RESEARCH PAPER

CAR T-Cell Therapy For Refractory Autoimmune Diseases: Rethinking Immune Tolerance Through Cellular Engineering

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Abstract

For decades, clinicians managing refractory autoimmune diseases have operated within a frustrating therapeutic ceiling — escalating immunosuppression that controls rather than cures, and biologics that must be sustained indefinitely at the cost of infection, toxicity, and diminishing returns. Chimeric antigen receptor (CAR) T-cell therapy, developed originally to hunt down malignant B cells in haematological cancers, is now being turned toward this unmet need with results that few in the field anticipated so soon. Early clinical series — small in number but striking in consistency — show that a single infusion of CD19-directed CAR T cells can bring patients with refractory systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and idiopathic inflammatory myopathies (IIM) into drug-free remission. Some have remained off all immunosuppression for more than two years. This is not incremental progress. It is a different kind of intervention entirely — one that appears to work not by suppressing the immune system indefinitely, but by depleting its autoreactive components and allowing something resembling a fresh immunological start.

This review traces the biology behind that possibility, examines what the clinical data actually show across individual disease contexts, considers how the technology is evolving through next-generation engineering, and confronts the real barriers — manufacturing, access, durability, resistance — that stand between early-phase promise and genuine clinical practice. As of mid-2025, 119 registered global trials are underway, the vast majority in Phase I. The science is moving fast; the standards it must meet are appropriately high.

Keywords: CAR T-cell therapy, autoimmune diseases, CD19, BCMA, systemic lupus erythematosus, immunological reset, systemic sclerosis, idiopathic inflammatory myopathy, allogeneic CAR T cells, cytokine release syndrome

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1. Introduction

Autoimmune diseases are among the most immunologically complex conditions in medicine. Across conditions as varied as SLE, rheumatoid arthritis (RA), multiple sclerosis (MS), myasthenia gravis (MG), and SSc, the shared denominator is a failure of immune self-tolerance — the mechanisms that normally prevent lymphocytes from attacking the body's own tissues have broken down. Autoreactive populations persist, proliferate, and cause organ damage. Collectively, these diseases affect somewhere between 5% and 10% of the global population, and for many patients, current treatments manage rather than resolve the underlying problem. A meaningful proportion — perhaps 10–20% across most conditions — fail multiple lines of therapy, including advanced biologics, and continue to accumulate damage with no remaining good options.

It is into this space that CAR T-cell therapy has moved. The concept is not entirely new — T cells have been engineered to recognise defined antigens for over three decades — but clinical success in oncology, particularly in relapsed or refractory B-cell malignancies, gave the field a credibility and urgency it had previously lacked. When the FDA approved tisagenlecleucel for B-cell acute lymphoblastic leukemia in 2017, based on complete remission rates approaching 83% in heavily pre-treated patients, the obvious question followed: if these cells could hunt down malignant B cells in cancer with that kind of precision, what might they do in autoimmune diseases, where pathological B cells and plasma cells are equally central to disease perpetuation? The answer, from the first compassionate-use cases in Erlangen through the most recent Phase 1/2 basket trials, has been more encouraging than many expected. But it would be a mistake to view current results as validation of an established therapy. What we have, as of early 2026, is compelling early-phase evidence across a limited number of patients, several mechanistic hypotheses that remain incompletely tested, a safety profile that looks considerably more favourable than in cancer — but also a set of unresolved questions about durability, manufacturing, patient selection, and access that will determine whether this intervention becomes genuinely transformative or remains niche.

This review attempts to engage honestly with all of that.

2. The Biological Logic: Why CAR T Cells Are a Different Kind of Tool

2.1 What a CAR T Cell Actually Is

A chimeric antigen receptor is a synthetic molecule that engineers antigen specificity into a T cell that would not otherwise have it. The extracellular portion — most commonly a single-chain variable fragment (scFv) derived from a monoclonal antibody — determines what the T cell will recognise. It is connected via a hinge and transmembrane region to one or more intracellular signalling domains that, upon target engagement, activate the T cell to kill, proliferate, and persist.

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The evolution from first-generation to second-generation constructs was critically important. First-generation CARs carried only the CD3ζ signalling chain and produced disappointing in vivo persistence. Adding a single co-stimulatory domain — either CD28, which promotes rapid expansion, or 4-1BB (CD137), which favours longer-lived memory-like populations — dramatically changed what these cells could do in the body. The CD28 and 4-1BB constructs that predominate in currently registered autoimmune trials are direct descendants of architectures refined over years of oncology experience, and the differential kinetics they impart matter considerably for how long disease suppression is maintained after infusion.

Third-generation constructs incorporating two co-stimulatory domains and fourth-generation "armored" designs that secrete cytokines or other payloads upon activation are under investigation but remain earlier in clinical development. The near-term clinical work in autoimmunity is being done predominantly with second-generation, 4-1BB co-stimulated constructs — architectures that balance expansion capacity, persistence, and a manufacturing complexity that is at least somewhat established from oncology experience.

