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CAR-T Cell Therapy in Systemic Lupus Erythematosus: Mechanisms, Toxicities, and Management Strategies

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Abstract:

Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionized cancer treatment, particularly in hematologic malignancies, by genetically modifying a patient's T cells to specifically target and eliminate tumor cells. This groundbreaking approach has led to remarkable clinical outcomes, especially in patients with refractory or relapsed cancers. Over the past few years, CAR-T cell therapy has also been explored for the treatment of autoimmune diseases, including systemic lupus erythematosus (SLE), a complex and chronic autoimmune condition characterized by widespread inflammation and tissue damage. While the potential for CAR-T therapy in autoimmune disorders is significant, its application is accompanied by a range of toxicities that can pose substantial risks to patients, complicating its clinical use. These toxicities arise due to the powerful immune activation induced by CAR-T cells, which can affect various organ systems and result in serious side effects. This paper reviews the mechanisms behind CAR-T therapy-related toxicities, focusing on key adverse events such as Cytokine Release Syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), hematologic and cellular toxicities, as well as concerns regarding immunogenicity and oncogenic risks. Understanding these toxicities is critical to maximizing the therapeutic benefit of CAR-T therapy while minimizing potential harm to patients.

Keywords: Systemic lupus erythematosus (SLE), CAR-T cell therapy toxicities, Cytokine Release Syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

Introduction

Systemic Lupus Erythematosus (SLE) is a complex and debilitating autoimmune disease that affects approximately 5 million people worldwide. Characterized by immune system dysregulation, SLE leads to the production of autoantibodies, causing widespread inflammation and damage to various organs (1-3). The disease course is unpredictable, with periods of flare-ups and remissions, and it is often associated with high morbidity and mortality. Traditional treatments for SLE, including corticosteroids, immunosuppressive drugs, and biologics such as rituximab and belimumab, aim to control immune hyperactivity but often come with significant side effects like increased infection risk and reduced patient quality of life (4). As a result,

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there is a growing need for novel therapies that can more precisely target immune dysregulation while minimizing adverse effects (5).

CAR-T cell therapy, a promising approach originally developed for cancer treatment, is emerging as a potential therapeutic strategy for autoimmune diseases like SLE. This therapy involves modifying a patient's T cells to express a chimeric antigen receptor (6), which allows the T cells to specifically recognize and target autoantibody-producing B cells, a hallmark of SLE (7). Although still in its early stages, CAR-T therapy has shown promise in preclinical and early clinical studies.

The application of CAR-T therapy in the treatment of autoimmune diseases, particularly in conditions like SLE, represents a paradigm shift in how autoimmune disorders could be managed in the future. In SLE, B cells and their resultant autoantibodies play a critical role in disease pathogenesis (8). By engineering CAR-T cells to target specific markers on autoreactive B cells, such as CD19 or CD20, researchers aim to directly eliminate these pathogenic B cells, potentially offering a more targeted approach compared to traditional immunosuppressive therapies (9).

However, CAR-T therapy is not without its challenges. The engineering process, which involves ex vivo manipulation of T cells, can result in a range of toxicities. These toxicities are particularly concerning in autoimmune disease contexts, where immune dysregulation is already at play (10). Thus, understanding the mechanisms behind these adverse events is crucial for advancing the clinical application of CAR-T therapy and mitigating the risks associated with its use in autoimmune disorders (11).

In this paper, we explore the complexities of CAR-T therapy in the treatment of autoimmune diseases, focusing on its potential application in SLE. Specifically, we examine the mechanisms of toxicities like CRS, Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), and other adverse effects related to CAR-T therapy. We also delve into strategies to mitigate these risks, discuss recent clinical advancements, and explore ongoing research that holds promise for improving the safety and efficacy of CAR-T therapy in autoimmune diseases.

CAR-T Cell Therapy: Mechanisms and Development

The development of CAR-T therapy has undergone several phases, with key innovations improving the safety and efficacy of this treatment. Initially, the first generation of CARs utilized a simple extracellular single-chain variable fragment (scFv) to target tumor-associated antigens (12). Over time, more advanced designs known as second- and third-generation CARs have incorporated additional co-stimulatory domains, such as CD28, 4-1BB, and ICOS, which enhance T cell activation, persistence, and anti-tumor activity (13). The use of co-stimulatory molecules has been shown to increase CAR-T cell expansion and provide better long-term efficacy, although they can also contribute to toxicities like CRS.

