Efficacy And Safety Of CAR-T Cell Therapy in Autoimmune Diseases: A Secondary Analysis of Emerging Clinical Evidence

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***Abstract*—Autoimmune rheumatic diseases are chronic, heterogeneous disorders driven by autoreactive B and T cells, immune dysregulation, and progressive tissue damage. Although conventional treatments such as glucocorticoids, immunosuppressants, biologics, and hematopoietic transplantation have improved disease control, many patients still experience refractory disease, relapse, incomplete B-cell depletion, and treatment-limiting toxicity. These limitations have created strong interest in CAR-T cell therapy as a more targeted strategy capable of eliminating pathogenic B-cell populations and potentially resetting immune tolerance.**

This review examines the mechanistic basis of CAR-T therapy, including receptor structure, CD19-directed targeting, immune reset, and cytokine-mediated T-cell persistence. It also summarizes manufacturing and clinical workflow considerations, recent advances in CAR-T engineering, and emerging applications in systemic and neurological autoimmune diseases. Current evidence suggests that CAR-T therapy may induce deep clinical responses in severe, treatment-resistant disease, with early reports showing remission in conditions such as SLE, systemic sclerosis, antisynthetase syndrome, ANCA-associated vasculitis, and selected neuroinflammatory disorders. At the same time, important limitations remain, including cytokine release syndrome, neurotoxicity, manufacturing complexity, high cost, and limited long-term data.

CAR-T therapy represents a promising next-generation immunotherapy for autoimmune disease, with the potential to move beyond symptom control toward durable immune reprogramming. However, broader clinical adoption will depend on stronger trial evidence, safer constructs, scalable manufacturing, and improved access.

I. INTRODUCTION

Autoimmune rheumatic diseases (ARDs) are conditions often characterized by the presence of autoreactive antibodies (autoantibodies) attacking self-organs and tissues in response to autoantigens, which can be triggered by various factors, including genetic variants, infections, and/or environmental influences. Autoimmune rheumatic diseases affect approximately 10% of the global population. These heterogeneous disorders are characterised by immune dysregulation, chronic inflammation and progressive multiorgan damage. Some of the most prevalent of these– Systemic lupus erythematosus (SLE), antisynthetase syndrome (ASS), systemic sclerosis (SSc), anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV), and rheumatoid arthritis (RA) —constitute a group of disorders with diverse clinical manifestations, triggered by an aberrant adaptive immune response. [1, 2]

These conditions arise when the body's own immune cells, specifically autoreactive B and T cells, initiate aberrant attacks on the body's own tissues through various effector mechanisms. Although very heterogeneous in their characterisation and symptoms, autoimmune diseases typically arise from a combination of genetic predisposition and environmental cofactors. Due to an often rather limited understanding and/or the complex nature of underlying molecular mechanisms, current standard approaches to treat diseases typically focus on managing diseases instead of offering cure. Therefore, the main concept to treat autoimmune disease remains to prevent autoreactive immune cells from attacking host tissues by broad (and mostly non-- targeted) immunosuppressive agents especially glucocorticoids and non-- steroidal anti-- inflammatory drugs. Subsequent research confirmed the clinical relevance of several immune targets, such as cytokines or their receptors interleukins (IL)-1, IL6, IL17, IL23, B

lymphocyte stimulator (BLyS) and interferon (IFN)-α receptors; cell surface markers (CD20, CD52), costimulatory molecules [cytotoxic T lymphocyte (CTLA)-4 and programmed cell death protein 1 (PD1)], and signalling pathways [Janus kinase (JAK) and tyrosine kinase 2 (Tyk2)]. This led to a diverse family of targeted treatments being approved by regulatory health authorities. With the emergence of new treatments, especially biological disease-modifying anti-rheumatic drugs (bDMARDs), managing these conditions has become more feasible. [1, 3, 4]

Detrimental immune cells can be more specifically blocked by therapeutic antibodies targeting B cells (by e.g., anti-- CD20 (Rituximab) or anti-- BAFF (Belimumab) antibodies), T cells (by e.g., anti-- CD52 antibodies (alemtuzumab) and proinflammatory cytokines (e.g., anti-- TNF antibodies (infliximab)) or by small molecules that mainly act on B and T cell signalling and thus function by blocking intracellular pathways (e.g., cyclosporine A or mycophenolate mofetil). Another more drastic option is to 'reset' the patient's immune system or to transplant a 'new' third-- party immune system by an autologous or allogeneic haematopoietic cell transplantation (HCT), respectively. However, this can come at the expenses of an increased treatment-- related mortality, such as severe cytopenic infections and graft-- versus-- host-- diseases in case of allogeneic HCT and in autologous HCT the resetting may only be transient. [3]

Despite therapeutic advancements with conventional approaches, including glucocorticoids, immunosuppressants, and biologics, a substantial proportion of patients experience refractory disease or relapse and continue to experience a poor response to immunosuppressing drugs, including bDMARDs, and persist in suffering from uncontrolled diseases. Furthermore, currently used immunosuppressants are often associated with serious side effects and still face challenges in providing prolonged remission from the disease. Conventional immunotherapies such as rituximab, an anti-CD20 monoclonal antibody are unfortunately not curative interventions. Alternative treatment modalities such as allosteric hematopoietic stem cell transplant (alloHSCT), although curative, are also fraught with potentially fatal complications, most notably graft versus host disease (GVHD), which is the main cause of non-relapse mortality in patients with B cell malignancies and accounts for a mortality rate between 15% to 40%. [1, 8, 10]

A critical limitation underpinning these therapeutic failures is the disability to achieve complete and sustained depletion of pathogenic B cell subsets and reservoirs. This failure allows the persistence of autoantibody-producing cells and auto- reactive immune niches, fuelling the self-perpetuating cycle of autoimmunity. This persistent therapeutic gap underscores the critical need for interventions capable of enforcing complete and sustained depletion of pathogenic B cell reservoirs, a prerequisite for disrupting the self-perpetuating cycle of autoimmunity. [8]

Chimeric antigen receptor (CAR)-T cell therapy is a brand-new cellular immunotherapy. Although commonly used as a treatment for cancers, effectiveness of CD19-directed CAR T cell therapy for eliminating CD19-expressing tumour cells demonstrated high complete remission rates and many patients experience progression-free survival of greater than 5 years. This success has motivated an extension of clinical CAR T cell therapy to the treatment of autoimmune diseases. CAR-T cell therapy has recently shown effectiveness against autoimmune disorders, particularly in refractory cases of rheumatic diseases, including SLE, ASS, and SSc. Furthermore, recent preclinical and in vitro studies using both animal- and human-derived samples have demonstrated its potential against AAV and RA.

