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Emerging Roles of CAR-T Cell Therapy in Refractory Autoimmune Diseases: A futuristic direction to engineer immune tolerance

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Abstract

Autoimmune diseases are long-term immune-mediated diseases that lead to lack of self-tolerance, continuous inflammation and progressive organ destruction. Despite the revolutionary nature of biologic therapies that have ensured the management of the diseases by addressing particular pathways of inflammation, a significant percentage of patients become refractory or relapse after the withdrawal or necessitate lifelong immunosuppression. Such restrictions have led to efforts to find ways of immune modulation that are more profound and withstand longer. Chimeric antigen receptor T-cell (CAR-T) therapy, which was originally initially developed as a treatment of hematologic malignancies, is becoming a potential immune reprogramming strategy in severe autoimmune diseases. As opposed to normal biologics that inhibit specific inflammatory mediators, CAR-T technology allows specific destruction of autoreactive B-cell groups, which may interfere with pathogenic immune memory and allow immune reset. Initial clinical experience especially in systemic lupus erythematosus can show long-term drug-free remission of specific refractory patients that was obtained after administration of CD19-directed CAR-T therapy. The growing research in the rheumatoid arthritis, multiple sclerosis and myasthenia gravis further indicates the translational aspect of the approach. However, precautionary consideration of the safety, long term immune reconstitution, cost effectiveness and ethical concerns is still critical particularly because autoimmune conditions are not malignant. The next-generation constructs, regulatory CAR-T cells, mRNA-based platforms, and allogeneic products could be improved in the future to increase precision and accessibility. The review is a synthesis of existing mechanistic understanding, clinical data, safety issues, and future opportunities, with CAR-T therapy as a paradigm shifting approach that can potentially alter the current management of autoimmune diseases to be no longer based on chronic suppression but on potential long-term immune re-programming.

Keywords: Chimeric Antigen Receptor T Cells; Autoimmune Diseases; Immune Reprogramming; CD19 CAR-T; B-Cell Depletion; Immune Reset; Refractory Autoimmunity; Cytokine Release Syndrome

1. Introduction

Autoimmune diseases form a heterogeneous group of chronic conditions, in which self-tissue destruction is caused by immune intermediaries mediating a loss of immune tolerance. Recent epidemiological studies show that the prevalence of autoimmune conditions in the world is gradually growing and it is estimated that as many as 10 percent of the population could have one or more autoimmune disorder (1). The clinical and socioeconomic implications of this expanding burden become important due to the fact that a number of autoimmune diseases occur early in life, and have a relapsing and progressive course (2). Systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and myasthenia gravis are some of the most clinically challenging disorders, which are correlated with long term morbidity and poor quality of life (3). Most of the current treatment approaches predominantly focus on general

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immunosuppression or specific blockage of cytokines. Traditional therapies, including corticosteroids and disease modifying antirheumatic agents, still form the main pillars of management, but they have been linked to accumulative toxicity and ineffective control of the disease (4). This has led to the introduction of biologic therapies that target tumor necrosis factor, interleukin 6, B cells, and co stimulatory pathways that have greatly enhanced the outcome of many patients (5). Nevertheless, clinical evidence shows that a significant percentage of patients respond inadequately or become non-responsive with time, which requires consecutive switching of therapy (6). Moreover, chronic immunosuppression predisposes the patients to infections, risks of malignancy, and metabolic complications, which necessitates more conclusive treatments (7).

Autoimmune diseases at the mechanistic level are maintained by long-lasting subsets of autoimmune B and T lymphocytes resistant to central and peripheral tolerance controls. The dysregulated B cell differentiation leads to the creation of the pathogenic autoantibodies, immune complex, complement activation, and tissue damage in disorders like systemic lupus erythematosus (8). The further intensification of inflammatory cascades and the continuation of immune dysregulations are further promoted by T helper 17 cell expansion and dysfunctional T cell regulatory (9). Notably, the prevalence of these destructive immune groups has been found to persist even in the presence of conventional immunosuppressive treatment and is perhaps the reason why lapses have been common when treatment is withdrawn (10). These observations have redirected the therapeutic treatment to therapies that can eradicate auto reactive immune clones and reestablish long term immune equilibrium. The use of chimeric antigen receptor T cell therapy is one of the most revolutionary developments in cellular immunotherapy. CAR T cells were originally genetically engineered to target hematologic malignancies with synthetic receptors that identify the surface antigen with no regard to major histocompatibility complex restriction (11). The success of CD19 driven CAR T cell therapy in the treatment of B cell acute lymphoblastic leukemia and diffuse large B cell lymphoma has revealed the possibility of this treatment to induce profound and sustained response (12). These findings have led to the desire to explore the use of CAR T technology outside of the oncology field, especially in diseases with an underlying pathogenic B cell expansion.

The decision to apply CAR T cell therapy to autoimmune disease is based on the fact that autoreactive B cells play a central role in the pathogenesis of the disease. Rituximab and monoclonal antibodies are used to destroy CD20 positive B cells, which frequently does not remove long lived plasma cells and does not result in long term remission (13). An opposition, however, is that CD19-directed CAR T cells have a wider cellular target range, comprising precursor and memory B lineage, causing deeper depletion (14). There is strong conceptual evidence presented by early clinical experience. In 2022, Mackensen and colleagues described how patients with severe refractory systemic lupus erythematosus treated with CD19 CAR T cells went to sustain drug free remission (15). The follow up studies subsequently established enduring depletion of B cells, loss of autoantibodies and restoration of normal immunologic parameters in the absence of persistent immunosuppression (16). These findings have been extrapolated into other refractory autoimmune diseases, including idiopathic inflammatory myopathies and myasthenia gravis by further case series and pilot trials, which propose that CAR T mediated immune reprogramming can broadly be applied to antibody driven diseases (17). The theory that has come out of these works is that of an immune reset, whereby the substantial depletion of autoreactive clones allows the generation of a naïve, tolerant immune repertoire (18). In contrast to traditional treatment options, which only suppress immunity in the short term, CAR T cell therapy has the potential to change the disease pathway, whereby immunologic memory is transformed.

Regardless of this promise, the auto-translation of CAR T therapy to autoimmune disease is a special case. The risk benefit ratio is very different compared to oncology where the life-threatening malignancy warrants increased tolerance to toxicity. Cytokine release syndrome, immune effecter cell associated neurotoxicity syndrome are also major issues despite pre-existing cases of autoimmune cohorts that reported mild to moderate cases of events (19). There is still a dearth of long-term safety data and uncertainties on the issue of relapse risks, tolerances maintenance and the best way to select patients (20). CAR T cell therapy is a paradigm shift in the refractory autoimmune disease in light of these advancements, as it is an immunosuppression therapy that is replacing immune reprogramming. This review embodies the mechanistic basis, clinical data, safety issues, and future of CAR T cell therapy in non-malignant immune mediated diseases. Through the combination of new data on translational results and clinical performance, we shall offer an overall analysis of whether CAR T cell therapy can transform the way severe autoimmune disease is treated.

2. Immunopathogenesis of Autoimmune Disorders

The development of autoimmune diseases is due to a complicated combination of genetic predisposition, environmental factors, and the inability of the immune system. The key in the formation of these is the disruption of central and peripheral tolerance systems that usually destroy or suppress autoreactive lymphocytes (3). The breakdown of tolerance checkpoints leads to the proliferation of autoreactive B and T cells and results in a cascade of immune events, which eventually cause chronic inflammation of tissues and organ injuries. Although, systemic lupus erythematosus,

rheumatoid arthritis, multiple sclerosis, and myasthenia gravis are different diseases with different clinical pictures, they have common immunopathogenic processes in which B-cell dysregulation, production of autoantibodies, T-cell imbalance, and inflammatory processes mediated by cytokines play a crucial role. The immunopathogenic network in autoimmune disease and therapeutic disruption by CD19 CAR-T Cells is depicted in Figure 1.