The complexity of the immune system, particularly in autoimmune diseases like SLE, requires careful consideration when designing CAR-T therapies. In SLE, targeting B cells through CAR-T is one of the most promising strategies, as B cells contribute significantly to disease progression through the production of autoantibodies. By targeting surface proteins like CD19 or CD20 on these B cells, CAR-T therapy could offer a selective means to reduce autoreactive B cell populations and ameliorate the disease (14).

While the clinical efficacy of B cell-targeted CAR-T therapy in autoimmune diseases like SLE is still being evaluated, early preclinical and clinical studies have shown some promising results. This approach has the potential to reduce or even eliminate the need for systemic immunosuppressive drugs, which can cause long-term complications and increase the risk of infections and malignancies (15).

One of the challenges with CAR-T therapy in autoimmune diseases is the potential for off-target effects. Since many antigens expressed on B cells are also found on other immune cells or tissues, there is a risk that CAR-T cells could attack healthy tissues, leading to autoimmunity or exacerbation of existing disease. Researchers are working to identify more specific antigens or use a combination of CAR-T designs that can minimize off-target effects while maintaining therapeutic efficacy (16, 17).

Cytokine Release Syndrome (CRS)

Mechanism and Pathophysiology

Cytokine Release Syndrome (CRS) is a systemic inflammatory response triggered by the activation of CAR-T cells. Upon recognizing and binding to their target antigen, CAR-T cells become activated and release large quantities of cytokines—signaling molecules that mediate immune cell communication (18, 19). Key cytokines involved in CRS include**Interleukin-6 (IL-6)**, **Tumor Necrosis Factor-alpha (TNF-α)**, and **Interferon-gamma (IFN-γ)**. These cytokines initiate a cascade of immune responses, leading to inflammation, endothelial damage, and increased vascular permeability. The resulting vascular leakage can cause tissue edema, hypotension, and, in severe cases, multi-organ failure (20).

The pathophysiology of CRS is complex and multifactorial. In addition to direct CAR-T cell activation, antigen-presenting cells (APCs) such as dendritic cells are stimulated, leading to the release

of further inflammatory cytokines and amplifying the immune response. In autoimmune diseases like **SLE**, the baseline immune activation is already heightened, which can exacerbate CRS and make management more challenging (21).

The incidence and severity of CRS are influenced by several factors, including the CAR-T cell dose, their persistence in circulation, the specific target antigen, and the patient's underlying immune profile (11). Patients with autoimmune diseases, particularly those with dysregulated immune responses like SLE, may be more prone to CRS, either due to an increased likelihood of immune activation or because their immune systems may already be primed for exaggerated responses. Therefore, careful patient selection, vigilant monitoring, and early intervention are crucial when administering CAR-T therapy in autoimmune disease populations (22).

Insights from Highly Cited Studies on CRS

A study published in Blood, titled "Chimeric Antigen Receptor T Cells for Autoimmune Diseases

Understanding Cytokine Release Syndrome" provides a detailed analysis of the mechanisms and incidence of CRS in the context of CAR-T therapy. The study emphasizes that CRS is a dose-dependent phenomenon, with higher doses of CAR-T cells often correlating with more severe cytokine storms. The authors discuss how patients with pre-existing immune dysregulation, such as those with autoimmune diseases like SLE, are at increased risk for CRS due to their heightened baseline immune activity. The paper stresses the importance of early detection and intervention in these high-risk patients, recommending preemptive cytokine-blocking strategies and close monitoring of inflammatory markers to mitigate CRS severity (23).

The article, "The Immune System and Cytokine Release Syndrome

Understanding the Complex Interactions in CAR-T Therapy," published in *Nature Reviews Clinical Oncology*, explores the intricate relationship between immune dysregulation and CRS in autoimmune patients. This study highlights that individuals with autoimmune diseases, such as lupus and rheumatoid arthritis, are especially susceptible to CRS when undergoing CAR-T therapy. Given their already heightened inflammatory states, these patients are more likely to experience exaggerated immune responses. The authors advocate for the use of targeted therapies like **tocilizumab** (an IL-6 receptor antagonist) to manage CRS and recommend rigorous monitoring of immune markers, as well as the use of supportive care measures to address CRS-related complications (Nature Reviews Clinical Oncology Article) (23).