CAR is a genetically modified transmembrane protein containing three parts: extracellular domain, transmembrane domain, and intracellular domain. These act as antigen-recognition domains and cell-activating domains that when expressed by T cells enable potent, MHC-unrestricted recognition and elimination of cells expressing the target antigen. The clinical application of CAR T cells has yielded dramatic results and advanced the treatment of haematological malignancies. In particular, the adoptive transfer of CAR T cells targeting the B cell protein CD19 is a well-established approach in oncology and is approved for the treatment of relapsed and/or refractory B cell malignancies [1, 8, 9, 10].

At present, the successively developed antigens include cluster of differentiation antigen 19 (CD19), CD138, natural killer cell surface activating receptor D (NKG2D), signaling lymphocyte activation molecule family member 7 (SLAMF7), CD38, and B

lymphocyte maturation antigen (BCMA). CAR constructs that recognize other proteins are also being developed to target other pathogenic cell populations, such as antibody-producing plasma cells. Given the functional versatility of T cells, including their capacity for tissue penetration, cytotoxicity and immunomodulatory activity, CAR T cell therapies have the potential to address the range of pathogenic mechanisms underlying autoimmune diseases. [7, 9]

Although existing clinical study has confirmed the efficacy of CAR-T therapy, most patients will develop nausea, vomiting, decreased white blood cell count, elevated transaminases, and other adverse reactions, and more severe adverse reactions even have the risk of disability and death. Cytokine release syndrome (CRS), a common toxicity during CAR-T treatment, is a systemic inflammatory response characterized by fever, rash, hypotension, tachycardia, respiratory distress, epilepsy, and organ failure, mostly caused by systemic immune disorders resulting from immunotherapeutic drugs. [7]

CAR-T cell therapies present a potentially safer, curative option. In this research paper we will look into the mechanism, evaluate efficacy, assess safety and Analyze durability of CAR-T cell therapies

II. MECHANISTIC BASIS OF CAR-T CELL THERAPY

CAR-T cell therapy is an attempt to reprogram a patient's own T cells so they can recognize disease-driving B cells with far greater precision than conventional immunosuppression. In autoimmune disease, that idea matters because the therapy is not just trying to calm the immune system down in a general way; it is aiming at the specific B-cell populations that may be sustaining auto-antibody production and immune dysregulation. CAR-T therapy is repeatedly presented as a strategy that combines antigen specificity, immune re-engineering, and the possibility of longer-lasting immune reset, which is why it has become such a big deal in autoimmune research. [1, 2, 3, 9, 11, 12]

The basic CAR-T structure has several moving parts, and each one serves a specific job. A CAR usually includes an extracellular antigen-recognition domain, a hinge or spacer region, a transmembrane segment, and intracellular signaling domains that translate antigen binding into cellular activation. The earliest versions were more limited because they relied mainly on a primary activation signal, but later generations added costimulatory domains that improved the strength, durability, and quality of the T-cell response. In practice, that evolution made CAR-T cells better able to expand, persist, and carry out their function after they encounter the target. This design evolution is one of the reasons newer CAR-T constructs are seen as more effective than earlier ones. [2, 3, 4, 9, 11]

The signaling part of the CAR is especially important because it determines what happens after the receptor binds antigen. Once the target is recognized, the intracellular activation domains transmit signals that trigger T-cell activation, proliferation, cytokine production, and cytotoxic function. The addition of costimulatory signaling domains in later CAR generations was a major upgrade because it helped the engineered cells behave more like fully activated immune effectors rather than short-lived responders. That matters in autoimmune disease because the goal is not merely a momentary reaction; the goal is a functional immune intervention that can keep working long enough to eliminate pathogenic B cells and potentially shift the immune system into a more stable state. [2, 3, 5, 9]

A major mechanistic reason CD19 CAR-T therapy has gained so much attention is that CD19 is expressed on B cells across much of their development, including the subsets that may contribute to autoimmunity. Because of that expression pattern, targeting CD19 allows the engineered T cells to recognize and remove B cells in a very focused way. The point is not to attack everything in sight; instead, the therapy tries to remove the cellular source of autoreactivity. CD19 targeting acts as a method to reduce autoreactive B-cell clones and interrupt the autoimmune process at one of its key sources. [1, 11, 12, 13]

That specificity is what makes CAR-T biologically different from broader immunosuppressive treatments. Traditional therapies may suppress B-cell activity indirectly or reduce inflammatory signaling more generally, but CAR-T can be directed toward a defined antigen. In autoimmune disease, that means the therapy has the potential to eliminate the cells most closely linked to pathogenic autoantibody production, memory responses, and disease persistence. This is especially relevant in treatment-refractory disease, where ordinary biologics or immunosuppressants may not be enough to break the cycle of immune activation.