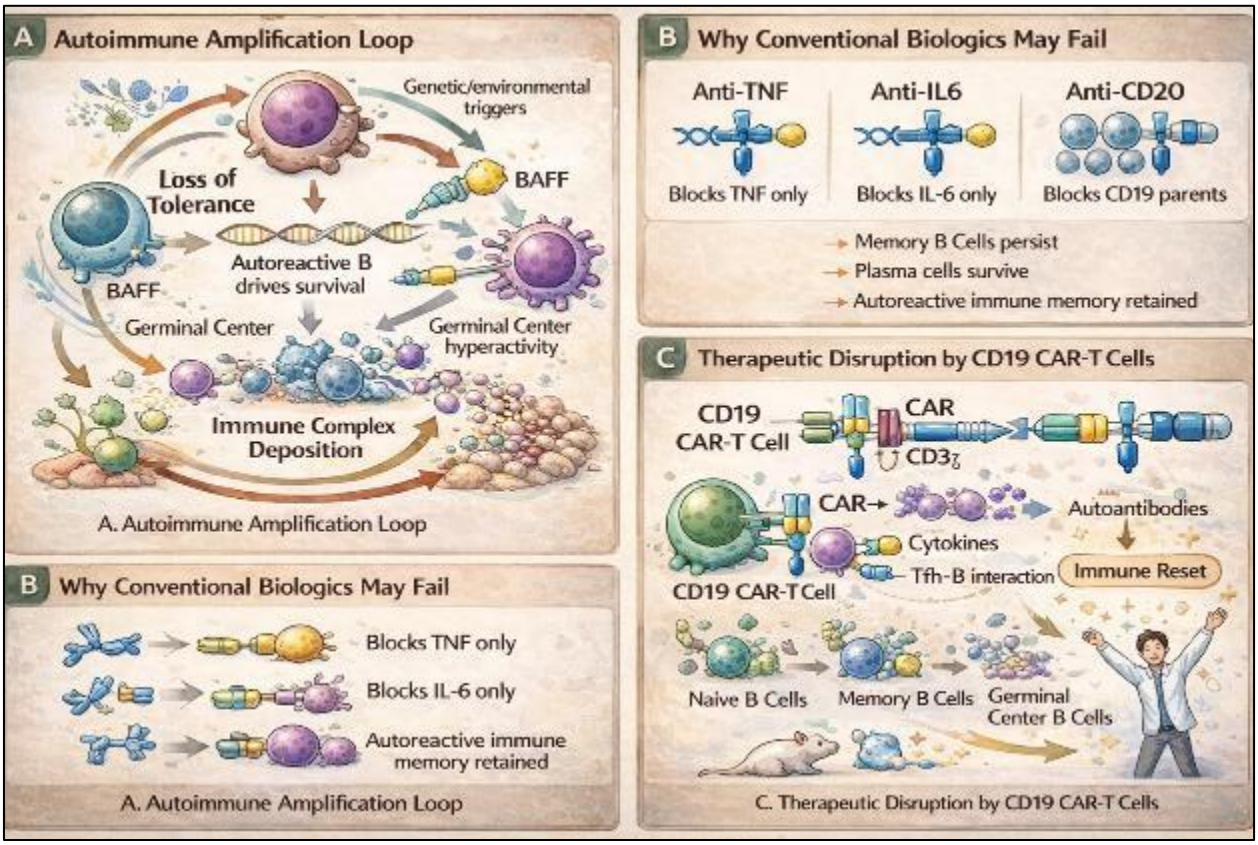

Figure 1 Immunopathogenic Network in Autoimmune Disease and Therapeutic Disruption by CD19 CAR-T Cells

2.1. B-Cell Dysregulation

B cells also have a role in the development of autoimmunity which is not limited to the production of antibodies. In the normal immune development, the autoreactive B cells are deleted or renewed in the bone marrow. Defects in these central tolerance mechanisms in autoimmune diseases permit the escape of self-reactive clones into the periphery (21). Mechanisms of peripheral checkpoints which control the survival and activation of B-cells are also broken resulting in growth of autoreactive naive and memory B-cells. In systemic lupus erythematosus, B-cell activating factor is increased to allow survival of autoreactive B cells and differentiation of plasmablasts (22). Other B-cell hyperactivity patterns are related to the rheumatoid arthritis disease, in which the synovial germinal center-like structures facilitate local B-cell maturation and maintenance. Besides secretion of antibodies, autoreactive B cells also act as antigen presenting cells, which activate T helper cells and also enhance adaptive immune responses (23). Proinflammatory cytokines like interleukin-6 are also generated by them supporting inflammatory loops. All these functionalities are the reason why the targeting therapy of B-cells has shown bi-partial effectiveness. Though, incomplete elimination of the pathogenic subsets and survival of long-lived plasma cells can be the reasons of relapse.

2.2. Autoantibody Production

Autoantibodies are a characteristic of most autoimmune diseases and may be an early predictor of the disease. The antibodies against anti-double stranded DNA create immune complexes in systemic lupus erythematosus that are deposited in the tissue and trigger complement pathways causing organ damage as in lupus nephritis (24). Complement activation increases the immune cell recruitment and tissue damage. Anti-citrullinated protein antibodies in rheumatoid arthritis are highly linked to progression of the disease and structural joint destruction (25). Neuromuscular transmission is interrupted in myasthenia gravis as a result of antibody against acetylcholine receptors, which causes muscle weakness. In multiple sclerosis, B-cell follicles in the meninges mediate demyelination via antibodies. Notably, the long-sustained plasma cells in bone marrow niches are fairly immune to traditional anti-CD20

therapy (26). This is the reason why it is possible to have reappearing antibody titers in the event of biologic withdrawal. Thus, therapies that can address more B-lineage compartments can provide more immunologic control.

2.3. T-Cell Imbalance: The Th17/Treg Axis

T cells play an important regulatory role in the autoimmune pathogenesis. The ratio of T helper subsets relative to the regulatory T cells is what dictates the loss or maintenance of immune tolerance. Th17 cell expansion has been noted in a number of autoimmune diseases and is also associated with the severity of the diseases (27). Th17 cells secrete interleukin-17 and others that invite neutrophils and cause the inflammation of tissues. On the other hand, the regulatory T cells that carry FOXP3 usually prevent the occurrence of autoreactive immunity by inhibitory cytokines including interleukin-10 and transforming growth factor beta. Deficient functionality of regulatory T cells or low counts of this group of cells allow unrivaled proliferation of pathogenic lymphocytes (28). There is also an amplification of immune dysregulation through interactions between B cells and T follicular helper cells. T follicular helper cells promote B-cell differentiation and affinity maturation and reinforce autoantibody responses and maintain chronic inflammation.

2.4. Cytokine-Mediated Chronic Inflammation

There is a coordination of autoimmune inflammation by cytokine networks. Active disease conditions are characterized by elevated levels of tumor necrosis factor, interleukin-6, type I interferons and interleukin-17. Signatures of type I interferon are especially salient in systemic lupus erythematosus and they aid in activating immune and losing tolerance. These cytokines provide a vicious cycle of inflammation increasing antigen presentation, prolonging the survival of lymphocytes and attracting innate immune cells. Persistent tumor necrosis factor signaling in rheumatoid arthritis mediates synovial hyperplasia and cartilage erosion. Inflammatory mediators impair blood brain barrier in multiple sclerosis and support demyelination (29). The autoreactive lymphocytes and the amplification of the cytokine's loops are the convergent factors that create a vicious cycle of chronic inflammation that cannot be eliminated solely through the conventional methods of immunosuppression. The knowledge of these reciprocal pathways gives the mechanism basis of therapeutic approaches that are focused on eradicating the pathogenic immune clones instead of inhibiting downstream mediators.

As described in **Table 1**, significant autoimmune diseases are associated with overlapping immunologic drivers even though they have organ-specific phenotypes.