2.2 Why B-Cell Targeting Makes Sense in Autoimmunity

The rationale for targeting B cells in autoimmune diseases is well established — indeed, the clinical use of anti-CD20 rituximab across multiple conditions demonstrated decades ago that depleting this lineage could have meaningful, if incomplete, therapeutic effects. The limitation of rituximab and related antibodies is precisely that incompleteness. Anti-CD20 antibodies do not reach CD20-negative long-lived plasma cells in bone marrow niches, which continue to produce autoantibodies even when peripheral B-cell counts are suppressed. They require repeated dosing. And they never quite clear the inflamed tissue compartments where autoreactive B cells are most actively contributing to pathology.

CAR T cells are different in several respects. CD19 is expressed across essentially the entire B-cell developmental spectrum, from pro-B cells through mature naïve and memory B cells, and CD19-directed CAR T cells can physically traffic into lymphoid and inflamed tissues, performing a depth of B-cell depletion that no antibody achieves. Work from the Erlangen group published in the Annals of the Rheumatic Diseases showed that CD19 CAR T-cell treatment induces depletion not just in blood, but in deep tissue compartments — data that help explain why clinical responses seem more durable than those achieved with conventional B-cell-depleting antibodies.

BCMA (B-cell maturation antigen, TNFRSF17) is the other major target of current interest. Expressed predominantly on long-lived plasma cells and a subset of memory B cells — but not on naïve B cells — BCMA fills the gap that CD19 targeting leaves. The combination of anti-CD19 and anti-BCMA constructs, either co-infused or engineered as bispecific molecules, theoretically eliminates both the memory B-cell reservoir and the terminally differentiated plasma cell niche simultaneously — a more complete eradication of the autoantibody-producing axis than either approach achieves alone.

Beyond these two dominant targets, the field is exploring other directions: CAAR (chimeric autoantibody receptor) T cells, in which the extracellular domain displays the autoantigen itself rather than an antibody, enabling precise selection of the antigen-specific B cells that drive a given disease; CAR-Tregs, which aim to reinforce tolerance rather than eliminate pathogenic cells; and constructs targeting autoreactive T-cell populations, including CD7-positive cells implicated in T-cell-driven autoimmune pathology.

2.3 The Immunological Reset Question

The most scientifically provocative finding from early clinical experience is not the remissions themselves — it is when those remissions occur and how long they last relative to the course of B-cell depletion. In multiple patients reported by the Erlangen group, drug-free remission persisted even after peripheral B-cell counts had recovered — typically within 90 to 150 days of infusion. That observation is hard to explain through simple depletion kinetics alone.

What appears to be happening, at least in part, is a qualitative reconstitution of the immune repertoire. When B cells return after CAR T-cell-mediated depletion, flow cytometric and transcriptomic analyses consistently show enrichment for naïve B-cell populations with a dramatic reduction in autoreactive memory B cells and in autoantibody-secreting plasmablasts. Autoantibody titers — anti-dsDNA, anti-Sm, anti-Jo-1, antinuclear antibodies — normalise and, in many patients, remain suppressed even as B-cell numbers rebound. This pattern resembles what one might imagine as an immune reset: the pathological memory of self-reactivity appears to have been erased or greatly diminished, and the reconstituted compartment does not, at least in the medium term, recapitulate it.

This hypothesis is intellectually compelling but mechanistically incomplete. How exactly does eliminating autoreactive B cells prevent their successor population from redeveloping the same specificities? What role do T follicular helper cells play in this process? Are bone marrow B-cell precursors themselves altered, or does the autoreactive memory simply fail to re-establish itself without the environmental signals that initially drove it? These are genuinely open questions, and their answers will determine both the durability of responses and the scientific understanding of what autoimmune memory actually requires to persist.

3. What the Clinical Evidence Shows

3.1 Systemic Lupus Erythematosus: The Anchor Indication

SLE has become the primary clinical test case for CAR T-cell therapy in autoimmunity, and for understandable reasons. It is a B-cell- and plasma-cell-dependent disease with clear serological biomarkers, validated remission criteria, and a subset of patients who suffer progressive, organ-threatening disease despite years of intensive treatment. It is also a disease in which the stakes of getting the immunology wrong are high — the same immune system dysfunction that drives lupus nephritis and cerebritis also puts patients at severe infectious risk if over-suppressed.

The clinical series began in 2021, when Mougiakakos and colleagues in Erlangen reported the first use of CD19-directed CAR T cells in a patient with refractory SLE in the New England Journal of Medicine — a proof-of-concept observation that the approach was feasible and suggested meaningful clinical benefit. The following year, Mackensen, Müller, Mougiakakos, Krönke, Schett, and colleagues published a more formal compassionate-use series of five patients in Nature Medicine. These patients — four women and one man, median age 22 years, median disease duration four years, and active disease with median SLEDAI scores of 16 — had each failed multiple lines of immunosuppressive therapy. After lymphodepletion with fludarabine and cyclophosphamide and a single infusion of autologous anti-CD19 CAR T cells at 1 × 10^6 cells per kilogram, all five achieved DORIS remission criteria within three months. Median SLEDAI scores fell to 0. More striking was what followed: drug-free remission was maintained over a median follow-up of eight months, including in patients whose peripheral B cells had already recovered — the first human clinical evidence supporting the immunological reset model.