So, the mechanistic appeal of CAR-T lies in how precisely it can focus on the B-cell compartment rather than suppressing the immune system in a blunt way. [1, 11, 12, 13]

Another key concept in the autoimmune CAR-T story is immune reset. After CD19-positive B cells are depleted, the immune system does not simply stay frozen in that depleted state forever. Instead, B cells gradually regenerate, and the post-treatment immune environment may become more balanced than before. Remission after CAR-T points towards evidence that the autoimmune process may have been interrupted deeply enough to permit a new immunologic equilibrium. In other words, CAR-T is not only a depletion strategy; it may also create conditions for immune reconstitution that are less permissive to autoreactivity. That is part of why these therapies are being described as potentially disease-modifying rather than just symptom-controlling. [1, 12]

This idea of immune resetting is closely tied to observations of clinical remission. In the autoimmune literature, remission after CAR-T is often interpreted as more than just temporary improvement; it is viewed as a sign that the pathogenic immune network has been substantially altered. The therapy's effect on B-cell depletion followed by regeneration suggests that the body may return with a changed immune architecture, and that changed architecture may be less prone to the same autoreactive behavior. Of course, the exact mechanism is still being explored, but the evidence supports the idea that CAR-T can produce a deeper immunological effect than standard B-cell depletion alone. It hints at possible durable benefits rather than short-lived control. [11, 12, 13]

Cytokine signaling and T-cell persistence are also central to how CAR-T therapy works. Once activated, CAR-T cells expand and produce signaling molecules that amplify the immune response, and that expansion is part of what gives the therapy its power. At the same time, the same biology can contribute to toxicity if activation becomes excessive. So, the therapeutic window is a balancing act: Enough cytokine-driven expansion and persistence to achieve meaningful B-cell depletion is needed, but not so much inflammatory activity that it becomes harmful. This link between persistence and response is a recurring theme in CAR-T research, and it is one reason signaling design remains such an important engineering problem. Persistence matters because CAR-T cells do not need to act only in the first few hours after infusion. Their value comes from remaining active long enough to continue recognizing target cells, expand in the body, and maintain pressure on the disease-driving B-cell population. That prolonged activity is one reason the therapy has been discussed as potentially capable of inducing long-term remission. But persistence also makes safety more complicated, since a stronger and longer-lived immune response can raise the risk of inflammatory adverse events. So again, the same mechanism that gives CAR-T its promise also creates its main challenges. [2, 5, 9, 13]

CAR-T cells are engineered with modular receptor designs that improve antigen recognition and intracellular signaling, they are often aimed at CD19 to eliminate autoreactive B cells, they can produce an immune reset through B-cell depletion and regeneration, and their cytokine-driven expansion and persistence help explain both their effectiveness and their toxicity profile. That combination is why CAR-T has moved from a cancer-focused platform to a serious candidate for autoimmune disease treatment. The science is still developing, but the basic mechanism already gives a very clear explanation of why researchers think this approach may be able to do what conventional therapies sometimes cannot. [1, 2, 3, 11, 12, 13]

III. MANUFACTURING AND CLINICAL WORKFLOW

CAR-T therapy is not just a biological idea; it is also a complicated production and clinical process that has to work reliably from the moment cells are collected to the moment the patient is monitored after infusion. The whole workflow starts with obtaining T cells from the patient, then modifying and expanding them, and finally administering them under controlled clinical conditions with close follow-up afterward. In other words, the therapy depends as much on logistics and manufacturing precision as it does on immunology. [1, 7, 11, 12, 13]

The first step in production is leukapheresis, which is used to collect T cells from the patient's peripheral blood. This collection stage matters because CAR-T is generally an autologous therapy, meaning the patient's own cells are harvested and later returned after engineering. The collected cells are transferred into a manufacturing process where the CAR gene is

introduced, commonly through viral gene transfer systems or other vector-based approaches, so the T cells can express the desired receptor. After that, the cells are expanded under controlled conditions until enough viable product is available for treatment. Quality control is a major part of this production phase because the final product has to be safe, viable, and correctly engineered before it reaches the patient. Checks such as confirming the CAR construct, verifying expression, and ensuring the product meets the required specifications before infusion are also important. This is not a minor technical step; it is what separates a clinically usable therapy from a cell product that could fail or cause harm. The overall manufacturing process is therefore a combination of cell collection, genetic modification, controlled expansion, and strict release testing. [7, 8, 11, 13]

Once the product is ready, the clinical workflow begins with preconditioning, often called lymphodepleting chemotherapy. This step is widely described as important because it creates a more favorable environment for the infused CAR-T cells to expand and function. In the modeling and clinical literature, preconditioning is not just about reducing competing immune cells; it can also influence whether remission is achieved at all. That makes the timing and design of the conditioning regimen a meaningful part of the treatment plan rather than a routine add-on. [2, 11, 12]

Bridging therapy may also be used when disease control is needed while the CAR-T product is still being manufactured. This becomes especially relevant because the production timeline can be long enough that the patient's condition may worsen before infusion. After preconditioning, the CAR-T product is infused according to protocol, and the patient is then followed closely because treatment responses and toxicities can emerge soon after administration. The workflow after infusion usually includes structured monitoring for adverse events, particularly cytokine release syndrome and neurotoxicity, since these are among the main concerns in the early post-infusion period. Monitoring is not just a formality; it is a core part of the clinical process because CAR-T can trigger strong immune activation after infusion. Patients may need to stay near the treatment center for a defined period, and some protocols include restrictions on travel or driving because toxicities can appear after the procedure. Recent discussions about post-infusion care show that monitoring requirements can be burdensome, but they also reflect the seriousness of the safety issues that come with this therapy. So, the administration phase is really a managed sequence of preparation, infusion, and surveillance. [1, 5, 11, 13]

Despite its promise, CAR-T manufacturing is still limited by cost, time, and scalability. Autologous production is expensive because each treatment is individualized, and that makes large-scale rollout difficult. Studies on industrialization and cost reduction suggest that automation, closed systems, and improved manufacturing efficiency can lower personnel needs, reduce cleanroom demands, and shrink the spatial footprint of production. Even so, the therapy remains resource-intensive, which is one reason accessibility is still limited in many settings. Scalability is another major challenge because the demand for treatment can outpace the ability of current facilities to produce cells quickly enough. The problem is not only technical but also structural: the more personalized the product, the harder it is to manufacture at high volume without increasing cost. Some of the newer literature argues that automation, decentralized manufacturing, and alternative production approaches may help improve access, but these solutions still need time and infrastructure to mature. For now, the field is advancing, but the gap between scientific success and practical availability remains very real. [6, 10, 11, 12]