Table 1 Key Immunopathogenic Mechanisms Across Major Autoimmune Diseases

Disease	Dominant B-cell Role	Major Autoantibodies	T-cell Imbalance	Key Cytokines	Target Organ Damage
Systemic Lupus Erythematosus	BAFF-driven autoreactive B-cell survival	Anti-dsDNA, Anti-Smith	Reduced Treg, Expanded Th17	IFN-alpha, IL-6	Kidney, skin, systemic
Rheumatoid Arthritis	Synovial B-cell activation	Anti-CCP	Th17 expansion	TNF, IL-6	Joints
Multiple Sclerosis	Meningeal B-cell follicles	Oligoclonal bands	Th17 predominance	IL-17, IFN-gamma	CNS myelin
Myasthenia Gravis	B-cell mediated autoantibody production	Anti-AChR	T helper dysregulation	IL-6	Neuromuscular junction

3. Overview of CAR-T Cell Technology

One of the latest and the most sophisticated advancements in cellular immunotherapy is chimeric antigen receptor T-cell therapy. Neither major histocompatibility complex restricted antigen recognition nor antigen presentation pathways is needed as the CAR-T cells are genetically engineered to recognize specific surface antigens directly, allowing targeted cytotoxicity to occur without reliance on antigen presentation pathways (11). This is especially required in pathological conditions whereby antigen presentation can be distorted or inefficient. Initially used in the treatment of hematologic malignancies, CAR-T therapy showed record remission in B-cell acute lymphoblastic leukemia and aggressive lymphoma (30). This was a demonstration of a proof of concept as the success of CD19-targeted CAR-T

therapy demonstrated that engineered immune cells are able to generate lasting responses when administered once. This paradigm in therapy has now been applied not only in oncology, but also in immune-mediated disease, such as refractory autoimmune disease (31).

3.1. Structural Architecture of CAR Molecules

Table 2 Core CAR modules and functional significance

CAR module	Typical components	Main function in CAR biology	Practical implications
Antigen binding domain	scFv	Direct antigen binding	Determines target specificity and affinity
Hinge or spacer	CD8 alpha, IgG derived spacers	Flexibility, synapse geometry	Alters target accessibility and activation thresholds
Transmembrane domain	CD8 alpha, CD28	Membrane anchoring and receptor stability	Influences receptor expression and signaling tone
Activation domain	CD3 zeta	Primary activation signaling	Required for cytotoxicity and cytokine release
Costimulatory domain	CD28 or 4 1BB	Enhances proliferation and persistence	Impacts durability, exhaustion risk, and cytokine profile

The CAR molecule consists of modular domains and each of them leads to its biologic behavior. Most frequently, the extracellular antigen recognition domain is a single chain variable fragment of monoclonal antibodies. This fragment endows antigen specificity as well as binding affinity to antigens like CD19 (32). This domain has an effect on the activation threshold, off-target effects, and therapeutic accuracy. The hinge or spacer region, which is the source of structural flexibility, follows directly after it and prevents the CAR and its target antigen to unfold in optimal spatial orientation. Hinge length differences may also affect the immune synapse formation and strength of signal (33). Transmembrane domain binds the receptor in the T-cell membrane and plays a part in the receptor stability and clustering dynamics. Activation of the T-cell requires the intracellular signaling machinery. The CD3 zeta chain is the main activation module and it has immunoreceptor tyrosine based activation motifs initiating cytotoxic signaling cascades on antigen binding (11). In order to increase expansion and persistence, more recent CAR constructs have costimulatory domains, including CD28 or 4-1BB. These domains regulate the proliferation kinetics, cytokine production pattern, metabolic programming, and exhaustion resistance (34). Clinical relevance of differences in costimulatory signaling. Constructs based on CD28 are likely to result in rapid expansion and high early cytokine release whereas constructs expressing 4-1BB may be linked to increased persistence and slower expansion kinetics (35). Such differences become especially significant when using CAR-T therapy to translate into autoimmune diseases, in which overreaction of inflammatory responses should be carefully restrained. In **Table 2**, the structural elements and their functional implications are described.

3.2. Generational Evolution of CAR-T Cells

The constructs of CAR-T are divided into generation according to their intracellular configuration of the signaling. The first-generation CARs had merely the CD3 zeta signaling, which was adequate to induce cytotoxicity but did not have long-term survival in vivo (4). Second generation CARs incorporated one extra costimulatory domain, which enhanced expansion, survival, and therapeutic durability to a great extent. These constructs have been the backbone of majority of the now approved CAR-T products (30). 3rd generation CARs have two costimulatory domains to control the intensity and persistence of activation. Even though they are hypothetically beneficial, they have not proved to be superior to second generation constructs in all clinical environments (34). Fourth generation CARs are also known as armored CARs, which are designed to secrete cytokines or express other modulatory molecules to manipulate the immune microenvironment (33). In autoimmune format, designs of CAR are more likely to focus on controllability and safety instead of the optimal cytotoxicity. Inducible or self-limiting CAR systems are being explored as an example to restrict the risks of immunodeficiency in the long term (31). **Table 3** contains a comparative overview of the generational characteristics.

Table 3 CAR-T generations and expected functional behavior

Generation	Signaling design	Intended advantage	Typical trade-offs
1st	CD3 zeta only	Basic activation and killing	Poor persistence and weaker expansion
2nd	CD3 zeta + one costimulator	Better expansion and durability	Higher cytokine production depending on design
3rd	CD3 zeta + two costimulators	Enhanced activation tuning	Complexity, variable clinical benefit
4th	2nd or 3rd + engineered payloads	Added functionality and immune shaping	Safety monitoring becomes more critical

3.3. Manufacturing Process and Quality Control

The autologous CAR-T products are manufactured through a series of steps that are well controlled. It starts with leukapheresis where T cells generated by the patient are harvested. They are then cloned to these cells in the ex vivo setting and genetically engineered through viral or non-viral methods of gene transfer to impart the CAR construct (36). The most popular platform has been lentiviral vectors because they have stable integration and good transduction. After transferring of the genes, the expansion of CAR-expressing T cells is done in a controlled culture. The culture duration, the strength of activation, and cytokine supplementation are parameters that affect phenotype, memory properties, and exhaustion properties (37). Before release, quality control testing is conducted; this involves identity and potency, sterility, viability, and transduction efficiency tests. In oncology, two to four weeks manufacturing time is quite acceptable depending on the severity of the disease. Nevertheless, in autoimmune diseases, the consistency of manufacturing, predictable growth, as well as safety control can be given even more weight because the toleration to severe toxicity is less (31). **Table 4** gives a summary of manufacturing workflow.

Table 4 Typical autologous CAR-T workflow and key control points

Step	What happens	Why it matters	Common bottlenecks
Leukapheresis	Collection of patient T cells	Determines starting cell quality	Low lymphocyte counts, prior therapies
Activation	Stimulates T-cell proliferation	Enables efficient gene transfer	Overactivation can increase exhaustion
Gene transfer	Viral or non-viral introduction of CAR gene	Establishes CAR expression	Vector availability, efficiency, cost
Expansion	Culture to reach dose	Influences phenotype and persistence	Contamination risk, variable growth
QC testing	Identity, viability, sterility, potency	Ensures safety and function	Time, assay standardization
Lymphodepletion	Pre-infusion conditioning	Supports CAR-T expansion in vivo	Infection risk, cytopenias
Infusion and monitoring	CAR-T infusion and toxicity surveillance	Detects CRS and neurologic events early	ICU resources, standardized grading

3.4. Differences Between Oncology and Autoimmune Applications

Although the principles of the engineering are common, the therapeutic goals vary in essence between the oncology and the autoimmune indications. In cancer, the objective is elimination of the malignant cells and in most cases, this will warrant an increase in the risk of toxicity (30). The aim in autoimmune disease is to destroy pathogenic immune subsets and maintain protective immunity and to limit long term immune suppressive effects. Selection of target antigens is also different. In hematologic malignancy, tumor specific/lineage specific markers are targeted in order to attain maximum cytoreduction. CD19 is now used more in autoimmune disease since it plays a pivotal role in autoreactive B-cell biology (31). Nevertheless, B-cell exhaustion and depletion should be weighed in full and long-term against the risk of infections

and hypogammaglobulinemia. Furthermore, endpoints vary. Oncology trials are keen on overall survival, progression-free survival whereas the autoimmune trials are keen on durable drug-free remission, normalization of serologic markers, and immune reconstitution profiles. These applications are compared in a structured way as shown in **Table 5**.