That series was substantially extended in the landmark February 2024 New England Journal of Medicine publication from Müller, Taubmann, and colleagues, which reported outcomes across 15 patients treated at Erlangen — eight with SLE, three with IIM, and four with SSc — at a median follow-up of 15 months, ranging up to 29 months. Every patient with SLE met DORIS remission criteria. Every patient with IIM achieved an ACR-EULAR major clinical response. Every patient with SSc showed a decrease in EUSTAR activity index scores. All 15 patients discontinued immunosuppressive therapy completely. Mean B-cell aplasia lasted 112 ± 47 days. In terms of safety, ten patients experienced Grade 1 CRS, one experienced Grade 2 CRS, one had Grade 1 ICANS, and one was hospitalised for pneumonia. No treatment-related deaths occurred.

These numbers, taken from a case series of 15, cannot be treated as definitive evidence of efficacy at a population level. But the consistency — 15 out of 15 showing disease improvement, 15 out of 15 discontinuing all medication — is not easily dismissed, and has been independently replicated in principle across multiple institutions and patient groups since.

The dual-targeting approach has advanced through Phase 1 in parallel. A trial published in Nature Medicine in 2025 reported outcomes in 15 patients with refractory SLE — 14 women and one man — who received co-infused autologous anti-CD19 and anti-BCMA CAR T cells after standard lymphodepletion. Most patients achieved either DORIS remission or Lupus Low Disease Activity State within 12 weeks. The dual infusion appeared to clear not only circulating B cells but also the CD19-negative, BCMA-positive long-lived plasma cells in bone marrow that a CD19-only approach would leave undisturbed — a mechanistically important observation given that these bone marrow-resident plasma cells are major ongoing autoantibody producers in lupus.

Allogeneic therapy entered the picture through a study published in Cell Research in 2025. Wang and colleagues treated four young women with refractory SLE using TyU19, a donor-derived allogeneic anti-CD19 CAR T product, at a single centre in China. All four achieved clinical remission. One patient who discontinued all medications remained in sustained, drug-free remission through follow-up. Peripheral BCMA-positive plasma cells declined alongside CD19-positive B cells, again raising the question of whether allogeneic CD19 CAR T cells may have broader immunological effects than their target specificity would predict. No graft-versus-host events were recorded. Prior vaccination responses, measured through hepatitis B antibody titers, were preserved after B-cell reconstitution — a practically important finding for managing long-term infectious risk.

At ACR Convergence 2025, preliminary results were presented for CTA313, a novel dual CD19/BCMA CAR T product, and for CTA311, a CD19-directed construct, in patients with active SLE. Both demonstrated encouraging safety, in vivo cellular kinetics, and early clinical signals — indicating that multiple independent programmes are converging on similar biological targets with consistent early results.

3.2 Systemic Sclerosis

SSc is a notoriously difficult disease to treat. Progressive fibrosis of skin and internal organs, microvascular injury, and a complex autoimmune component — characterised by anti-topoisomerase I, anti-centromere, and other antibodies — combine to produce a condition where available therapies slow rather than arrest progression, particularly in patients with interstitial lung disease. The B-cell component of SSc pathogenesis, including autoantibody-secreting plasma cells and IL-6-producing B cells, makes CD19 CAR T-cell therapy biologically rational.

Within the Müller et al. NEJM 2024 series, all four SSc patients showed decreased EUSTAR activity index scores and stopped all immunosuppressants. The CASTLE basket trial, whose results were published in Nature Medicine in January 2026, evaluated zorpocabtagene autoleucel in SSc patients as a component of its multi-disease design, reporting improvements in skin fibrosis and patient-reported global health, with no ILD progression observed during the study period. Individual case reports have extended these observations to patients with SSc-associated pulmonary involvement, describing resolution of skin fibrosis, improvement in dyspnea, normalisation of inflammatory markers, and improvement in pulmonary imaging — outcomes that, if reproducible in controlled trials, would represent a genuine advance in a condition with very limited therapeutic options.

3.3 Idiopathic Inflammatory Myopathies

The three IIM patients in the NEJM 2024 series all achieved ACR-EULAR major clinical response, including normalisation of muscle enzymes and, in individual cases, complete serological remission. These results — in a condition where anti-Jo-1, anti-Mi-2, and anti-MDA5 autoantibodies drive persistent inflammation — have been reinforced by earlier case reports and the ongoing CASTLE trial data.

Perhaps the most clinically instructive case in the entire field, however, is one that describes a failure and how it was salvaged. Published in Nature Medicine in April 2025, this case involved a 45-year-old woman with treatment-refractory Jo-1-associated antisynthetase syndrome who achieved disease remission after an initial CD19 CAR T-cell infusion, then relapsed at nine months. Re-infusion of the same product was attempted but failed: the patient had mounted a T-cell response directed against the murine-derived scFv domain of the CAR construct itself — an immune reaction to the therapy that prevented CAR T cells from expanding. Despite full-dose lymphodepletion, there was no clinical response on re-infusion. After bridging treatment with daratumumab, BCMA-directed CAR T-cell therapy was administered. BCMA CAR T cells expanded successfully, cleared plasma cells in lymphoid tissue, reduced autoantibody levels, and re-induced drug-free remission.

This case carries several important lessons. It shows that relapse after CAR T-cell therapy is a real possibility and that reinfusion with the same product may not be viable. It demonstrates a novel resistance mechanism — immune rejection of the therapeutic construct — that points directly to the clinical need for humanised or fully allogeneic products. And it establishes that sequential BCMA targeting is a viable salvage strategy, which has implications for how future treatment algorithms are designed.