So, the workflow of CAR-T therapy is a chain of dependent steps: cell collection, gene transfer, expansion, quality control, preconditioning, infusion, and close monitoring. If any one of those steps becomes delayed or poorly executed, the overall treatment can be affected. That is why manufacturing and clinical administration are such central topics in CAR-T research. The biology is important, but the real-world success of the therapy depends on whether the whole pipeline can be carried out safely, consistently, and at a cost that more patients can actually bear. [7, 11, 13]

IV. ADVANCEMENTS IN CAR-T TECHNOLOGIES

CAR-T technology has evolved from a simple first-generation design into a much broader engineering platform aimed at improving activity, durability, precision, and safety. The basic CAR-T concept

works, but the first versions were limited by weak persistence, incomplete activation, and toxicity concerns that pushed researchers to redesign the cells in smarter ways. In the newer literature, the field is moving toward constructs that are more effective against resistant disease while also being safer and more adaptable in real-world clinical use. [1, 3, 7, 11, 12]

The progression across CAR-T generations is one of the most visible signs of this development. Early CARs mainly provided antigen recognition plus a basic activation signal, but later generations added costimulatory domains that improved expansion, persistence, memory formation, and overall functional activity. Some of the newer "armored" or enhanced CAR concepts are described as reducing systemic toxicity while simultaneously improving anti-tumor or anti-disease performance, which shows how engineering has shifted from simple activation toward performance tuning. The field keeps trying to make CAR-T cells stronger without making them recklessly attack cells. [2, 3, 5, 7, 11]

A big reason these changes matter is persistence. If CAR-T cells expand well but fade too quickly, they may not give any long-term benefits. Later-generation CARs were designed to last longer, stay active in the body, and keep exerting pressure on the target cells over time. That persistence can improve therapeutic effect, but it also creates a need for better control because a more durable immune attack can increase inflammatory side effects. So, the engineering goal is not just power; it is sustained, controlled power. [2, 5, 7, 12]

Multi-target and bi-specific CAR-T approaches are a response to one of the main reasons CAR-T can fail: antigen escape. If therapy focuses on only one antigen, disease cells may survive by losing or downregulating that target. CD19/20, CD19/22, and other multispecific constructs as ways to reduce this escape problem by making it harder for the target population to evade recognition. In other words, when the CAR can recognize more than one antigen, the disease has fewer ways to sneak around it. These multi-target strategies are attractive not only because they reduce escape, but also because they may improve therapeutic precision. A properly designed dual-target or tandem CAR can be built to better discriminate between intended and unintended targets, and logic-gated designs can make recognition more selective. The idea is to keep the therapy focused on pathogenic cells while minimizing off-target activity. The ideal target combination, construct design, and durability of response are still under active investigation, so this area remains promising rather than fully settled. [5, 7, 12, 13]

Safety-focused innovations are another major part of the technology shift. Humanized CARs are designed to reduce the chance that the immune system will see the engineered receptor as foreign, which can help improve compatibility and potentially reduce unwanted immune reactions. This idea fits well with the broader trend in CAR-T engineering: the more biologically "natural" the construct looks to the body, the easier it may be to keep the therapy effective without provoking unnecessary immune complications. Humanization is therefore less about cosmetic design and more about improving long-term usability. [3, 7, 11]

Transient CAR-T cells are another safety-oriented approach. Instead of staying active for a long time, these cells are designed to operate for a shorter period, which can be useful when the main concern is limiting prolonged toxicity. This strategy is especially relevant when researchers want a controlled effect rather than permanent immune alteration. It does the therapeutic work, but does not stay activated in the body forever if that creates more risk than benefit. [3, 7, 13]

CAR-T regulatory cells, or CAR T-regs, represent a different and interesting safety direction. Instead of being built to destroy target cells, these engineered regulatory cells are intended to preserve or restore immune tolerance. These are potentially useful in autoimmune disease and transplantation, with a strong emphasis on purity, stability, and preserving cellular identity after infusion. The cells have to remain regulatory and not drift into something less predictable. [6, 12, 13]

These innovations show that CAR-T is no longer just a single therapy platform; it is a flexible engineering space. The field is now exploring ways to make CAR-T cells more persistent, more specific, less toxic, and in some cases even more regulatory than destructive. That matters a lot for autoimmune disease, because the ideal therapy there is not simply a stronger immune weapon, but a smarter one that can correct the immune problem without creating a new one. The trajectory of the technology suggests exactly that kind of shift. [2, 5, 7, 12, 13]

V. CLINICAL APPLICATIONS IN AUTOIMMUNE DISEASES

CAR-T therapy is starting to look especially important in autoimmune disease because it can target the B-cell compartment more directly than many standard treatments. Across the studies, the strongest signal is in treatment-refractory disease, where the usual biologics or immunosuppressants may not fully control inflammation or prevent relapse. CAR-T shows evidence of reduced disease activity by removing autoreactive B cells and potentially resetting the immune system rather than only suppressing symptoms. [1, 2, 3]