Table 5 Key differences between CAR-T use in oncology and autoimmunity

Domain	Oncology CAR-T focus	Autoimmune CAR-T focus
Therapeutic goal	Tumor eradication	Immune reprogramming and durable remission
Target strategy	Maximal malignant antigen coverage	Pathogenic immune circuit interruption
Tolerated toxicity	Higher acceptable risk	Lower acceptable risk
Persistence preference	Often longer persistence desired	Balanced persistence to avoid prolonged immunodeficiency
Monitoring	CRS, neurotoxicity, cytopenias	CRS, neurotoxicity plus immune reconstitution and infection risk
Success endpoint	Response rates and survival	Drug free remission, relapse prevention, immune restoration

3.5. Rationale for CAR-T in Autoimmune Diseases

The use of CAR-T cell therapy in autoimmune diseases is based on the fact that most cases of refractory immune diseases are caused by the presence of sustained autoreactive B-cell populations that do not face immune tolerance checkpoints. Although traditional therapies cause the subduction of inflammation or a temporary depletion of specific groups of immune cells, they can rarely remove pathogenic clones that cause persistence of the disease. Relapse in patients undergoing biologic therapy can be often due to the persistence of auto anti-inflammatory memory B cells and long-lived plasma cells (38). This drawback has changed focus to strategies that can be able to induce more profound immune modulation as opposed to cyclical suppression. CD19 has also become one of the most desirable targets of antibody-mediated autoimmune diseases. As contrasted to CD20 which is found on mature B cells but not on the early progenitors and plasma cells, CD19 is widely expressed on most stages of B-cell differentiation, both precursors and memory B-cells (39). Attack on CD19 will thus enable a more effective depletion of auto-receptive B-cell compartments. This increased targeting approach has theoretical advantages compared with the conventional anti-CD20 therapy in diseases like systemic lupus erythematosus, in which pathogenic autoantibodies are produced due to the aberrant germinal center responses (40). In addition to the production of antibodies, autoreactive B cells perform the role of antigen-presenting cells which activates T follicular helper cells and maintains inflammatory cycles. Removal of these B-cell subsets can thus break both humoral as well as cellular pathology in autoimmunity. Initial trials in the field have shown that CD19-targeted CAR-T treatment results in rapid and extensive proliferation of wandering B lymphocytes, which later vanish with the autoantibodies of the illness (41). These results imply that the mode of action of CAR-T therapy is, potentially, upstream in the pathogenic cascade and not merely prevents downstream cytokines.

One of the key ideas to have arisen as a result of initial clinical observations is that of immune reconstitution. Immuno-recovery following CAR-T-mediated B-cell depletion is seen to be accomplished by regenerating naïve B-cell populations, and not by re-expanding the already autoreactive memory clones (15). This has been termed as an immune reset even though there is a likelihood that the potentially pathogenic immunologic memory may be efficiently abraded and substituted with a tolerant repertoire. CAR-T therapy has the potential to produce long-term suppression following a single infusion unlike monoclonal antibodies, which need repeated dosing (42). Detailed immunophenotyping of patients with refractory lupus after CD19 CAR-T cells therapy supports the immune reset hypothesis. It was found that investigators noticed the normalization of B-cell subsets, interferon signatures resolution, and long-term clinical remission without the requirement of continued immunosuppressive treatment (15). The results of these findings differ with the traditional B-cell depletion approaches, in which the memory compartments usually re-emerge with maintained autoreactivity. The other reason why CAR-T therapy can be used to treat autoimmune diseases is that it can eliminate autoreactive clones irrespective of antigen specificity. Multiplexed autoantigens play a pathological role in complex systemic diseases like lupus, and antigen-specific tolerization cannot be easily applied in these conditions. CAR-T therapy bypasses the identification of the individual pathogenic epitopes by directing the treatment to a common lineage marker, like CD19 (43). This is a wide but specific strategy which offers practical method of diseases that have polyclonal autoimmunity.