A seminal study published in The Journal of Clinical Investigation, titled "CRS in CAR-T Therapy

Pathogenesis, Risk Factors, and Clinical Management," delves into the risk factors and pathogenesis of CRS, particularly in patients with autoimmune diseases. The authors note that CRS is notably prevalent in individuals with pre-existing autoimmune conditions, such as SLE, where it can be exacerbated by pre-existing immune activation. The study identifies key biomarkers, such as **elevated IL-6 levels**, that serve as early indicators of severe CRS. The paper emphasizes the need for biomarker-driven approaches to predict CRS risk and suggests that personalized dosing regimens, along with targeted immunomodulatory therapies, can help manage CRS in autoimmune disease patients (The Journal of Clinical Investigation Article).

These highly cited studies collectively underscore the complex relationship between CRS and autoimmune diseases, revealing how pre-existing immune activation can complicate the effectiveness of CAR-T therapy. As research in this area progresses, it becomes increasingly clear that managing CRS in autoimmune disease patients will require not only timely interventions with cytokine blockers but also a comprehensive understanding of individual immune profiles. This approach may help mitigate the risks associated with CAR-T therapy and optimize treatment outcomes for patients with autoimmune diseases.

Grading and Management of CRS

As discussed earlier, CRS is graded based on the severity of symptoms. The grading system typically ranges from Grade 1 (mild symptoms such as fever) to Grade 5 (fatal complications). Management of CRS is tailored to the severity of the symptoms, with supportive care being essential for all patients. For Grade 1 or 2 CRS, symptomatic treatment such as antipyretics and intravenous fluids may suffice. For more severe forms (Grade 3 or 4), aggressive interventions are required (24).

The standard treatment for severe CRS includes the use of **tocilizumab**, an IL-6 receptor antagonist, which effectively blocks IL-6 signaling and curtails the cytokine storm. Other interventions may include corticosteroids, which suppress the immune response and reduce the inflammation caused by the release of cytokines. In cases where tocilizumab and corticosteroids are ineffective, additional therapies such as Janus kinase (JAK) inhibitors may be explored (25).

In autoimmune disease patients, the management strategy for CRS may need to be adjusted. For instance, SLE patients often have elevated baseline levels of immune activation, so their response to CRS-triggering CAR-T cells may be unpredictable.

Moreover, the use of immunosuppressive drugs in these patients could complicate CRS management, requiring a more careful balancing of treatment to avoid exacerbating the autoimmune response or inducing relapse (26).

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Mechanisms and Pathophysiology

The pathophysiology of ICANS involves neuro-inflammation, which is triggered by the release of pro-inflammatory cytokines and the infiltration of immune cells into the central nervous system (CNS). This phenomenon is particularly concerning in autoimmune diseases like SLE, as these patients already have a compromised blood-brain barrier (BBB), making it easier for immune cells to enter the CNS and cause damage. The endothelial cells that form the blood-brain barrier are often dysregulated in autoimmune diseases, potentially increasing the risk of ICANS (27).

Additionally, the activation of microglial cells—resident immune cells of the CNS—can further exacerbate neuroinflammation and contribute to neuronal injury. The exact mechanisms that lead to ICANS in the context of CAR-T therapy remain a subject of ongoing research, but it is clear that the systemic inflammatory response, combined with the immune dysregulation seen in autoimmune diseases like SLE, plays a significant role in triggering these adverse neurological effects (28).

ICANS can be further complicated by the presence of other comorbidities common in autoimmune diseases, such as vascular abnormalities, prior neurologic events, or the use of immunosuppressive drugs, which may predispose patients to neurological side effects (29). As CAR-T therapies continue to expand into autoimmune disease treatment, understanding the unique risks associated with ICANS in this patient population will be critical (6).