In systemic autoimmune diseases such as SLE, RA, and SSc, the main rationale for CAR-T use is that these diseases often involve persistent B-cell-driven immune dysfunction. CD19-directed CAR-T can lead to marked clinical improvement in severe autoimmune cases, including reduction in autoantibody-related activity and broader immune rebalancing. The case-based evidence is still limited, but the pattern is notable: when disease is difficult to control with standard therapy, CAR-T appears capable of producing responses that are deeper than what is usually seen with routine biologics. SLE is one of the clearest examples of where CAR-T has generated excitement. The remission after CD19 CAR-T demonstrates that B-cell depletion followed by reconstitution may interrupt the autoreactive cycle. That is important because lupus is often characterized by recurrent immune activation, and the possibility of a more durable remission makes CAR-T different from therapies that require ongoing repeated dosing. In simple terms, the appeal is not just that symptoms improve, but that the disease mechanism itself may be pushed into a quieter state. RA and SSc are also discussed as potential targets for CAR-T-based intervention, especially in severe or refractory settings. In these diseases, the concern is not simply inflammation but long-term immune-driven tissue damage, which is why a more decisive B-cell-directed intervention is attractive. The available reports do not yet establish CAR-T as a routine option, but they do suggest that the same mechanism used in hematologic malignancy may be relevant when pathogenic B cells are central to autoimmune progression. For rare and severe conditions such as ANCA-associated vasculitis, antisynthetase syndrome, and idiopathic inflammatory myopathies, the literature is even more limited but still encouraging. These are the kinds of diseases where patients may be treatment-refractory, meaning standard regimens have failed or are not tolerated well enough to sustain control. In that setting, CAR-T is being discussed as a possible rescue approach, especially because many of these disorders also involve B-cell-mediated autoimmunity and persistent immune activation. [1, 11, 12, 13]

The evidence base in these rare disorders is still emerging, so it is best viewed as an early clinical signal rather than established proof. Still, the reports point to meaningful improvement in severe refractory cases, and that matters because it suggests the approach may extend beyond lupus into a wider group of autoimmune diseases. The common thread is that when disease biology seems to depend on pathogenic B cells, CAR-T may be able to do more than conventional agents that only blunt immune pathways. [1, 11, 12]

A fair comparison between CAR-T and biologics is that biologics are currently much more established, easier to administer, and better studied in standard autoimmune care. But CAR-T has a different kind of promise: it may produce remission with fewer repeated treatments and a deeper biological reset. That is a major conceptual advantage, especially in patients who cycle through multiple biologics without lasting benefit. So, the comparison is not really between two identical strategies; it is between ongoing immune suppression and a more targeted attempt at immune reprogramming. [2, 9, 11]

At the same time, current data still have important limitations. The evidence is mostly based on small studies, case reports, early trials, and translational reasoning borrowed partly from oncology. That means we still do not know enough about long-term durability, relapse rates over many years, the best patient selection criteria, or whether the apparent benefits will hold across broader populations. So, while the remission signal is exciting, the data are not yet strong enough to say CAR-T is ready to replace biologics in routine autoimmune care. [1, 11, 12, 13]

The clinical picture is promising but still early. CAR-T seems most compelling in severe, refractory autoimmune diseases where standard treatment has failed and where B-cell-driven pathology is clearly involved. The strongest advantage so far is the possibility of deep and durable remission, but the

strongest limitation is the modest size and early stage of the evidence base. That combination makes CAR-T one of the most exciting developments in autoimmune medicine, while still leaving plenty of unanswered questions.

VI. CAR-T IN NEUROLOGICAL AUTOIMMUNE DISORDERS

CAR-T therapy is being explored in neurological autoimmunity because several central nervous system disorders appear to be driven, at least in part, by pathogenic B cells and antibody-producing cells. Currently monoclonal antibody therapies can help many patients, but they may not fully produce drug-free remission, which is why cell-based therapies like CAR-T are being investigated as a deeper immune intervention. The field is still early, but the clinical signal is strong enough that researchers are now discussing MS, NMOSD, MOGAD, and autoimmune encephalitis as realistic targets rather than distant possibilities. [2, 4, 13, 14]

In multiple sclerosis and neuromyelitis Optica spectrum disorder, B cells are important because they help sustain the inflammatory and antibody-mediated processes that damage the CNS. Monoclonal antibodies against B cells have already shown safety and efficacy in MS and AQP4-IgG positive NMOSD, but those therapies do not necessarily lead to drug-free remission. That is where CAR-T, by more deeply depleting the relevant B-cell compartment, may offer a more durable reset than conventional antibody-based suppression. [1, 6, 11, 12]

Some pathogenic B-cell populations may be difficult to reach with standard monoclonal antibodies or may persist in protected immune niches. The rationale for CAR-T in NMOSD relates to the roles of B cells, antibody production, and plasma cells in disease pathophysiology, which makes the biological case for a cell-based strategy especially strong. So, the central idea is not just better suppression, but more complete removal of the disease-driving cells. [4, 6, 11, 13, 14]

Clinical evidence in CNS diseases is still limited, but it is growing. The systematic review reports on ongoing phase I study show safety and benefit signals for anti-BCMA CAR T cells in patients with AQP4-IgG seropositive NMOSD, and it also notes case reports in progressive MS and stiff-person syndrome treated with anti-CD19 CAR T cells with manageable safety profiles. In addition, recruitment has begun for larger MS studies, and a basket study is underway for antibody-associated inflammatory diseases including MOGAD. The field is no longer purely theoretical; early human evidence is already shaping the next stage of research. [8, 11, 12, 13, 14]

CAR-T is also being investigated in MOGAD and autoimmune encephalitis because these disorders can be antibody-mediated and may therefore respond to deeper B-cell or plasma-cell targeting. Promising preclinical data in NMDA receptor antibody autoimmune encephalitis suggests that CAR-T could address CNS-directed autoimmunity that is not well controlled by existing approaches. [1, 4, 8, 13, 14]

The potential benefits are fairly straightforward: stronger depletion of pathogenic immune cells, possible drug-free remission, and a treatment response that may be more durable than repeated monoclonal antibody dosing. Evidence repeatedly contrasts this with current therapy, which can work but often requires continued administration and may not fully stop disease activity. If CAR-T performs as hoped, it could become especially valuable for refractory patients who have not responded adequately to standard B-cell therapies. That is why the early case experiences have attracted so much attention. [1, 4, 14]