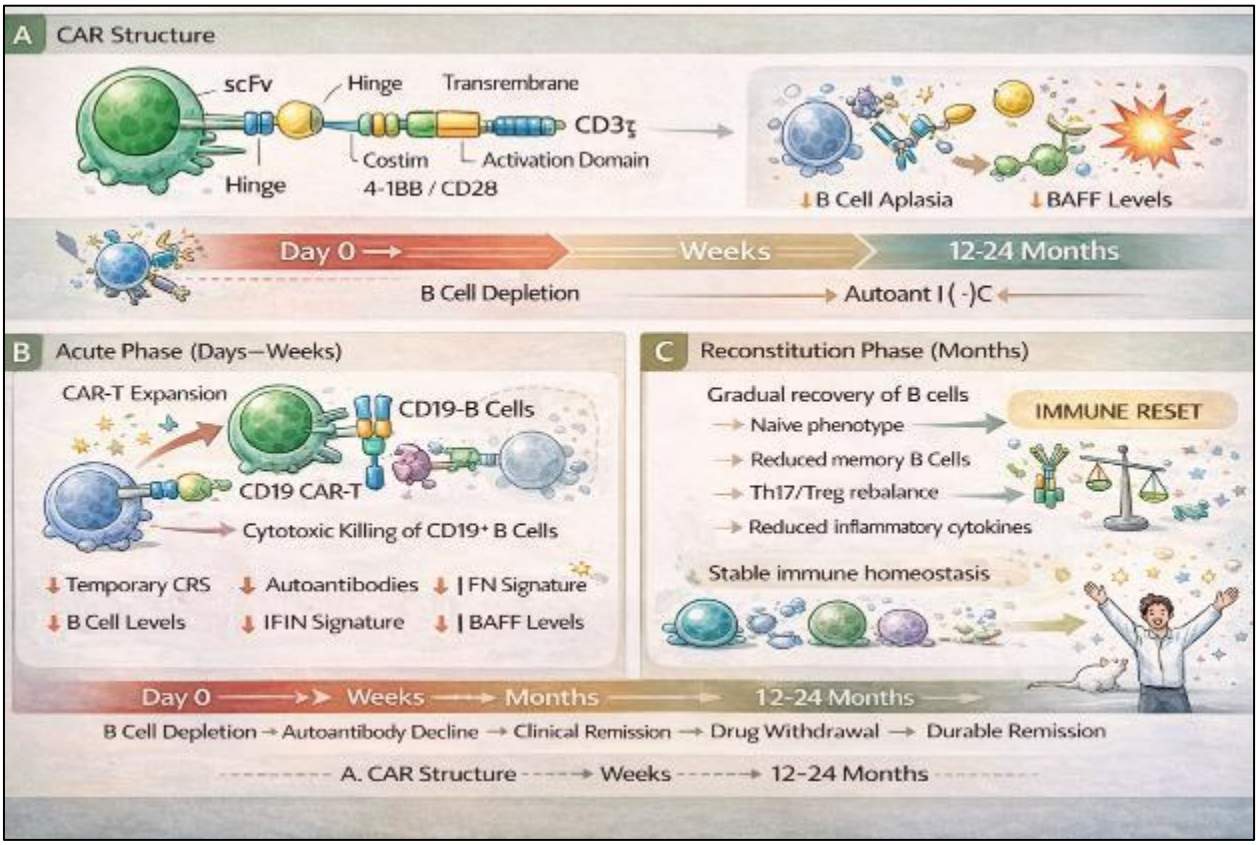

Figure 2 Mechanistic Model of CD19 CAR-T–Induced Immune Reprogramming

Most impressive evidence of clinical breakthrough has occurred in severe systemic lupus erythematosus. Early case series showed such positive results as a rapid clinical response, steroid and immunosuppressant withdrawal, and long-term remission without drugs after CD19 CAR-T treatment (17). The follow up reports revealed long-lasting reactions over a period of one year in a number of patients with tolerable toxicity profiles. The results of such have created a great deal of excitement since, in the past, refractory lupus was synonymous with a lack of treatment Cure and high morbidity. Notably, CAR-T therapy is fundamentally different as compared to temporary B-cell depletion. The anti-CD20 antibodies destroy mature B cells, but leave early progenitors and plasma cells intact, which frequently causes autoreactive clones to re-develop. Conversely, CAR-T cells grow in vivo and have cytotoxic activity over weeks and can offer continued surveillance in the early immune reconstitution (44). Such kinematic profile can be the cause of the depth and permanence of response witnessed in preliminary autoimmune applications. However, one should be careful. The longitudinal immune effects are still being examined and the best selection criteria of patients are yet to be developed. It is uncertain that CAR-T therapy will be used only in severe cases of refractory treatment or be implemented earlier in the treatment algorithm as safety data continues to demonstrate its safety. Moreover, there are still concerns about whether durability will be possible in those who have survived more than several years and whether immune reset can be obtained in homogeneous autoimmune phenotypes.

Nevertheless, the biological support of CAR-T therapy in autoimmune disease is strong despite these uncertainties. Directly doing away with pathogenic B-cell compartments and enabling immune reconstitution, CAR-T therapy represents a conceptual change in chronic immunosuppression to the possibility of disease reprogramming. With the ever-growing clinical evidence, the method can shift the paradigm of therapeutic objectives in the field of refractory autoimmune disorders by shifting the paradigm of the field to focus on durable immunologic remission rather than symptom control. The overall mechanistic model of CD19 CAR-T–induced immune reprogramming is shown in Figure 2.

4. Clinical Evidence in Specific Autoimmune Diseases

CAR-T therapy translationally shifting to autoimmune disease is one of the greatest changes in the field of immunotherapy in the present day. Mechanistic rationale is very convincing but the most important factor of long-term adoption is clinical validation. In the last three years, initial phase clinical experiences and well-observed case series

have started to identify the therapeutic potential of CD19- targeted CAR-T therapy in refractory autoimmune disorders. In order to bring out systematic clarity, critical published clinical findings on all major autoimmune diseases are tabulated in **Table 6**. These findings are discussed in the following sections.

Table 6 Summary of Clinical Experience of CAR-T Therapy in Autoimmune Diseases

Disease	Target	Patient Number (reported)	Remission Outcome	Follow-up Duration	Notable Toxicity
SLE	CD19	Small case series (≤10)	Drug-free remission	12–24 months	Mostly grade 1–2 CRS
Rheumatoid Arthritis	CD19	Limited early reports	Clinical improvement	Short-term	Mild CRS
Multiple Sclerosis	CD19	Early translational cases	Reduced inflammatory markers	Limited	Mild CRS
Myasthenia Gravis	CD19	Case reports	Improved muscle strength	Short-term	Mild CRS

4.1. CAR-T in Systemic Lupus Erythematosus

Systemic lupus erythematosus has become the most convincing autoimmune pointer of CAR-T therapy up to date. The breakthrough 2022 report of CD19-targeted CAR-T therapy in patients with severe and treatment-refractory lupus, although in small early-phase cohort, showed quick and immense clinical reactions (15). Such patients had already failed numerous rounds of treatment such as corticosteroids, mycophenolate mofetil, cyclophosphamide, and biologic treatment. After infusion of CAR-T, all the patients were characterized by significant decrease in the scores of disease activity, complement normalization, and the disappearance of anti-dsDNA antibodies.

Notably, the remission occurred without the continuous immunosuppressive treatment. In a few months patients could stop using glucocorticoids and other immunomodulators. The data that was followed up after more than one year showed that the therapeutic effect was not temporary as it indicated sustained drug-free remission (45). Immunologic profiling provided evidence of total B-cell depletion in days of infusion followed by gradual reconstitution by naive phenotype B-cells, but not B-cell memory (46). The lack of autoreactive memory B-cell response is in favor of the immune reset hypothesis put forward above. Also, interferon signatures that are usually high in active lupus normalized after treatment. Follow-up studies of this cohort have further supported the sustainability of response, including in those patients who already have had an organ-threatening manifestation of the disease, such as lupus nephritis (47). Although the number of patients is still limited, there is uniformity in the remission effects, which has created great interest in the current multicenter trials.

4.2. CAR-T in Rheumatoid Arthritis

Rheumatoid arthritis is a more heterogeneous disease entity, and it can be seropositive and seronegative. CAR-T therapy should be employed to treat seropositive patients with high serum levels of anti-citrullinated protein antibodies and unresponsive disease to biologic therapy. In models of collagen-induced arthritis, preclinical experiments showed that the B-cells of the models are depleted through the signaling of CD19 CAR-T cells, which decreases the number of autoantibodies and suppresses the inflammation in the joints (48). These observations formed a translational basis on initial clinical investigation.

There are positive indications of initial compassionate-use in patients with highly refractory rheumatoid arthritis. Within weeks of infusion, treated individuals had a reduction in synovial swelling, a decrease in the inflammatory markers, and an improvement in the scores in disease activity (49). But, as opposed to lupus, the sustainability of long-term remission is less clear, because of shorter-term follow-up and smaller groups of patients. Safety and longer-term remission endpoint trials are undergoing initial trials in patients that have exhausted several classes of biologic therapy including anti-tumor necrosis factor and anti-interleukin-6 therapy (14). In case of confirmation of durable responses, CAR-T therapy might offer an alternative to patients with treatment-resistant seropositive disease.

4.3. CAR-T in Multiple Sclerosis

CAR-T therapy application in multiple sclerosis poses exceptional challenges because of a combination of both T cells and B cells in the pathogenesis of the disease. B-cell targeting has already been proven as an effective therapeutic approach with regard to its clinical success on anti-CD20 monoclonal antibodies (50). This gave reason as to why deeper depletion through CD19 CAR-T therapy may cause long-term disease control. In experimental autoimmune encephalomyelitis models, preclinical studies have identified the reduction in the inflammatory infiltration and demyelination in the central nervous system with B-cell depletion mediated by CAR-T (51). Preliminary case-based translational experiences have indicated a drop in the levels of inflammatory markers and disease activity stabilization in the selected refractory patients. Nevertheless, there are no large-scale human data, and neurotoxicity issues are especially difficult to be overlooked given the involvement of the central nervous system in multiple sclerosis. The longitudinal imaging and immunologic follow-up will be required to assess the possibility of CAR-T therapy to preclude the neuroinflammation with lasting suppression with no unwarranted neurologic harm risk (52).

4.4. CAR-T in Myasthenia Gravis

Myasthenia gravis is a paradigm autoantibody-mediated disease where autoantibodies have direct effects of impairing neuromuscular transmission. CAR-T therapy can provide a mechanistically accurate intervention due to its central pathogenic role of B cells. Small early phase studies and case reports of recent cases have reported a rapid recovery in muscle strength, and acetylcholine receptor antibody titers after CD19 CAR-T infusion (53). The long-term, treatment-resistant disease patients showed significant clinical severity score improvement in weeks. Corticosteroid and other immunosuppressive agent tapering were realized in some cases. There has been an early safety experience that cytokine release syndrome occurrences in myasthenia gravis cohorts are mainly of low grade and can be treated with standard supportive care (54). However, close respiratory attention is essential due to the background neuromuscular weakness that is peculiar in the disease.