3.4 Neurological Autoimmune Diseases

The extension of CAR T-cell therapy into neurological autoimmunity carries specific biological and practical challenges. The CNS is protected by the blood-brain barrier, which must be penetrated for cellular therapy to be effective in MS and other central nervous system conditions. The heterogeneity of progressive versus relapsing disease, the theoretical risk of exacerbating neuroinflammation, and the general absence of validated remission biomarkers for most neurological autoimmune conditions all complicate translation.

Despite these obstacles, early data are accumulating. Fischbach and colleagues demonstrated in 2024 that KYV-101, an investigational CD19 CAR T product, expanded within the cerebrospinal fluid of two patients with progressive MS — establishing that these cells can cross the blood-brain barrier and persist within the CNS environment. Both patients tolerated the treatment with only low-grade CRS and experienced no inflammatory relapses during follow-up. On the strength of these early signals, two Phase 1 trials (NCT06138132 and NCT06451159) and a Phase 2 study (KYSA-7, NCT06384976) of KYV-101 in progressive MS subtypes have been approved.

In myasthenia gravis, two mechanistically distinct approaches are advancing simultaneously. CD19-directed CAR T cells produced a 70% reduction in anti-AChR antibody levels in a patient with treatment-resistant MG and produced dramatic clinical improvement — with the Phase 1/2 KYSA-6 trial (NCT06193889) now enrolling. The conceptually more elegant approach for this condition is the CAAR T-cell strategy: constructs bearing the acetylcholine receptor or MuSK on their surface as the recognition domain, which selectively engage and eliminate the specific B-cell clones whose B-cell receptors bind those autoantigens. A Phase 1 trial of MuSK-CAAR T cells (NCT05451212) is enrolling. In CIDP, a male patient treated with bispecific CD19-BCMA CAR T cells in 2024 showed clinical improvement and remained free of immunosuppressants during a one-year follow-up. A notable observation from Haghikia and colleagues: a patient carrying both AChR-positive MG and ACPA-positive RA received KYV-101 and achieved complete MG remission while ACPA titers normalised concurrently — raising the intriguing possibility that a single CAR T-cell course might address co-existing autoimmune conditions that share an autoreactive B-cell pathobiology.

3.5 Rheumatoid Arthritis and Emerging Indications

The clinical logic for CAR T-cell therapy in RA is sound in principle but requires more careful phenotypic stratification than any other indication. RA already has an extensive set of effective targeted therapies — JAK inhibitors, IL-6 receptor antagonists, abatacept, multiple TNF inhibitors — and most patients who fail one biologic mechanism can switch to another. The patients most likely to benefit from CAR T-cell therapy are those with what EULAR has defined as difficult-to-treat RA (D2T-RA), and within that group, specifically those with persistent inflammatory refractory RA (PIRRA) — objectively documented ongoing synovial inflammation despite failure of multiple advanced therapies. Distinguishing PIRRA from the non-inflammatory refractory RA phenotype (NIRRA), where symptoms persist through mechanisms unrelated to active immune inflammation, will be essential before meaningful trials can be conducted. Administering a complex cellular therapy to NIRRA patients carries all the risks and costs with none of the theoretical benefit.

Elsewhere, early applications and preclinical data are accumulating across pemphigus vulgaris, ANCA-associated vasculitis, neuromyelitis optica spectrum disorder, and juvenile-onset SLE. Paediatric considerations — manufacturing from lymphopenic patients on active immunosuppression, developmental immune implications, growth concerns, and ethical frameworks for enrolment — deserve dedicated attention as this population begins to be considered for trials.

4. Engineering the Next Generation of Constructs

4.1 Dual and Multi-Target Constructs

The case for combining CD19 and BCMA targeting was not initially obvious from oncology experience, where these two targets tend to be used sequentially rather than simultaneously. In autoimmunity, the rationale emerged from careful immunological analysis of the disease itself. Bone marrow studies in SLE patients show that CD19-negative, BCMA-positive long-lived plasma cells are a major and sustained source of anti-dsDNA and other pathological autoantibodies — cells that a CD19-only approach leaves entirely untouched. When these plasma cell niches are cleared alongside circulating B cells, the depth and duration of autoantibody suppression appears greater, and the window of drug-free remission may widen accordingly. Whether this translates into meaningfully longer relapse-free survival is the central question that randomised trials will need to answer.

4.2 Inhibitory CARs

The fundamental limitation of a conventional CAR T cell is that it does not discriminate between cells that happen to carry the target antigen and cells that carry it but should not be touched. Activation happens whenever the receptor finds its antigen — context, function, and the broader tissue environment are invisible to it. Inhibitory CARs attempt to address this by giving the T cell a second input to weigh before committing to a kill decision.

The concept works like this: alongside the activating CAR, the T cell is also engineered to express a receptor that recognises a separate "safety" antigen — one that is preferentially or exclusively present on non-pathological cells sharing the primary target marker. When both signals arrive simultaneously, the inhibitory receptor — which signals through the cytoplasmic tails of PD-1 or CTLA-4, molecules the immune system normally uses to dampen its own responses — overrides the activating signal. The cell stands down. When only the activating signal arrives, because the pathological target cell lacks the protective marker, the T cell proceeds to kill.