At the same time, targeting the CNS comes with real challenges. One issue is the blood-brain barrier, which makes delivery and immune access more complicated than in many peripheral diseases. Another issue is neurotoxicity, including ICANS and other neurotoxic syndromes associated with CAR-T therapy. The neurological safety research makes clear that neurotoxicity is a serious concern, and that close monitoring is essential whenever CAR-T is used in disorders involving the nervous system. So, the promise is real, but the margin for error is small. [5, 7, 9, 10]

The evidence base is also still thin. Even though the case reports and early trials are promising, case review points that there is still minimal evidence overall for benefits in CNS-directed autoimmunity, and that controlled multicentre trials are needed. At this stage, the best interpretation is that CAR-T is a highly promising investigational strategy for neurological autoimmune disorders, but not yet a settled clinical standard. CAR-T in neurological autoimmunity is exciting because it addresses a real gap in current care: the need for therapies that can go beyond symptom

control and possibly produce durable immune reset. The same features that make CAR-T attractive in systemic autoimmune disease also apply here, but the nervous system adds extra complexity through delivery barriers and neurotoxicity risks. This section of the field is quite active right now. [1, 4, 6, 8, 11, 12, 13, 14]

VII. EFFICACY AND CLINICAL OUTCOMES

CAR-T therapy has moved from a purely experimental concept to a clinically credible strategy because early studies have shown that it can induce deep responses in severe autoimmune disease. The main efficacy signal is strongest in treatment-refractory patients, where conventional biologics or immunosuppressants had been insufficient and CAR-T was associated with marked clinical improvement, B-cell depletion, and in some cases remission. [1, 2, 3, 11, 12, 13, 14]

The clinical trial evidence is still early, but it is becoming more structured. Several papers describe case reports, first-in-human experiences, early phase studies, and basket-style investigations across different autoimmune phenotypes. In rheumatic autoimmune disease, the published work emphasizes CD19-directed approaches and the use of standard trial endpoints such as disease activity scores, serologic markers, and clinical remission criteria. In neurological autoimmunity, the evidence includes initial safety and efficacy signals in NMOSD, progressive MS, and antibody-associated inflammatory diseases. The consistent theme is that the populations studied so far are usually small, highly selected, and often heavily pre-treated, which is typical for an emerging therapy in a refractory setting. [1, 4, 6, 8]

Study design matters here because the current evidence base is not dominated by large randomized trials. Instead, it consists of early clinical reports, proof-of-concept cohorts, and translational studies that connect immunologic mechanisms to clinical outcomes. That means the conclusions have to be interpreted carefully. Even so, the findings are notable because they often show rapid B-cell depletion followed by clinical improvement, which supports the mechanistic hypothesis that CAR-T may interrupt the autoreactive cycle more completely than conventional biologics. The data are still limited, but they are directionally consistent across multiple disease settings. [8, 11, 12, 13]

One of the most important outcome questions is durability. Short-term remission can happen after many immunotherapies, but the real issue is whether the response lasts after treatment is finished. There is a possibility of sustained immune reset, meaning that the disease state may remain quiet even after B-cell reconstitution begins. This is one of the most striking differences from regular antibody therapy, which often needs to be repeated or maintained indefinitely. CAR-T is therefore being studied not only for immediate disease control but also for the potential to generate a durable remission phenotype. [1, 2, 3, 11, 12, 13, 14]

That said, durability is not yet fully established. The available studies do not provide long-term population-level relapse rates across broad autoimmune cohorts, so the field still cannot say with confidence how many patients will remain in remission after one, two, or five years. It does, however, suggest that some patients have maintained improvement after CAR-T-induced depletion and reconstitution, which supports the idea of a sustained immunologic reset. The key unanswered question is whether this response will remain stable over time in larger and more diverse patient groups. [1, 4, 8, 11, 12, 13, 14]

From a translational perspective, oncology has provided the conceptual and technical foundation for this work. CAR-T cells were first developed and optimized in hematologic malignancies, where they demonstrated the ability to expand, persist, and eradicate target cells through antigen-specific cytotoxicity. That experience gave researchers a detailed framework for understanding signaling domains, costimulatory engineering, cytokine release, persistence, and toxicity management. Autoimmune disease research is now borrowing that framework and adapting it to a different biological goal: not eliminating malignant cells, but removing pathogenic B-cell clones and potentially restoring tolerance. [9, 11, 12, 13]

The oncology-to-autoimmunity translation is powerful, but it is not perfect. Cancer targets and autoimmune targets are not the same, and the clinical goals are different as well. In oncology, the aim is often maximal cytotoxicity against a malignant population, whereas in autoimmunity the goal is controlled elimination of autoreactive B cells without unnecessary tissue damage or prolonged immune

suppression. This means that efficacy must always be interpreted alongside safety, manufacturing feasibility, and the possibility of immune reconstitution that preserves normal host defense. So, while oncology offers strong proof of principle, it does not automatically solve the autoimmune problem. [2, 3, 5, 8]

The limitations of extrapolation are especially important when discussing remission. In cancer, tumor burden and response can be measured with established oncology endpoints, but autoimmune disease often involves more heterogeneous clinical manifestations, fluctuating disease activity, and different organ-specific outcomes. A remission signal in lupus may not translate directly to myositis, vasculitis, or neuroinflammatory disease. This is why the autoimmune CAR-T literature keeps emphasizing the need for disease-specific studies, longer observation, and careful patient selection. The same platform may work across diseases, but the expected outcome cannot simply be copied from one condition to another. [1, 4, 6, 8, 11, 12, 13, 14]

Another translational issue is that the oncology experience also revealed important toxicity trade-offs, particularly cytokine release syndrome and neurotoxicity. Those outcomes matter in autoimmunity too because they influence the risk-benefit calculation. A treatment can be biologically effective yet still fail clinically if toxicity is excessive or if the monitoring burden becomes too heavy for routine use. So, efficacy in this field is not just about remission rates; it is about whether the therapy can produce that remission with a manageable safety profile and with reasonable feasibility in real-world practice. [5, 7, 8, 9,]

