RESEARCH PAPER

Car T Cell Therapy in Refractory Systemic Lupus Erythematosus: Emerging Evidence and Future Prospects

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition characterized by dysregulated immune responses, the production of pathogenic autoantibodies, and inflammation affecting multiple organs. The disease can involve the kidneys, skin, joints, nervous system, and other tissues, leading to considerable morbidity and impaired quality of life. Although current therapeutic strategies, including immunosuppressive drugs and biologic agents, have improved disease management, a proportion of patients continue to experience treatment-resistant disease with repeated exacerbations and progressive organ involvement. Chimeric antigen receptor T-cell (CAR-T) therapy, initially developed for the treatment of B-cell malignancies, has recently emerged as a potential targeted immunotherapy for severe forms of SLE. This strategy involves genetically modifying T lymphocytes to recognize and eliminate CD19-expressing B cells, thereby disrupting autoreactive immune pathways and potentially restoring immune tolerance. Preliminary clinical studies have demonstrated encouraging remission rates along with manageable adverse effects and sustained immunological changes following treatment. This review outlines the underlying biological basis, summarizes the available clinical evidence, discusses safety considerations, and highlights future research directions regarding the use of CAR-T therapy in refractory SLE.

Keywords: CAR T-cell therapy, Systemic lupus erythematosus, Autoimmune disease, CD19, Immunotherapy, Refractory SLE.

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Introduction

Systemic lupus erythematosus is a complex and heterogeneous autoimmune disorder marked by a breakdown of immune tolerance and persistent activation of autoreactive B lymphocytes. These cells produce pathogenic autoantibodies, including antibodies directed against double-stranded DNA, which contribute to the formation of immune complexes that deposit in tissues and trigger inflammatory damage across multiple organ systems.

Clinical manifestations may include lupus nephritis, arthritis, skin lesions, hematological abnormalities, and

neurological complications. Despite significant advances in therapeutic approaches—such as corticosteroids, conventional immunosuppressants, and biologic agents targeting B cells—many individuals fail to achieve long-term disease remission. Moreover, prolonged use of these medications is frequently associated with adverse effects including increased susceptibility to infection, metabolic disturbances, and cumulative organ toxicity.

Given these limitations, there is increasing interest in innovative therapies that more directly target the underlying immune dysregulation responsible for SLE. CAR-T cell therapy has transformed the treatment landscape of several hematologic cancers by enabling engineered T cells to specifically recognize and eliminate CD19-positive B cells. Considering the central role of B cells in lupus pathogenesis, applying this technology to autoimmune diseases represents a logical extension.

Unlike conventional B-cell–depleting treatments that often provide only temporary benefit, CAR-T therapy has the potential to induce a deeper and more sustained immunologic reset by eliminating autoreactive B-cell populations and allowing the immune system to regenerate in a more balanced state.

Biological Rationale for CAR-T Therapy in SLE

B lymphocytes play a critical role in the development and progression of lupus not only through the generation of autoantibodies but also through their functions in antigen presentation and cytokine production.

These activities contribute to continuous activation of T cells and amplification of inflammatory responses. Targeting CD19, a surface protein expressed on most stages of B-cell development, allows for broad depletion of pathogenic B-cell populations.

Experimental studies conducted in lupus animal models have demonstrated that anti-CD19 CAR-T cells can markedly reduce disease activity and extend survival.

Following CAR-T treatment, immune reconstitution appears to occur in a manner that favors the emergence of naïve B-cell populations rather than previously expanded autoreactive memory cells.

This shift suggests that CAR-T therapy may restore immunological equilibrium by rebuilding the B-cell compartment in a less autoreactive form. The concept of “immune resetting” therefore distinguishes CAR-T therapy from traditional immunosuppressive treatments, which primarily suppress immune activity without fundamentally correcting the underlying immune imbalance.

Clinical Evidence in Refractory SLE

Early clinical experiences with CAR-T therapy in SLE have mainly involved small groups of patients suffering from severe disease that was unresponsive to conventional treatments. In initial reports using autologous CD19-directed CAR-T cells, treated individuals experienced rapid and profound depletion of circulating B cells.

This effect was accompanied by reductions in autoantibody levels, improvements in disease activity indices, and in several cases the discontinuation of ongoing immunosuppressive medications. Remarkably, some patients maintained drug-free remission for months following therapy, indicating the possibility of long-lasting disease control.

More recent investigations have also evaluated allogeneic CAR-T cell products as a means of addressing manufacturing delays associated with patient-derived therapies. Preliminary data suggest that these approaches may produce comparable clinical benefits with acceptable safety profiles.

Furthermore, newer CAR constructs designed to target both CD19 and B-cell maturation antigen (BCMA) are being studied to eliminate long-lived plasma cells that may persist despite CD19-focused therapies. Such strategies aim to enhance the durability of therapeutic responses and minimize the likelihood of disease recurrence.

Data from early-phase clinical studies demonstrate high remission rates and significant reductions in disease activity among treated patients. Systematic analyses of available case reports and small trials consistently reveal improvements in both clinical manifestations and serological markers of disease. Although the current evidence base remains limited in scale, these findings collectively indicate substantial therapeutic promise.

Safety and Adverse Effects

In oncology settings, CAR-T therapy is commonly associated with complications such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity. However, reported adverse events in SLE patients treated with CAR-T therapy have generally been milder in severity.

Most documented cases involved transient fever or moderate inflammatory symptoms that responded well to standard supportive management. Severe toxicities appear to occur less frequently than those observed in cancer patients, which may be related to differences in immune activation and lower antigen burden.

Nevertheless, potential risks remain. Prolonged cytopenias, reduced immunoglobulin levels, and increased susceptibility to infections are concerns that

require careful clinical monitoring. Establishing standardized treatment protocols and long-term follow-up strategies will therefore be essential to fully evaluate the safety profile of CAR-T therapy in autoimmune disease populations.

Discussion

Current evidence suggests that CAR-T therapy may represent a groundbreaking therapeutic option for patients with refractory SLE. The ability of this approach to induce profound disease remission and allow withdrawal of long-term immunosuppressive therapy marks a significant advancement in the treatment of severe autoimmune disease. Achieving sustained remission could greatly improve patient outcomes and reduce complications related to chronic medication use.

However, several important questions remain unanswered. Most available studies involve small patient cohorts and lack long-term follow-up data. Consequently, the durability of remission, the likelihood of disease relapse after B-cell recovery, and the overall cost-effectiveness of this treatment require further investigation. Additionally, identifying biomarkers that predict treatment response and refining CAR-T cell design may help optimize therapeutic outcomes. Determining the most appropriate stage of disease for intervention will also be an important consideration for future clinical research.

Conclusion

CAR-T cell therapy represents an innovative and potentially transformative immunotherapeutic strategy for individuals with severe, treatment-resistant SLE. By selectively targeting pathogenic B cells and potentially restoring immune tolerance, this approach may significantly alter the current management paradigm for autoimmune disease. While early clinical results are encouraging, large-scale controlled trials and extended safety evaluations are necessary before CAR-T therapy can be widely adopted in routine practice. Should ongoing studies confirm the promising preliminary findings, this technology could become a key component in the management of difficult-to-treat lupus and may open new avenues for the treatment of other autoimmune conditions.

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