In principle, this kind of dual-sensing architecture could solve one of the most stubborn problems in B-cell-targeted autoimmune therapy: how to spare regulatory B cells, tissue-resident populations, or other functionally important cells that happen to share CD19 or another surface marker with the autoreactive B cells driving disease. Whether this level of discrimination can actually be implemented reliably in the chaotic in vivo environment of an inflamed tissue — where antigen expression levels fluctuate, cells are in dynamic states of activation and differentiation, and CAR T cells are themselves changing — is the question that preclinical and early clinical work will need to address. The concept is elegant; the execution is hard.

4.3 CAR-Regulatory T Cells

Most cellular therapy for autoimmunity is built around the same core idea — find the cells causing the problem and eliminate them. CAR-Treg therapy starts from a different premise entirely. Rather than asking which cells to destroy, it asks which cells could be empowered to restore the immune balance that has been lost. The answer it reaches is the regulatory T cell: a lineage whose natural function is to police immune responses, suppress autoreactive effectors, and maintain peripheral tolerance. The engineering challenge is giving these cells the antigen specificity to do that job at the right place and time, rather than non-specifically throughout the immune system.

In practice, antigen-specific CAR-Tregs are generated by transducing regulatory T cells with a chimeric receptor directed toward a disease-relevant target. When those Tregs encounter cells or tissue expressing the target antigen, they activate — and instead of killing, they suppress. The suppression is local: cytokines like IL-10 and TGF-β are released in the tissue microenvironment, dampening autoreactive effector T cells and reducing inflammatory signalling at the site of injury, ideally without touching immune activity elsewhere in the body.

The most clinically advanced example of this approach is in transplantation rather than classical autoimmunity. HLA-A2-specific CAR-Tregs — developed as TX200-TR101 — target donor HLA-A2 on transplanted tissue, directing regulatory activity precisely where graft rejection is initiated. These constructs are approaching first-in-human evaluation, making this the first CAR-Treg programme on a regulatory pathway toward clinical use. The transplant setting is in some ways an ideal proving ground: the target antigen is defined, the site of immune conflict is anatomically predictable, and the clinical endpoint — graft survival without chronic immunosuppression — is clear.

In autoimmunity, the same logic is being applied to disease-specific antigens that the immune system is attacking. Insulin and islet-associated antigens in type 1 diabetes, myelin basic protein and myelin oligodendrocyte glycoprotein in multiple sclerosis, and CD19 itself — repurposed to direct regulatory rather than cytotoxic activity — in lupus, have all shown preclinical proof of activity in relevant animal models. The insulin-specific CAR-Treg work by Tenspolde and colleagues demonstrated that these cells could be generated with stable FOXP3 expression, maintained suppressive function over time, and remained durable in vivo — addressing the long-standing concern that engineered Tregs might lose their regulatory identity and convert toward an inflammatory phenotype under inflammatory conditions.

The honest caveat is that everything said above is based on animal models and in vitro data. What happens when these cells encounter the actual inflammatory milieu of active human autoimmune disease — with its complex cytokine networks, competing effector signals, and epigenetically entrenched autoreactive populations — remains genuinely unknown. Maintaining Treg stability and suppressive potency in that environment is a different challenge from anything the preclinical systems have fully modelled. The first human trials will be instructive not only for safety and efficacy, but for whether the underlying biological assumptions of the approach hold in the species and context that ultimately matter.

4.4 Allogeneic Products: Promise and Remaining Gaps

The argument for allogeneic, or "off-the-shelf," CAR T cells is essentially logistical and clinical: manufacturing an autologous product for a patient who is lymphopenic, on high-dose corticosteroids, or with profoundly dysfunctional T cells is difficult, slow, and subject to variable product quality. Donor-derived products from healthy T cells, edited to remove the endogenous TCR and, in some constructs, the HLA loci, can be manufactured at scale, banked, and infused without a 2–4 week manufacturing window. The first clinical demonstration that allogeneic CD19 CAR T cells can induce remission in refractory SLE — published in Cell Research in 2025 — is a meaningful step, but the cohort was small (n=4), follow-up is limited, and validation in larger, longer-term studies is essential before conclusions about durability and safety equivalence to autologous products can be drawn.

4.5 Addressing Immunogenicity: The Case for Humanised Constructs

The relapsing IIM case described above gave the field an important and uncomfortable early warning: murine scFv sequences in CAR constructs can elicit host immune responses that prevent re-treatment. When a patient's recovered immune system recognises the murine-derived binding domain as foreign and mounts a T-cell response against it, re-infusion of the same product will fail regardless of lymphodepletion intensity. This is not a theoretical concern — it has been documented clinically. Fully humanised scFv domains, whether derived from human antibody libraries or from rationally humanised existing sequences, should now be considered a priority in new construct design rather than an optional refinement. Similarly, CAR designs that incorporate stealth modifications to reduce immunogenicity, or that use allogeneic cells to circumvent the issue entirely, deserve particular emphasis in next-generation development programmes.