Taken together, the efficacy literature supports a cautious but genuinely optimistic interpretation. CAR-T has shown that it can produce deep clinical responses, including remission-like states, in severe autoimmune disease. The strongest current signals come from refractory disease, B-cell-driven conditions, and early studies that show sustained depletion followed by immune reconstitution. What remains missing is large-scale confirmation, standardized endpoints, and multi-year follow-up that would tell us whether these early results can hold up across broader populations. Even so, the current evidence is strong enough to justify why CAR-T is now considered one of the most promising translational advances in autoimmune therapy. [1, 2, 3, 4]

VIII. SAFETY PROFILE AND TOXICITY ANALYSIS

The safety profile of CAR-T therapy is one of the most important reasons the field is being studied so carefully. The therapy can be highly effective, but its immune activation is strong enough to cause systemic inflammatory toxicity, neurological complications, and delayed adverse events that require active surveillance. In the autoimmune setting, these risks matter even more because the target population may not tolerate the same degree of toxicity that is sometimes accepted in life-threatening malignancy, so the safety bar has to be very high. [1, 2, 3]

Cytokine release syndrome, or CRS, is one of the best-known toxicities associated with CAR-T. Mechanistically, it reflects a rapid and amplified immune response after CAR engagement, with high levels of inflammatory cytokines driving fever, fatigue, hypotension, and in more serious cases, organ dysfunction. The post-marketing and toxicity literature consistently shows that CRS is among the most frequent adverse events after infusion, and it often appears early, particularly in the first days after treatment. That timing is clinically important because it means patients need close observation soon after infusion, not just later in follow-up. The clinical presentation of CRS can range from mild, flu-like symptoms to severe hemodynamic instability. Fever is usually the earliest and most common sign, but the syndrome can progress to hypotension, hypoxia, and multiorgan stress if the inflammatory cascade becomes intense. Grading systems are used to standardize severity assessment, and this is important because the clinical response depends on how serious the event is. The literature on toxicity management emphasizes that CRS is not just an adverse event to note in passing; it is a core complication that shapes monitoring protocols, hospitalization decisions, and treatment planning. [5, 7, 8, 9, 10]

Management strategies generally focus on early recognition, supportive care, and targeted cytokine blockade when needed. The broader CAR-T toxicity literature highlights the importance of structured monitoring because many CRS cases cluster in the

early post-infusion window. In practical terms, that means frequent vital sign checks, symptom surveillance, and readiness to treat escalating inflammation before it becomes dangerous. In real-world post-marketing data, CRS remains one of the dominant safety signals, which is why it continues to drive most of the concern around CAR-T deployment outside oncology as well. Neurological toxicity, especially immune effector cell-associated neurotoxicity syndrome or ICANS, is the other major acute safety issue. The pathophysiology is still being worked out, but the evidence points to neuroinflammation, blood-brain barrier dysfunction, endothelial activation, and cytokine-mediated effects as likely contributors. Clinically, ICANS can include confusion, reduced attention, aphasia, tremor, seizures, and in severe cases, decreased consciousness. Because the neurologic presentation can evolve quickly, it is treated as a serious safety endpoint rather than a minor side effect. The risk factors for neurotoxicity are important because they help identify who needs the closest observation. Post-marketing surveillance has shown that neurotoxicity is frequently reported together with CRS, and some products appear to carry stronger neurotoxicity signals than others. In addition, more intense immune activation, older age, or underlying disease features may increase vulnerability to neurologic complications. In the CNS-autoimmunity setting, this issue becomes especially relevant because the patients being treated already have neurologic disease, so distinguishing therapy-related toxicity from baseline disease activity can be tricky. [9, 10, 11, 12, 13, 14]

Monitoring after infusion remains a major challenge because both CRS and ICANS can emerge early, but delayed events also occur. The post-marketing data shows that most CRS and neurotoxicity events appear within the first 10 days, yet other studies emphasize that late adverse events can still arise months or even years later. This means the safety burden does not disappear once the early infusion period is over. Instead, CAR-T requires an immediate high-intensity monitoring phase followed by extended follow-up for infections, cytopenias, cardiovascular issues, dermatologic events, and other delayed toxicities. [11, 12, 13]

The long-term safety literature also shows why post-marketing surveillance matters. FAERS analyses and cohort data reveal that beyond the classic CRS and ICANS signals, there are emerging product-specific and disease-specific adverse event patterns, including infections, autoimmune complications, and organ-specific toxicities. Some studies suggest that late adverse events can remain clinically relevant long after infusion, which supports the idea that CAR-T safety cannot be judged only by short hospital-based observation. In that sense, the field is moving from acute toxicity management to a broader model of pharmacovigilance. Another practical issue is that patient monitoring is resource-intensive. CAR-T programs need protocols for rapid symptom recognition, neurologic assessment, infection surveillance, and laboratory follow-up, and this can be demanding even in experienced centers. For autoimmune disease patients, the bar may be even higher because the treatment is being considered outside the original oncology context, where risk tolerance and expected benefit are different. So, the real challenge is not only knowing how to treat toxicity once it occurs, but also designing systems that detect it early enough to prevent severe outcomes. [6, 7, 8, 14]

The safety profile of CAR-T is best understood as manageable but nontrivial. CRS and ICANS remain the main acute toxicities, while late infectious, neurologic, hematologic, dermatologic, and autoimmune adverse events remind us that follow-up must continue well beyond the infusion window. The current research suggests that safety has improved through better grading, better management protocols, and better post-marketing awareness, but it also makes clear that CAR-T still requires careful selection, close monitoring, and a strong clinical infrastructure to be used responsibly. [5, 7, 8, 9, 10, 11, 12, 13, 14]

IX. CHALLENGES AND LIMITATIONS

Despite the excitement around CAR-T therapy, it is clear that the field is still facing major scientific, practical, and regulatory barriers. The central issue is that the technology is promising enough to justify rapid development, but not yet mature enough to be treated as a fully settled therapy for autoimmune disease. That gap between promise and readiness is exactly where most of the current limitations sit.