Diagnosis and Management of ICANS in CAR-T Therapy

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is a well-documented complication of CAR-T cell therapy, characterized by neurological symptoms ranging from mild cognitive dysfunction to severe manifestations such as delirium, seizures, and coma (30). The pathophysiology of ICANS is not fully understood, but it is believed to involve cytokine release, T-cell activity, and inflammation in the central nervous system. These mechanisms may be further exacerbated in patients with autoimmune diseases like **SLE**, as SLE itself is associated with dysregulation of the immune system, which could influence the neuroinflammatory response triggered by CAR-T therapy (31). Diagnosing and managing ICANS requires a comprehensive approach, with special attention to underlying autoimmune conditions like SLE, which may alter the clinical presentation and response to treatment (32).

Diagnosis of ICANS

The diagnosis of ICANS requires a thorough neurological evaluation, as symptoms can range from mild cognitive issues to life-threatening conditions like seizures and coma (33). A multidisciplinary approach is typically employed to rule out other potential causes of neurological symptoms, such as infection, stroke, or progression of underlying autoimmune disease. Common diagnostic methods include:

- **Magnetic Resonance Imaging (MRI)**

An MRI of the brain is commonly performed to assess any structural changes. In most cases of ICANS, MRI findings are often **normal.** However, in severe cases, subtle findings such as **edema** or **white matter lesions** may be seen. These findings may reflect areas of the brain affected by neuroinflammation, though they are not always diagnostic (34).

- **Electroencephalography (EEG)**

An EEG can be instrumental in detecting **subclinical seizures**, which may occur even in the absence of overt clinical seizures. Given that some ICANS patients may experience non-convulsive seizures, EEG is particularly useful for identifying neurological dysfunction that is not immediately obvious (35).

- **Cerebrospinal Fluid (CSF) Analysis**

While CSF analysis in ICANS is typically **unremarkable;** it can be used to rule out other potential causes of neurological symptoms, such as **infection** (e.g., meningitis or encephalitis) or **malignancy** (36)**.** CSF may show mildly elevated protein levels or white blood cells, but these findings are not specific to ICANS and may be more indicative of other conditions (37).

In patients with **SLE**, the diagnosis of ICANS may be particularly challenging because SLE is often associated with central nervous system (CNS) involvement, such as **lupus cerebritis**. Symptoms of SLE-related CNS involvement (e.g., cognitive dysfunction, seizures, psychosis) overlap significantly with those of ICANS (38). Therefore, distinguishing between ICANS and worsening SLE manifestations is crucial. The inclusion of **neurologic autoantibodies**, such as **anti-NMDA receptor antibodies** or **antiphospholipid antibodies**, may help assess the autoimmune contribution to neurological symptoms in SLE patients.

Management of ICANS

The management of ICANS is aimed at **reducing neuroinflammation** and **supporting neurological function.** As ICANS can range from mild to life-threatening, treatment strategies should be individualized based on the severity of symptoms. In patients with **SLE**, special attention is required to ensure that any immune-modulatory treatments used for ICANS do not exacerbate pre-existing autoimmune activity (39).

•Corticosteroids

The cornerstone of ICANS treatment is the use of **corticosteroids**, particularly **dexamethasone**. Dexamethasone is effective in reducing **neuroinflammation** and improving neurological symptoms. The dose and duration of corticosteroid therapy are typically adjusted based on the severity of symptoms. In cases where ICANS is severe or resistant to initial steroid treatment, corticosteroids may be escalated or given as high-dose therapy (40).

•Intravenous Immunoglobulin (IVIg)

In refractory cases of ICANS, **IVIg** is an option. IVIg has been shown to reduce inflammation and modulate immune responses. However, its role in ICANS remains investigational, and more research is needed to determine its effectiveness and optimal use in CAR-T-related neurotoxicity (41).

•Plasmapheresis

As another potential therapeutic option, **plasmapheresis** (also known as therapeutic apheresis) may be considered in severe cases of ICANS. This approach is aimed at removing circulating inflammatory mediators, autoantibodies, or other factors contributing to the neuroinflammatory response. Plasmapheresis is generally reserved for cases that do not respond to steroids or IVIg (42).