In the autoimmune diseases investigated so far, the clearest observation has been the extent of remission in deep lupus groups where drug-free remission seems to be possible in a few patients. The data on rheumatoid arthritis and myasthenia gravis are still in the emerging stages and may indicate biologic plausibility. The uses of multiple sclerosis are experimental but encouraging. Though the number of patients is still low and still, randomized controlled clinical trials are being done, the existing evidence is favorable to the idea that CAR-T therapy could offer a longer-lasting disease modification than conventional biologic agents. These preliminary clinical findings are used to establish bigger clinical studies to establish the best dosing, patient selection and long-term effects.

5. Safety Considerations in the Autoimmune Setting

The application of CAR-T therapy to autoimmune diseases is something that needs to be reassessed on safety thresholds and risk tolerance. In cancerous situations, large toxicity can be tolerated because of life threatening illness. Conversely, autoimmune disorders are severe with refractory forms, but need a more rational consideration of risk versus benefit. The autoimmune population is often younger and can otherwise be expected to live long, which must also be scrutinized more closely. The most widely known acute toxicity of CAR-T therapy is the cytokine release syndrome. This inflammatory complication is the consequence of the rapid activation of immune and amplification of cytokines after the engagement of antigens. Moderate to severe cytokine release syndrome has been reported in a considerable percentage of patients in oncology cohorts, and sometimes leads to intensive care support (55). Nevertheless, newer cohorts of autoimmune patients have indicated that the profile of toxicity is less severe. A series of early cases of lupus and myasthenia gravis indicate that grade 1 or 2 cytokine release syndrome is predominant and can be treated with supportive therapy or with restricted cytokine inhibition (56). This has been attributed to a reduced antigen load in autoimmune disease than in hematologic malignancies which leads to less explosive immune activation. Another severe safety issue is neurotoxicity (also known as immune effector cell-associated neurotoxicity syndrome). In cancer patients, the syndrome can manifest itself as confusion, aphasia, seizures, or cerebral edema (57). Even though autoimmune patients have so far been reported to have lower incidence of severe neurotoxicity, careful attention is still necessary especially in diseases like multiple sclerosis that have a prior neurologic impairment baseline. The exact pathophysiology of neurotoxicity remains to be clarified, and endothelial activation and disruption of blood-brain barrier have been considered to have significant roles (58).

Risk of infection is a primary issue in the autoimmune environment. CAR-T therapy causes extreme depletion of B-cells that can lead to hypogammaglobulinemia and humoral immunity. Oncology evidence shows that patients are more vulnerable to bacterial and viral infection after treatment (59). Whereas, in autoimmune cohorts, the initial reports on severe infection are relatively low, the trends on long-term immune reconstitution are still being studied. Aplasia of B-cells may be chronic in some patients and may necessitate immunoglobulin replacement therapy. There are other

concerns that are created by long-term immune suppressions. Although the immune reset theory indicates that the regeneration can be done on naïve B-cell populations with no autoreactivity, it is not clear whether the immune recovery will be durable and complete. It is reported to cause prolonged cytopenias and delayed immune reconstitution in groups of oncology(60). The question of whether parallel trends will occur in the autoimmune patients with a long follow up is yet to be completely defined. This will require continuous longitudinal follow-up to explain the risks of secondary malignancy or chronic immune deficiency. Safety evaluation is also worsened by the cost and accessibility issues. CAR-T therapy is also one of the costliest forms of biologic therapies in the medical field. The additional factors that add to the overall cost are manufacturing complexity, personalized production, and hospitalization needs (61). In conditions where there are other biologic treatments available at a reduced price and have a proven safety profile such as autoimmune diseases, economic factors impact risk-benefit analysis. The readiness of the health system and equal access will become crucial factors of clinical adoption.

Table 7 Safety Profile Comparison of CAR-T Therapy in Oncology versus Autoimmune Diseases

Safety domain	Oncology CAR-T experience	Autoimmune CAR-T experience (emerging)	Typical monitoring	Common mitigation
Cytokine release syndrome (CRS)	More frequent; moderate to severe CRS reported in several malignancy cohorts	Predominantly low-grade CRS reported in early autoimmune cohorts; severe cases rare so far	Vital signs, inflammatory markers, oxygen requirement	Supportive care; IL-6 blockade if needed; corticosteroids for persistent cases
Neurotoxicity (ICANS)	Ranges from mild confusion to seizures or cerebral edema in severe cases	Severe neurotoxicity appears less common in early autoimmune reports but long-term data limited	Neurologic assessment, cognitive scoring, imaging if indicated	Corticosteroids; intensive monitoring for severe cases
Infection risk	Increased susceptibility due to cytopenias, prior therapies, and B-cell aplasia	Infection risk expected with prolonged B-cell depletion; long-term rates still under evaluation	CBC, immunoglobulin levels, infection surveillance	Antimicrobial prophylaxis; IVIG replacement if indicated
Prolonged cytopenias	May persist weeks to months post-infusion in oncology cohorts	Reported less frequently so far in autoimmune settings; follow-up ongoing	Serial blood counts	Growth factor support; transfusion if required
Hypogamma-globulinemia	Common in patients with durable B-cell depletion	Likely in CD19-targeted autoimmune therapy; duration under investigation	Serum IgG monitoring	Immunoglobulin replacement when clinically indicated
Viral reactivation	Possible in heavily pretreated oncology patients	Similar theoretical risk in autoimmune patients with prior immunosuppression	Viral screening based on risk profile	Antiviral prophylaxis or pre-emptive therapy
Long-term immune suppression	Prolonged immune alterations reported in some oncology populations	Immune reconstitution patterns under study; risk-benefit balance critical	Long-term immune phenotyping	Vaccination planning; longitudinal monitoring
System-level considerations	CAR-T delivery established in oncology centers	Requires expansion into rheumatology and neurology practice settings	Multidisciplinary coordination	Dedicated CAR-T programs and referral pathways

Comparing the severity profile of oncology and autoimmune applications, the existing evidence indicates that the toxicity of patients with autoimmune diseases might be less common and fewer. Reduced tumor burden equivalents,

the lack of malignant microenvironment cytokine amplification, and possible reduced kinetics of CAR-T expansion might explain a better tolerability (62). However, there are unique susceptibilities in the autoimmune population, such as a history of immunosuppression, and the presence of comorbid organ damage that have to be included in the selection criteria of the patient. A systematic review of the toxicity frequency, severity, and management plans of oncology and autoimmune CAR-T therapy is outlined in **Table 7**. In short, positive aspects of initial signs of safety in autoimmune cohorts are optimistic, but only more substantial controlled studies and follow-ups can allow conclusive conclusions. The selection of patients, the standardization of the toxicity levels, and the unified monitoring methods will become the key to successful integration of CAR-T therapy in the management of autoimmune diseases. Maintaining an equilibrium between immune reprogramming and protection immunity is the main safety issue in this area of progress.

6. CAR-T vs Existing Biologics

Biologic agents have changed the management of autoimmune diseases in the past two decades by selecting the main inflammatory mediators. Tumor necrosis factor blockers, interleukin-6 receptor blockers, B-cell depleting antibodies and costimulatory pathway blockers have played a significant role in diseases like rheumatoid arthritis, systemic lupus erythematosus as well as multiple sclerosis in terms of disease control and quality of life (63). These therapies have altered the treatment paradigm of immunosuppression-based treatment to a more specific immune modulation. However, a significant number of the patients are refractory, become unresponsive with the course of time, or need lifelong treatment in order to achieve remission (64). Traditional biologics mainly work by disrupting the action of certain inflammatory cascades as opposed to destroying the underlying autoreactive immune repertoire. In the case of B cells, anti-CD20 monoclonal antibodies like rituximab will wipe out the B cells in circulation but fail to always eliminate the long-lived plasma cells or autoreactive memory niches entrenched in lymphoid tissues (65). Disease relapse therefore commonly occurs after B-cell populations are rejuvenated. Likewise, cytokine inhibitors do not affect the downstream immune responses but preserve much of the upstream immune dysregulation. CAR-T therapy is a completely novel approach to therapy. Instead of activating a single pathway, the CD19-targeted CAR-T cells cause successive and sustained depletion of the B-cell lineage, such as naïve, memory, and germinal center B cells (17). Preliminary autoimmune evidence CAR-T induced depletion could then result in immune restoration leading to the production of newly arisen B-cell subsets with lower autoreactive capabilities. This idea of immune reprogramming differentiates the CAR-T treatment approach with maintenance-based biologic approaches.