5. Understanding the Safety Profile in Context

5.1 Cytokine Release Syndrome — A Milder Manifestation Than in Cancer

CRS is the most anticipated complication of CAR T-cell therapy and the one about which most physicians without cellular therapy experience are most concerned. The oncology experience — where Grade 3–4 CRS occurs in 20–40% of patients treated for large B-cell lymphoma or ALL — reasonably prompts this concern. What the autoimmune experience consistently shows, however, is a dramatically more favourable pattern. Across multiple independent cohorts and case series, Grade 1 CRS has been the predominant presentation — fever, fatigue, and flu-like symptoms lasting days and resolving with supportive care. Grade 2 events requiring tocilizumab have occurred in a small minority. Severe CRS has been essentially absent.

The biological explanation is intuitive in retrospect: the total number of target cells in autoimmunity — even in heavily diseased patients — is orders of magnitude lower than in haematological malignancy, where billions of tumour cells may be present at the time of infusion. Lower target burden means lower CAR T-cell activation intensity and, correspondingly, lower cytokine output. This does not mean CRS monitoring can be relaxed — all patients require careful post-infusion surveillance in appropriate clinical settings — but the risk-benefit calculation in autoimmunity is fundamentally different from oncology.

5.2 ICANS and Neurological Toxicity

Immune effector cell-associated neurotoxicity syndrome remains uncommon in autoimmune series. In the Müller et al. NEJM 2024 series of 15 patients, a single case of Grade 1 ICANS was recorded. The absence of severe neurotoxicity is consistent across published experience. The specific context of neurological autoimmune diseases warrants additional vigilance: when CAR T cells are intentionally engineered to penetrate the CNS, the potential for inflammatory consequences within the central nervous system must be prospectively and carefully monitored in ongoing trials.

5.3 Infection Risk: Managing B-Cell Aplasia

The period of B-cell aplasia — typically 90 to 120 days — is the main window of infectious vulnerability. During this time, patients lack the capacity for de novo antibody production and are susceptible to bacterial respiratory infections, viral reactivation, and opportunistic pathogens. Published series manage this period with antimicrobial prophylaxis, intravenous immunoglobulin replacement, and antiviral treatment when indicated. In practice, infections reported across the Erlangen cohorts and Chinese allogeneic series have been manageable and non-fatal, though one hospitalisation for pneumonia was recorded among the 15 NEJM 2024 patients.

A reassuring finding across multiple cohorts is preservation of prior vaccination responses after B-cell reconstitution. Hepatitis B antibody titers measured before and after CD19 CAR T-cell treatment showed no substantial decline — suggesting that memory plasma cells responsible for existing immunity are not uniformly eliminated, or that sufficient immune memory reconstitutes during the recovery period. This has direct clinical implications for ongoing infection risk management and for decisions about re-vaccination after treatment.

5.4 Resistance and Relapse: What We Know and What We Don't

The documented cases of disease relapse after CAR T-cell therapy, while limited in number, raise questions that the field has not yet fully answered. Some relapses may reflect incomplete plasma cell depletion — a gap that dual CD19/BCMA targeting is designed to address. Others, as the antisynthetase syndrome case demonstrates, may involve acquired immunological resistance to the therapeutic product itself. The outer boundary of durability remains undefined: the longest published follow-up in any autoimmune series is 29 months. Whether patients who are in DORIS remission at two years will remain so at five years, or whether the autoreactive repertoire will gradually re-establish itself, is unknown. Answering this question rigorously will require structured, standardised, long-term follow-up registries — a resource that does not yet exist at the scale needed.

6. The Clinical Trial Landscape

Global analysis of registered trials through July 2025 identified 119 studies of CAR T-cell therapy in autoimmune diseases — a number that would have seemed implausibly large ten years ago. Of these, 70 are Phase I, 30 are Phase I/II, and 15 are Phase II, with the remainder unclassified or in planning stages. The peak of new trial registrations was 25 in 2024, reflecting sharply accelerating interest. Autologous products account for approximately 89% of trials; allogeneic programmes, which did not appear until 2023, now represent around 10%. Non-leading pharmaceutical firms sponsor approximately 75% of studies; academic institutions contribute 17%. The geographic concentration is currently in Germany, China, and the United States, though international expansion through multi-site and multinational protocols is occurring rapidly.

The CASTLE basket trial (NCT06347718) deserves particular attention as a methodological model. Published in Nature Medicine in January 2026, it evaluated zorpocabtagene autoleucel — an autologous CD19 CAR T product — across SLE, SSc, and IIM simultaneously using a Phase 1/2a two-stage optimal design. The basket architecture is well-suited to this setting: it allows multiple disease cohorts to be evaluated under a unified protocol without requiring the patient numbers that individual disease-specific trials would demand, making it practically feasible at a time when the eligible population at any single centre is inherently small. The safety outcomes — CRS rate, ICANS rate — were the primary endpoints; disease-specific remission criteria, ILD non-progression, and ACR-EULAR myositis response were secondary. The results, showing improved disease activity and patient-reported global health in most patients with an acceptable safety profile, provide the strongest controlled early-phase evidence to date and will inform the design of pivotal studies.

No CAR T-cell product has yet received regulatory approval for any autoimmune indication. What the regulatory path should look like — which endpoints, what follow-up duration, how to define the comparator arm, what post-marketing surveillance commitments are required — is actively under discussion between sponsors, investigators, and agencies.