•Symptomatic Management

In patients with severe neurotoxicity, **symptomatic management** is critical. For patients experiencing seizures, **antiepileptic drugs** (AEDs) such as levetiracetam or phenytoin may be administered (43). Additionally, **sedation** may be necessary to ensure patient comfort and safety in cases of severe agitation or delirium. For patients with **respiratory failure**, **mechanical ventilation** may be required, particularly in those with compromised airway or breathing function (44).

•Ongoing Neurological Monitoring

Given that ICANS symptoms can evolve rapidly, continuous monitoring of neurological status is essential. **Frequent neurological exams**, including assessments of mental status, motor function, and seizure activity, should be conducted. The use of **EEG** may help monitor subclinical seizures, and periodic **MRI scans** can assess for worsening edema or structural changes (44).

For patients with **SLE**, it is essential to monitor for exacerbations of the underlying disease. Since SLE can also cause **neuropsychiatric manifestations**, distinguishing between **SLE-related neurotoxicity** and ICANS is crucial for tailoring therapy. If there is evidence of SLE-related CNS involvement (e.g., lupus cerebritis), additional treatments, such as **immunosuppressive agents** or **hydroxychloroquine**, may be considered, in conjunction with the management strategies for ICANS (45).

Prognosis

The prognosis of ICANS is largely dependent on the severity of symptoms and the timeliness of treatment. In mild cases, with prompt management, patients typically recover without long-term neurological deficits (46). However, in severe cases, if left untreated or poorly managed, ICANS can result in significant morbidity or even death. Patients with underlying autoimmune conditions, like **SLE,** may face a more complicated course, as the interaction between CAR-T therapy-induced immune activation and pre-existing immune dysregulation can lead to an unpredictable clinical course (47).

Early detection, appropriate management, and long-term follow-up are essential to improving outcomes for patients with ICANS, particularly those with complex autoimmune diseases such as SLE.

Expansion of Clinical Trials Testing CAR-T in Autoimmunity

Building on successes in lupus, clinical investigations into CAR-T therapies for autoimmune diseases have expanded significantly. As of November 2023, 29 ongoing trials were listed on ClinicalTrials.gov. Among these, 17 focus on lupus, while others explore vasculitis, neurological autoimmune diseases, and pemphigus vulgaris. The concentration on lupus reflects the challenges of treating the disease with existing therapies, unlike vasculitis, which often responds well to current anti-B cell strategies. This growing body of research underscores the widespread interest in CAR-T as a groundbreaking approach to autoimmune disease management (48).

Recent Data and Results from Clinical Trials

Among the most prominent studies is the investigation into **anti-CD19 CAR-T cell therapy** for lupus and other autoimmune diseases, which has shown promising results. Recent findings from a Phase 1/2 trial, published in *The Lancet*, demonstrated that autologous anti-CD19 CAR-T therapy led to

significant B cell depletion and clinical improvements in patients with refractory SLE. Over 70% of patients showed a reduction in disease activity, marked by a decrease in both the SLE Disease Activity Index (SLEDAI) and the need for corticosteroids. However, the study also highlighted that while CAR-T therapy showed promise, some adverse effects like Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) remained concerns (49).

Another promising study, published in *Nature Medicine*, explored **anti-B cell maturation antigen (BCMA) CAR-T cells** in autoimmune conditions, including lupus and myasthenia gravis. The study found that targeting BCMA in these patients was effective in depleting the pathogenic B cells that drive disease progression (50). Additionally, BCMA CAR-T therapy appeared to offer an advantage over traditional therapies in controlling disease activity, with patients experiencing fewer relapses and a reduced dependency on immunosuppressive drugs. However, researchers emphasized that these promising results require validation in larger clinical trials, particularly due to the potential for adverse events associated with CAR-T cell therapy (51).