These modalities also vary in terms of duration of therapeutic effect. Biologics have to be administered continuously in order to maintain the control of the disease. The repeated autoreactive immune memory is often manifested in withdrawal flare (64). The longitudinal registry studies show that secondary loss of response results in many patients going through several biologic agents (66). CAR-T therapy on the contrary is a single intervention strategy. The earliest cohorts of lupus have reported long-term drug-free remission (over a year) in a number of cases which is a promising indicator of long-term disease remedies (67). There is also a difference in the relapse dynamics between the two approaches. In the case of biologic therapy, relapse is quite predictable when doses are either decreased or stopped. In CAR-T therapy, the relapse has been found to be more directly connected with the B-cell reconstitution and immune remodeling kinetics. Mechanistic studies at an earlier stage suggest that restoration of certain autoreactive clones and not global immune recovery may be the determinant of relapse (68). These findings highlight the necessity of a longitudinal immune surveillance after CAR-T infusion.

The safety concerns pose an alternative. Biologics typically have their well-characterized long-term safety history that has been accrued over decades of use. Nevertheless, long-term immunosuppression raises the risk of cumulative infections and can make them prone to opportunistic events (69). In contrast, CAR-T therapy accumulates toxicity during the initial post-infusion phase, namely, cytokine release syndrome and immune effector cell-associated neurotoxicity. New autoimmune data exhibits lesser severity that is observed in oncology cohorts, which may be attributed to less antigen burden and inflammatory amplification (70). Another axis of comparison is provided by cost structure. It is a distribution of financial load in the context of long courses of treatment, as a rule, years or decades long. There is high initial manufacturing and hospitalization expenses associated with the CAR-T therapy. Economic modeling in cellular therapy postulates that the long-term cost-effectiveness is based on the durability of remission and prevention of recurring biologic cycling (71). This economic calculus will play a central role in policy decisions in autoimmune diseases, the horizons of which will be life-long.

The changing therapeutic environment is characterized by the philosophical differentiation between chronic and immune suppression. Biologic therapies are essential and keep being readily accessible by the majority of patients. Nevertheless, CAR-T therapy proposes the attribute of intense immunologic recalibration among patients with refractory disease. The future applicability of this approach as a complement to existing treatment algorithms or redefining would be based on the ongoing controlled trials, the duration of remission, safety data, and long-term

immune reconstitution data. A systematic review of mechanism of action, duration of effect, relapse dynamics, safety profile, and costs between CAR-T therapy and conventional biologic is summed up in **Table 8**.

Table 8 Comparative Analysis of CAR-T Therapy and Conventional Biologics in Autoimmune Diseases

Parameter	Conventional Biologics	CAR-T Cell Therapy
Mechanism of action	Targeted pathway suppression (TNF, IL-6, CD20, JAK, CTLA-4)	Deep B-cell lineage depletion and immune reprogramming
Therapeutic intent	Control inflammation	Reset immune system architecture
Duration of effect	Requires chronic administration	Single infusion with potential durable remission
Relapse pattern	Common after drug discontinuation	Relapse may correlate with B-cell reconstitution
Immune memory impact	Partial suppression of autoreactive clones	Potential elimination of autoreactive memory compartments
Acute safety risks	Generally mild to moderate; infection risk	CRS and neurotoxicity risk in early phase
Long-term safety	Accumulated immunosuppression over years	Long-term immune reconstitution under investigation
Cost structure	Repeated long-term dosing	High upfront manufacturing cost
Infrastructure need	Widely available infusion models	Specialized CAR-T centers required

7. Future Directions

The accelerated development of CAR-T cell therapy into autoimmune disease has created various prospects of the future that could transform the field of immune engineering other than by the process of cytotoxic lymphocyte elimination. Although clinical trials have been successful in the early stages by targeting B- cells with CD19, the emerging stage in evolution involves optimization of precision, safety, scalability, and persistence of immunomodulation. A potential future line of endeavor is by creating CAR-modified regulatory T cells, often referred to as CAR-Tregs. Contrary to the traditional CAR-T cells that destroy populations of targets, CAR-Tregs have been developed to boost immune tolerance. With antigen specificity and regulatory capacity, the cells can also suppress antigen-specific pathogenic immune responses in an antigen-targeted manner without causing general immunosuppression (72). CAR-Tregs have preclinical evidence that indicates it can stabilize the autoimmune inflammation in organ specific disease, whilst maintaining systemic immune competence. When translated effectively, this method may change the form of therapy that focuses on depletion to restoration of immune balance. The other future approach is the application of mRNA-based CAR platforms. Conventional CAR-T production involves virus vectors, which do not trouble to excise the CAR construct permanently into the genome. Conversely, the mRNA CAR-T cells contain the receptor transiently, which may help decrease the toxicity rates in the long term and create a more manageable therapeutic index (73). The platform can be very useful especially in autoimmune disorders where permanent immune depletion is not always required. Transient CAR expression enables the dosing of these cells on a repeat basis and it might reduce the risk of long-term B-cell aplasia.

Another important frontier is allogeneic or off the shelf CAR-T products. The nature of current autologous CAR-T therapy is the need to collect and produce cells individually, which makes them more accessible and expensive. To create universal donor CAR-T cells with a lower chance of graft-versus-disease, the gene-editing technologies, such as CRISPR-based ones, are under investigation (74). Allogeneic platforms made scalable in autoimmune contexts have the potential to substantially increase access to global patients, in particular where the time and cost of production is minimized. Constructs of safety-engineered CAR are also being developed. Other innovations like suicide switches, tunable signaling domains, and split-CAR system are meant to improve controllability following infusion (75). These processes can be especially applicable in the autoimmune disease where the risk tolerance is not as high as in oncology. Easy to adjust signal intensities and reversible will allow individual patient disease-based immune modulation. Individualized autoimmune CAR platforms can further improve the targeting approaches. Instead of relying on CD19 only, the design of the future can include disease-specific antigens or B-cell subsets responsible for pathogenesis detected on the basis of deep immune profiling (76). Recent developments in single-cell sequencing and immune repertoire scanning have

made it possible to identify clonally expanded autoreactive populations, which may be used to develop a tailored depletion approach to individual patients.

In addition to cellular engineering, there are strategies of combination that are being considered. The CAR-T therapy may be combined with the biologic agent, checkpoint modulation, or antigen-specific tolerization strategies to improve the remission longevity (77). These kinds of multimodal approaches could also be of great use in complex systemic disease like lupus or multiple sclerosis where multiple immune axes are involved in pathology. With the maturity of these innovations, the regulatory systems and long-term monitoring systems will have to adapt to the changes. The coming decade will prove or refute the fact that CAR-T therapy is just a rescue therapy that still works with the refractory disease or it is an immune programmable platform that can transform autoimmune treatment algorithms. The emerging CAR-T engineering strategies for precision and safety is depicted in Figure 3.