7. The Harder Questions: Barriers Between Promise and Practice

7.1 Manufacturing Is Not a Technical Detail

Autologous CAR T manufacturing is, by its nature, bespoke. Each product begins with a leukapheresis from a patient whose T cells may be numerically depleted, phenotypically exhausted, or functionally impaired by years of immunosuppressive treatment. The manufacturing process — viral transduction, ex vivo expansion, quality release testing — takes two to four weeks under ideal conditions, during which disease may progress. Commercial oncology CAR T products carry per-patient costs of USD 300,000 to 500,000 in high-income markets, and autoimmune patients would likely face similar pricing absent substantial restructuring of the value chain.

These are not peripheral concerns. They are structural barriers that will determine whether this therapy reaches the patients who need it or becomes confined to academic centres treating carefully selected patients within funded trials. Allogeneic manufacturing, centralised banking, and point-of-care or semi-automated manufacturing platforms are the most plausible solutions — but each requires regulatory validation, clinical safety data specific to the platform, and health economic modelling that does not yet exist for the autoimmune application.

7.2 Selecting the Right Patients

Not every patient with a refractory autoimmune disease label is an appropriate CAR T-cell candidate. Patients with predominantly non-inflammatory symptoms — fibromyalgia-dominant RA, SSc patients whose fibrosis has outpaced their immunological activity, MS patients at a stage where progressive neurodegeneration is independent of active inflammation — are unlikely to benefit from B-cell depletion and would bear all the risks of the intervention without therapeutic gain. Developing and validating biomarkers that can reliably identify active, immunologically driven disease — comprehensive B-cell and plasma cell subset phenotyping, autoantibody profiling, and potentially single-cell transcriptomic or genomic signatures of autoreactive clones — is as important to the success of this field as any engineering advance.

7.3 Outcome Measures Need Work

The standard remission criteria used across published autoimmune trials — DORIS for SLE, ACR-EULAR for IIM, EUSTAR for SSc — were developed for conventional immunosuppressive treatment and were not designed with the kinetics of cellular therapy in mind. CAR T-cell responses may involve early inflammatory signals before clinical improvement, delayed responses as reconstituted immune populations stabilise, and eventual relapse patterns that look different from biologics-treated patients. The field needs consensus definitions of CAR T-specific remission, relapse, and durable response, along with patient-reported outcome instruments validated for the cellular therapy context. Without these, comparison across trials and, eventually, regulatory assessment, will remain imprecise.

7.4 Equity Cannot Be an Afterthought

Autoimmune diseases disproportionately affect women and, in conditions such as SLE and RA, are more prevalent in certain ethnic and socioeconomic groups who are consistently under-represented in clinical trials and who face greater barriers to accessing expensive advanced therapies. If CAR T-cell treatment reaches clinical practice as a USD 400,000-plus intervention available only at academic centres in high-income countries, the pattern of therapeutic inequity that characterises advanced biologics will simply repeat itself at greater scale. This requires engagement — by investigators, funders, regulators, health technology assessment bodies, and payers — before it becomes entrenched rather than after.

8. Where This Field Is Likely to Go

Looking at the next five years with reasonable objectivity rather than optimism alone: the trajectory strongly suggests that at least one CAR T-cell product will enter pivotal Phase 3 evaluation for SLE within the next 24 to 36 months, likely on the basis of extended CASTLE data or analogous basket trial results. Allogeneic products will either validate themselves clinically or reveal immunological barriers — host rejection, inconsistent expansion, shorter persistence — that require further engineering to overcome. CAAR T cells for MuSK-MG represent probably the most mechanistically precise cellular therapy ever designed for any autoimmune condition, and if Phase 1 results are favourable, this approach could become a model for antigen-specific cellular therapy across the spectrum of antibody-mediated diseases.

The open scientific questions are the interesting ones. Will the immunological reset hold at three, four, five years — or will autoreactive memory eventually re-emerge and require re-treatment? If re-treatment is needed, can it be delivered safely with humanised or allogeneic products? What is the minimum depth of B-cell and plasma cell depletion required to achieve durable remission? Are there disease subgroups within SLE or SSc — defined by genetics, autoantibody profile, or tissue involvement pattern — that respond better or worse, and can these be identified prospectively? These questions have answers. Finding them will require the kind of coordinated, well-resourced, internationally collaborative clinical research infrastructure that the field is still assembling.

9. Conclusions

There is a meaningful distinction between promising early-phase results and a validated therapy ready for broad clinical practice, and it is important to maintain that distinction clearly when evaluating the current state of CAR T-cell therapy in refractory autoimmune disease. What the evidence through early 2026 establishes — from the original Erlangen compassionate-use series through the NEJM 2024 case series, the Phase 1 dual CD19/BCMA trial in SLE, the allogeneic TyU19 results, the CASTLE basket trial, and early neurological disease data — is proof of concept for a form of remission that conventional therapy cannot reliably achieve. Patients who had exhausted every available treatment option entered drug-free remission after a single cellular therapy infusion and maintained it for periods reaching nearly two and a half years. That is a result worth taking seriously.

It is not, however, a result that translates automatically into a therapy that is safe, accessible, and appropriate for a broad population of refractory autoimmune patients. Manufacturing remains the domain of specialised centres. Long-term durability is uncharacterised beyond 29 months. Resistance mechanisms exist and are incompletely understood. Patient selection criteria require biomarker-informed refinement. And the economic and equity dimensions of deploying a therapy of this cost and complexity across a patient population this large and diverse are not solved problems.