One of the biggest scientific limitations is the small size of the autoimmune evidence base. Most published data come from case reports, small cohorts, early-

phase studies, or proof-of-concept experiences rather than large randomized controlled trials. That matters because strong clinical claims are difficult to make when the patient numbers are limited and the populations are highly selected. In practical terms, we still do not have enough data to know how broadly the results will generalize across different autoimmune diseases, disease severities, age groups, or prior treatment histories. A related problem is the lack of long-term follow-up. The early results are encouraging, especially with respect to B-cell depletion and remission-like responses, but autoimmune disease is often chronic, relapsing, and heterogeneous. That means short-term improvement is not enough to establish durable benefits. It is repeatedly seen that we still need better evidence on relapse rates, immune reconstitution, and the persistence of remission over years rather than months. Without that longer horizon, it is hard to know whether CAR-T truly changes the natural history of autoimmune disease or simply delays relapse. [1, 2, 3, 4, 6, 8]

The scientific challenge is also partly methodological. Different studies use different targets, different conditioning regimens, different disease endpoints, and different follow-up schedules. That makes cross-study comparison difficult and slows down consensus building. One paper may report remission using clinical symptoms and serologies, while another focuses more heavily on immune cell kinetics or adverse events. So even when the findings are positive, the field still lacks the kind of uniform evidence framework that would make it easy to compare therapies across centers and disease types. [1, 4, 6, 8]

Manufacturing is another major barrier. CAR-T remains an expensive, individualized therapy because most products are still autologous and must be manufactured separately for each patient. The workflow involves cell collection, genetic modification, expansion, quality testing, and controlled release, all of which take time and money. Production and industrialization emphasize that these steps require specialized infrastructure and trained personnel, which pushes the therapy far beyond the simplicity of standard drug administration. [7, 10, 11, 12, 13]

Time is a practical limitation as well. In aggressive disease, patients may need treatment sooner than the manufacturing pipeline can provide it. Even with bridging therapy, the delay between leukapheresis and infusion can be clinically significant. That means CAR-T is not just a therapy problem; it is a timing problem. If the disease worsens while the cells are being produced, the therapeutic window may narrow before the product even reaches the patient. Scalability and accessibility are equally serious concerns. Because production is individualized, the current model does not scale easily to large populations. Even if the biology works extremely well, access can remain limited by cost, hospital capability, regulatory oversight, and geographic availability. This is especially important in autoimmune disease, where the patient population is broader than in highly specialized oncology indications and the demand for treatment could eventually be much larger. So, the question is not only whether CAR-T works, but whether it can be delivered widely enough to matter in routine care. Economic barriers also shape who can realistically receive the therapy. The combination of expensive cell manufacturing, prolonged monitoring, specialized clinical staffing, and management of acute toxicities creates a financial burden that is difficult to ignore. Even if CAR-T becomes technically successful, it may still remain concentrated in wealthier health systems or major urban centers. That would leave many patients without practical access to a therapy that could potentially help them. That creates a tension between scientific progress and equitable implementation, which is one of the biggest real-world problems in advanced biologic therapy. [6, 7, 10, 11, 12, 13]

The ethical and regulatory challenges are just as important. CAR-T can produce deep responses, but it can also cause serious toxicities such as CRS and ICANS, so the risk-benefit balance must be justified very carefully, especially when the therapy is being used outside life-threatening cancer. Regulators therefore have to think not only about biological plausibility but also about whether the available evidence is strong enough for approval in a new disease category. Since autoimmune disease patients may already be vulnerable to cumulative immunosuppression, the decision to use CAR-T must be made with a careful eye on both safety and necessity. [5, 7, 8, 14]

Approval pathways are still evolving, which adds another layer of complexity. Autoimmune indications

require disease-specific trial designs, meaningful endpoints, and convincing evidence of durability and safety before they can move toward routine authorization. That process can be slow, especially when the clinical evidence is still being built through small studies and early reports. As a result, CAR-T may continue to grow first in academic and highly specialized settings before it becomes more broadly regulated for autoimmune use. [1, 11, 12, 13, 14]

The limitations of CAR-T are not signs that the therapy is failing; rather, they are signs that it is still transitioning from breakthrough science to real-world medicine. The current evidence is exciting but incomplete, the manufacturing process is powerful but expensive, and the ethical questions are still unfolding alongside the technology itself. That combination is exactly why CAR-T remains one of the most important and most carefully watched developments in autoimmune therapy.

X. FUTURE DIRECTIONS AND CONCLUSION

The future of CAR-T therapy in autoimmune disease looks focused on making the platform more precise, safer, and easier to use in everyday care. Researchers are exploring new targets beyond CD19, improved receptor designs, and approaches that can better match therapy to the biology of each patient's disease. At the same time, ongoing trials are testing whether these advances can produce more durable remissions with fewer toxicities and better long-term control. Another important direction is combination treatment. CAR-T may eventually be used alongside stem cell transplantation, bridging therapies, or other immune-modifying strategies to improve depth and durability of response. This kind of hybrid approach fits well with precision medicine, since different autoimmune diseases do not behave the same way and may need different treatment sequences. The goal is not just stronger therapy, but smarter therapy that can be tailored to disease mechanism, severity, and patient risk. At the same time, important research gaps remain. The field still needs larger trials, longer follow-up, standardized endpoints, and better evidence across a wider range of autoimmune diseases. Questions about relapse, durability, safety in diverse populations, and the best patient selection criteria are still open. Manufacturing cost and access also remain major obstacles, so future progress has to happen in both the laboratory and the clinic. CAR-T has moved from an exciting experimental idea to a serious candidate for redefining autoimmune treatment. Its main promise is the possibility of deep immune reset rather than temporary suppression, and that makes it one of the most interesting developments in modern immunotherapy. Even so, the field is still early, and the next phase will depend on whether researchers can turn early success into a practical and scalable treatment model.

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