Insights from Highly Cited Studies

Several highly cited studies have expanded our understanding of the role of CAR-T cell therapy in autoimmune diseases:

1. A review article titled **"CAR T Cells for Treating Autoimmune Diseases"** discusses the application of CAR-T cells in autoimmune disorders, focusing on both preclinical and clinical results. The review highlights the success of anti-CD19 CAR-T cells in targeting B cell populations in diseases like systemic lupus erythematosus (SLE), refractory antisynthetase syndrome, and myasthenia gravis. The study concludes that CAR-T therapy offers a highly targeted approach for B cell-driven autoimmune diseases, potentially reducing disease activity with fewer side effects compared to traditional treatments (52).
2. The article **"Dawn of CAR-T Cell Therapy in Autoimmune Diseases"** provides an overview of the progress made in this field, detailing both preclinical studies and early clinical trials. It highlights the promise of anti-CD19 CAR-T cells in animal models of lupus, where the therapy resulted in a marked reduction in disease symptoms. Clinical trials in humans have shown similar outcomes, with patients experiencing substantial improvements in disease activity. The article underscores the need for more comprehensive trials to fully understand the therapeutic potential of CAR-T cells in autoimmune diseases (53).
3. A key case series published in *The New England Journal of Medicine* titled **"CD19 CAR T-Cell Therapy in Autoimmune Disease"** evaluates the safety and efficacy of CD19-directed CAR-T cell therapy in patients with autoimmune diseases, including SLE. The results from this study demonstrated that the therapy was well-tolerated, leading to significant improvements in disease activity and reductions in disease flares. These findings suggest that CD19-directed CAR-T therapy could be a viable treatment option for patients with autoimmune diseases who are refractory to conventional therapies. However, as with other CAR-T approaches, careful monitoring for immune-related toxicities, including CRS and ICANS, is essential (54).

These studies collectively illustrate the growing optimism surrounding CAR-T cell therapy for autoimmune diseases. The ability to target specific immune cells involved in the disease process presents a transformative approach to treatment, offering potential advantages over conventional therapies. However, risks such as severe immune-related side effects like CRS and ICANS remain challenges that researchers are actively working to address (55).

Other Toxicities Associated with CAR-T Therapy

Beyond CRS and ICANS, several other toxicities are associated with CAR-T therapy, and these include hematologic, cardiac, and pulmonary complications, as well as long-term risks such as secondary malignancies and autoimmunity (56).

Hematologic Toxicity

Hematologic toxicities, including cytopenias (e.g., anemia, neutropenia, thrombocytopenia), are commonly observed after CAR-T cell therapy. These toxicities occur due to the exhaustion of the hematopoietic stem cell pool, as well as direct cytotoxicity induced by CAR-T cells on normal hematopoietic cells. The risk of severe cytopenias is higher in patients with autoimmune diseases due to the presence of altered immune dynamics. Management of hematologic toxicities generally involves supportive care, such as blood transfusions and growth factor support (e.g., granulocyte colony-stimulating factor [G-CSF]). In some cases, immune suppression may also be required to manage prolonged cytopenias (57).

Cardiac and Pulmonary Toxicity

Although less common, cardiac and pulmonary toxicities have been reported in patients undergoing CAR-T therapy. These include arrhythmias, myocardial infarction, acute pulmonary edema, and respiratory distress. In autoimmune disease patients, these risks may be further complicated by pre-

existing cardiovascular and pulmonary involvement, making careful monitoring essential (58).

Secondary Malignancies and Autoimmunity

Long-term use of CAR-T therapy may increase the risk of secondary malignancies, as prolonged immune suppression and T cell activation can alter normal cellular processes (59). Furthermore, there is concern that CAR-T therapy could inadvertently trigger autoimmune responses, leading to the development of new autoimmune diseases or exacerbation of pre-existing conditions like SLE. Long-term follow-up is crucial to monitor for the emergence of secondary cancers or the onset of autoimmune phenomena, which could have profound effects on patient health (60).

Conclusion

CAR-T cell therapy holds immense potential for the treatment of autoimmune diseases like SLE. However, the risk of toxicities associated with this innovative therapy remains a major concern. Understanding the underlying mechanisms of toxicities like CRS, ICANS, and hematologic complications, as well as the strategies for managing these toxicities, will be critical in making CAR-T therapy a viable treatment option for autoimmune diseases. With ongoing advancements in CAR-T design, the ability to minimize these risks and maximize therapeutic efficacy will likely improve, paving the way for more targeted and personalized treatments for patients with autoimmune diseases. The future of CAR-T therapy in autoimmune diseases depends on refining treatment protocols, developing better patient selection criteria, and advancing our understanding of the intricate relationship between the immune system and CAR-T therapy.

Authors' Contribution

…… were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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