, F., Marasco, E., Caiello, I., Prencipe, G., Algeri, M., Cefalo, M. G., Becilli, M., Quintarelli, C., Sinibaldi, M., Hanssens, L., De Benedetti, F., & Locatelli, F. (2024). Autologous CD19-targeting CAR T cells in a patient with refractory juvenile dermatomyositis. *Arthritis & Rheumatology, 76*(10), 1560–1565. https://doi.org/10.1002/art.42933
66. Wischnewski, S., Rausch, H., Ikenaga, C., Leipe, J., Lloyd, T., & Schirmer, L. (2025). Emerging mechanisms and therapeutics in inflammatory muscle diseases. *Trends in Pharmacological Sciences*. https://doi.org/10.1016/j.tips.2025.01.005
67. Aggarwal, A., Almackenzie, M., & Aggarwal, R. (2025). Role of CD19 chimeric antigen receptor T cell therapy in idiopathic inflammatory myopathies. *The Journal of Rheumatology, 52*(6), 532–542. https://doi.org/10.3899/jrheum.2024-1115
68. Taubmann, J., Knitza, J., Müller, F., Völkl, S., Aigner, M., Kleyer, A., Gary, R., Kretschmann, S., Boeltz, S., Atzinger, A., Kuwert, T., Roemer, F., Uder, M., Mackensen, A., & Schett, G. (2023). Rescue therapy of antisynthetase syndrome with CD19-targeted CAR-T cells after failure of several B-cell depleting antibodies. *Rheumatology, 63*, e12–e14. https://doi.org/10.1093/rheumatology/kead330
69. Müller, F., Wirsching, A., Hagen, M., Völkl, S., Tur, C., Raimondo, M. G., Taubmann, J., Bucci, L., Zhang, L., Kretschmann, S., Aigner, M., Eckstein, M., Spörl, S., Kharboutli, S., Böltz, S., Atzinger, A., Munoz, L., Schett, G., Mackensen, A., & Grieshaber-Bouyer, R. (2025). BCMA CAR T cells in a patient with relapsing idiopathic inflammatory myositis after initial and repeat therapy with CD19 CAR T cells. *Nature Medicine, 31*(6), 1793–1797. https://doi.org/10.1038/s41591-025-03718-3
70. Ma, Y., Meng, J., Jia, J., Wang, M., Teng, J., Zhu, D., Yang, C., & Hu, Q. (2021). Current and emerging biological therapy in adult-onset Still's disease. *Rheumatology, 60*, 3986–4000. https://doi.org/10.1093/rheumatology/keab485
71. Tomaras, S., Goetzke, C., Kallinich, T., & Feist, E. (2021). Adult-onset Still's disease: Clinical aspects and therapeutic approach. *Journal of Clinical Medicine, 10*. https://doi.org/10.3390/jcm10040733
72. Feist, E., Mitrovic, S., & Fautrel, B. (2018). Mechanisms, biomarkers and targets for adult-onset Still's disease. *Nature Reviews Rheumatology, 14*, 603–618. https://doi.org/10.1038/s41584-018-0081-x
73. McGonagle, D., Ramanan, A., & Bridgewood, C. (2021). Immune cartography of macrophage activation syndrome in the COVID-19 era. *Nature Reviews Rheumatology, 17*, 145–157. https://doi.org/10.1038/s41584-020-00571-1

74. Liu, Y., Dong, M., Chu, Y., Zhou, L., You, Y., Pang, X., Yang, S., Zhang, L., Chen, L., Zhu, L., Xiao, J., Wang, W., Qin, C., & Tian, D. (2024). Dawn of CAR-T cell therapy in autoimmune diseases. *Chinese Medical Journal, 137*, 1140–1150. https://doi.org/10.1097/CM9.0000000000003111
75. Cheever, A., Kang, C., Neill, K., Weber, K., Nunez-Cruz, S., & Rui, X. (2024). Application of novel CAR technologies to improve treatment of autoimmune disease. *Frontiers in Immunology, 15*. https://doi.org/10.3389/fimmu.2024.1465191
76. Lungova, K., & Putman, M. (2024). Barriers to CAR T-cell therapy in rheumatology. *The Lancet Rheumatology*. https://doi.org/10.1016/S2665-9913(24)00240-6
77. Shargh, M., Mahmoudi, M., Agah, S., Forouzanfar, F., Javanmardi, Z., Fadaee, A., Haghmorad, D., & Esmaeili, S. (2025). CAR T-cell therapy in autoimmune diseases: Opportunities and challenges, with implications for RA. *Tissue & Cell, 98*, Article 103164. https://doi.org/10.1016/j.tice.2025.103164