Science has moved remarkably fast. What is needed now is the infrastructure — standardised trials, long-term registries, international collaboration, regulatory clarity, and genuine engagement with access — to determine whether the early results mean what they appear to mean, and to ensure that if they do, the patients who stand to benefit most are the ones who actually receive treatment.

Ethics Declarations

Ethics Approval and Consent to Participate

No patient data were collected, no clinical interventions were performed, and no biological samples were handled in the preparation of this work. This manuscript reviews and synthesises findings from studies already available in the peer-reviewed literature, all of which underwent independent ethical oversight through their respective institutional review processes. Under these circumstances, a separate ethics committee submission for this review was neither required nor sought.

Consent for Publication

As no individual patient data, images, or identifiable clinical information are presented in this review, a formal consent for publication is not applicable to this work.

Competing Interests

The author has no financial relationships, institutional affiliations, personal connections, or professional obligations that could be reasonably perceived as influencing the positions taken or the evidence presented in this article. No pharmaceutical company, biotechnology firm, clinical trial sponsor, or commercial entity provided any input — financial or otherwise — into the writing or content of this manuscript. The author declares no competing interests of any kind.

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Author Contributions
This review was conceived, designed, researched, and written in its entirety by Shehzma Pirani. The literature search, critical appraisal of sources, synthesis of evidence across disease areas and engineering strategies, and all stages of drafting and revision were carried out by the author alone. Shehzma Pirani takes full responsibility for the accuracy, completeness, and intellectual integrity of all content presented in this manuscript and confirms that the final submitted version has been read and approved.

Key References

1. Mougiakakos D, Krönke G, Völkl S, et al. CD19-targeted CAR T cells in refractory systemic lupus erythematosus. *N Engl J Med.* 2021;385:567–569.
2. Mackensen A, Müller F, Mougiakakos D, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat Med.* 2022;28:2124–2132.
3. 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.
4. Schett G, Mackensen A, Mougiakakos D. CAR T-cell therapy in autoimmune diseases. *Lancet.* 2023;402:2034–2044.
5. CASTLE Basket Trial. CD19 CAR-T cells for treatment-refractory autoimmune diseases: the phase 1/2 CASTLE basket trial. *Nat Med.* 2026. doi:10.1038/s41591-025-04185-6.
6. Dual CAR Phase 1 Investigators. Co-infusion of CD19 and BCMA CAR-T cells in refractory SLE: a phase 1 trial. *Nat Med.* 2025.
7. Wang et al. Allogeneic anti-CD19 CAR-T cells induce remission in refractory systemic lupus erythematosus. *Cell Res.* 2025.
8. BCMA rescue case. BCMA CAR T cells in a patient with relapsing IIM after CD19 CAR T-cell failure. *Nat Med.* 2025.
9. Hu Z, Cai S, Yu Y, et al. BCMA-targeted CAR T cell therapy effectively induces disease remission in refractory lupus nephritis. *Ann Rheum Dis.* 2025;84(10):1675–1683.
10. Krickau T, Naumann-Bartsch N, Aigner M, et al. CAR T-cell therapy rescues adolescent with rapidly progressive lupus nephritis from haemodialysis. *Lancet.* 2024;403(10437):1627–1630.
11. Tur C, et al. CD19-CAR T-cell therapy induces deep tissue depletion of B cells. *Ann Rheum Dis.* 2025;84:106–114.
12. Fischbach F, Richter J, Pfeffer LK, et al. CD19-targeted CAR T cell therapy in two patients with multiple sclerosis. *Med.* 2024;5:550–558.
13. Haghikia A, et al. Clinical efficacy and autoantibody seroconversion with CD19-CAR T cell therapy in a patient with RA and coexisting myasthenia gravis. *Ann Rheum Dis.* 2024;83:1597–1598.
14. Lodka D, et al. CD19-targeting CAR T cells protect from ANCA-induced acute kidney injury. *Ann Rheum Dis.* 2024;83:499–507.
15. Schett G, et al. B-cell depletion in autoimmune diseases. *Ann Rheum Dis.* 2024;83:1409–1420.
16. Avouac J, Scherlinger M. CAR T-cell therapy for rheumatic diseases: what does the future hold? *BioDrugs.* 2025;39:5–19.
17. Ohno R, Nakamura A. Advancing autoimmune rheumatic disease treatment: CAR-T cell therapies — evidence, safety, and future directions. *Semin Arthritis Rheum.* 2024;67:152479.
18. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377:2531–2544.
19. Chung JB, Brudno JN, Borie D, Kochenderfer JN. Chimeric antigen receptor T cell therapy for autoimmune disease. *Nat Rev Immunol.* 2024;24:830–845.

20. Isaacs JD. CAR T cells — A new horizon for autoimmunity? *N Engl J Med.* 2024;390:758–759.
21. Tenspolde M, et al. Regulatory T cells engineered with a novel insulin-specific chimeric antigen receptor as a candidate immunotherapy for type 1 diabetes. *J Autoimmun.* 2019;103:102289.
22. Doglio M, et al. Regulatory T cells expressing CD19-targeted chimeric antigen receptor restore homeostasis in systemic lupus erythematosus. *Nat Commun.* 2024;15:2542.