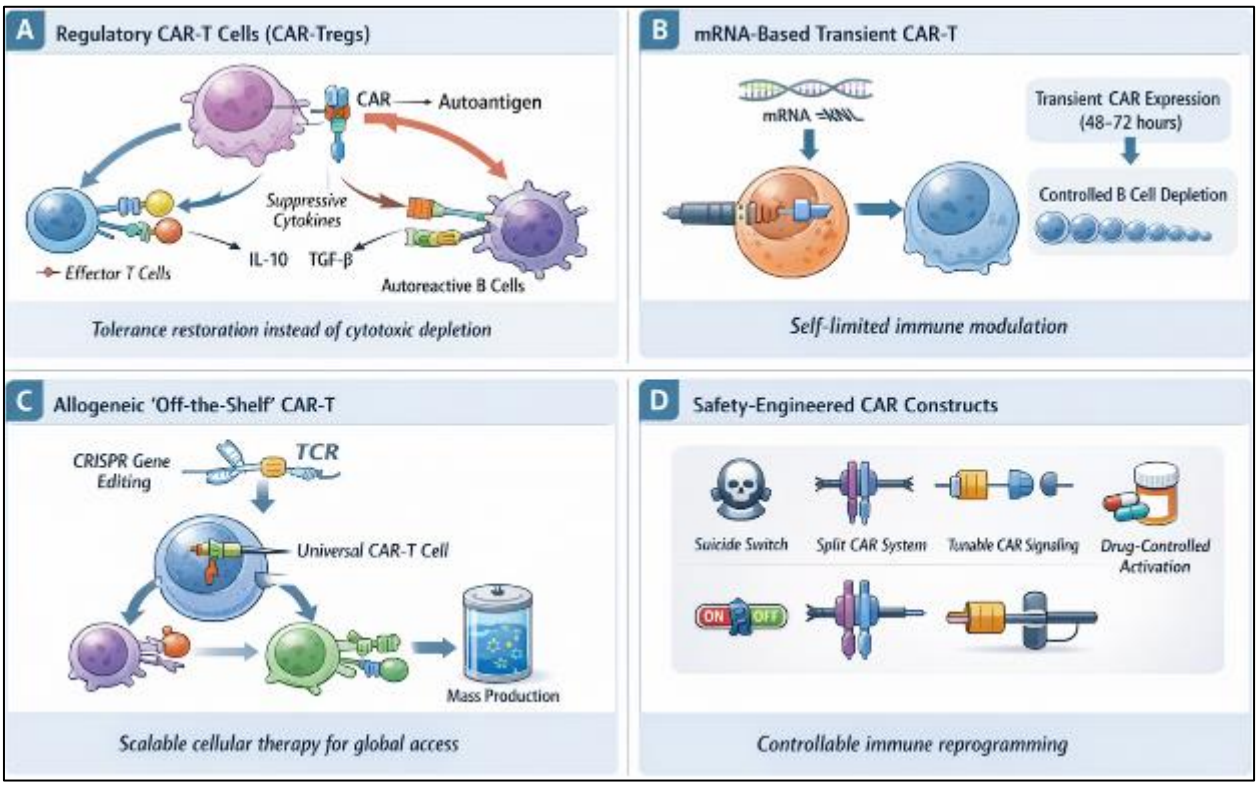

Figure 3 Emerging CAR-T Engineering Strategies for Precision and Safety

8. Challenges and Ethical Considerations

When it comes to the development of CAR-T therapy in autoimmune disease, the translation of a technology developed in oncology generates complex economic, ethical and regulatory concerns that are not limited to scientific feasibility. However, unlike hematologic malignancies, in which CAR-T is commonly implemented in refractory and life-threatening environments, a significant number of autoimmune diseases have chronic, but non-malignant outcomes. The difference changes the morality calculus of acceptable risk, cost optimization and uncertainty over time. One of the biggest impediments is an economic burden. CAR-T treatment is characterized by customized production, sophisticated cell-processing plants and extended hospital care. Initial cost of one infusion is significantly more expensive than the majority of biologic therapies, although biologic treatments have long-term costs. The mathematical studies of cellular immunotherapy indicate that the long-term value such as cost-effectiveness of any treatment is closely connected with the durability of a remission and the absence of repeated treatment cycles (61). Economic modeling in the case of autoimmune diseases, where the treatment can start in early adulthood and can span decades, requires to take into account lifetime healthcare costs, costs related to lost productivity, as well as the impact on society.

The other ethical difficulty in non-malignant disease risk-benefit assessment. CAR-T therapy results in extensive immune-modulation and even though initial autoimmune cohort studies have shown favorable safety profiles, immune-reconstitution kinetics have not been fully established in the long-term. Proportionality as an ethical principle takes into account the possibility of durable remission versus the risk of cytokine release syndrome, neurotoxicity, lasting B-

cell depletion and long-term effects of dubious nature. Genetic based, cellular therapies also create an issue with regard to genomic integration, off-target effects and the survival of engineered cells (78). Regulatory agencies might also require more rigorous data over time, however, before approving wider application in the case of disabling, although not immediately fatal, diseases. The ethical factors are also complicated by access on the global level. The CAR-T therapy is now based on the highly specialized production facilities that are located in high income states. Low- and middle-income environments have the potential to endanger availability of patients due to logistical, financial, and regulatory factors. The widening of the access would entail creation of scalable production models, regional manufacturing centers and international regulatory harmonization. The disparities in access may be increased without conscious planning of policies, which will result in unequal distribution of emerging transformative candidate therapies.

The key aspects of responsible implementation are regulatory control and long-term monitoring. The post-marketing surveillance that is normally required over several years to observe delayed adverse effects and secondary malignancies is typical of gene-modified cell therapies. The advanced therapy medicinal products such as immune phenotyping, malignancy surveillance and pharmacovigilance reporting systems are part of the regulatory systems that are established internationally in order to provide structured follow-up in the long term (79). Follow-up programs should be developed to be very specific in cases of autoimmune where the patient may need long life expectancy following the treatment. Finally, the future of CAR-T therapy in autoimmune disease lies in the possibility of being ethical due to effective risk communication, collecting long-term data, having access to strategies, and continued engineering safe practices. With the future of the field being innovation and responsibility, it will be up to regulatory balancing of the two aspects whether immune reprogramming can become a viable and ethically warranted treatment paradigm.

9. Conclusion

The treatment environment of autoimmune disease is changing radically. The chronic immunosuppression-based approach of management has been used over decades, and the goal is to reduce the inflammation and avoid organ damage without a radical change in the underlying immune dysfunction. Although biologic agents have played a major role in the control of the disease and the overall outcome of the patients, a number of the affected patients still suffer refractory disease, recurrence of the disease post-withdrawal of therapy, or accumulated toxicity of the treatment in an extended regimen. These constraints underscore the need to adopt strategies that are beyond suppression to long-lasting immune recalibration. There is a paradigm shift in this case that is represented by Car-T cell therapy. Instead, CAR-T therapy focuses on autoreactive immune compartments by specifically destroying their origin instead of suppressing the action of inflammatory mediators. The initial clinical trials especially in systemic lupus erythematosus have indicated that deep B-cell depletion and subsequent immune restructuring might result in long-term drug-free remission among those patients who once depleted the existing treatment modalities. This principle of immune reset may be a challenge to the conventional treatment algorithms, and it opens options of disease modification in the long-term following one intervention.

Significantly, CAR-T therapy can be expanded to the autoimmune disease with much attention paid to safety levels, ethical considerations, and follow-up. This is in contrast to oncology where the aggressive interventions may be justified by the life-threatening malignancy. Autoimmune conditions require an equal evaluation of benefit versus risk. Positively, first-generation autoimmune cohorts have already shown tolerable toxicity, but further clinical validation and follow-up needs are necessary to get the widespread adoption. Autoimmune CAR-T therapy will probably reach further than the CD19-guided B-cell depletion in its future. The next generations of regulative CAR-T cells, targeted approaches to the selection of targets, temporary mRNA-based constructs, and safety-enhanced platforms can be used to enhance the specificity of therapeutic interventions and reduce adverse effects. With the increasing development of cellular engineering technologies, CAR-T treatment can become not only a rescue therapy in case of an incurable disease but a programmable immune platform that can perform immune reprogramming. Finally, the introduction of the CAR-T therapy in the autoimmune disease is an indication of the transition between lifelong immunosuppression and strategic immune redesign. Whether this innovation will become an integral part of mainstream clinical practice will rely on larger controlled trials, uniform safety structures and strategies of equal access. When a long-term remission at a reasonable level of safety is achieved, CAR-T therapy could alter the conceptualization and treatment of autoimmune diseases in the coming decades.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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