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# CELLULAR THERAPIES IN THE TREATMENT OF REFRACTORY AUTOIMMUNE DISEASES: EFFICACY, SAFETY AND FUTURE PROSPECTS

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**Abstract**: Cell therapies have been gaining prominence in the treatment of refractory autoimmune diseases, offering alternatives to conventional immunosuppressants. This study analyzed the efficacy and safety of these approaches, with an emphasis on CAR-T cells, mesenchymal stem cells (MSCs) and regulatory T cells (Tregs). A literature review based on the PVO strategy was carried out, with searches in the PubMed-MEDLINE database, considering articles published between 2021 and 2025 and selected according to inclusion and exclusion criteria. The review indicated that these therapies can modulate the immune response, reduce chronic inflammation and restore immune tolerance, providing sustained remission in diseases such as systemic lupus erythematosus and rheumatoid arthritis. However, challenges such as cytokine release syndrome, neurological toxicity and limitations in target selection restrict its wide clinical application. Advances in genetic engineering, including CRISPR-Cas9 and artificial intelligence, could improve the safety and efficacy of these treatments. It is concluded that, despite the limitations, cell therapies represent a promising advance in personalized medicine, requiring further studies to validate their viability on a large scale.
**Keywords:** Cell therapies, autoimmune diseases, CAR-T cells, immunomodulation.

## INTRODUCTION

Autoimmune diseases represent a heterogeneous group of pathologies characterized by an inadequate immune response against the body's own tissues, leading to progressive damage and functional impairment. Traditionally, the management of these conditions involves the use of immunosuppressants, corticosteroids and biological therapies, which, although effective in many cases, have limitations, such as significant adverse effects and inadequate therapeutic response in refractory

patients (Guffroy *et al.,* 2024). In this context, cell therapies have emerged as a promising alternative, offering an innovative approach to modulate the immune response and promote sustained remission of severe autoimmune diseases (Yang; Liu; Zhao, 2024).

The introduction of CAR-T cell therapy, originally developed for oncology, revolutionized the treatment of hematological neoplasms and sparked interest in its application in the management of autoimmune diseases. Recent studies have shown that this approach can be effective in eliminating pathogenic B lymphocytes in diseases such as systemic lupus erythematosus and rheumatoid arthritis, providing significant clinical improvement (Tian *et al.,* 2024). In addition, the immune modulation provided by CAR-T cells can restore immune tolerance, reducing the need for chronic immunosuppressive therapies (Orvain *et al.,* 2021).

Despite these advances, the use of cell therapies in the autoimmune context still faces important challenges. These include the safety of the approach, especially with regard to complications related to cytokine release syndrome and neurological toxicity, as well as the need to improve the selection of antigenic targets to optimize specificity and minimize adverse effects (Wang; Wang, 2023). However, new strategies are being developed to overcome these limitations, such as the use of RNA-modified CAR-T cells, which may offer a safer and more controllable alternative (Konen *et al.,* 2022).

Recently, studies have explored the application of cell therapies in autoimmune neuromuscular diseases, such as myasthenia gravis, showing encouraging results in terms of efficacy and safety (Cingireddy *et al.,* 2024). The possibility of modulating the immune response in a targeted manner represents a significant advance, allowing for a more personalized approach with less risk of systemic side effects. In addition, new research continues to expand the horizons of these therapies, including the development of CAR-NK cells and CAR-Tregs, which could further improve the safety and efficacy of treatment (Yu *et al.,* 2024).

Given this panorama, it is essential to understand the real efficacy and safety of cell therapies in the management of refractory autoimmune diseases. This study aims to analyze the effectiveness of these approaches, highlighting their benefits, limitations and future prospects, in order to contribute to improving the management of these pathologies and expanding the therapeutic options available (Granit *et al.*, 2023).

## METHODOLOGY

A literature review developed according to the criteria of the PVO strategy, which stands for: population or research problem, variables and outcome. This strategy was used to develop the research question "What are the efficacy and safety of cell therapies in the treatment of patients with autoimmune diseases refractory to conventional treatments?". The searches were carried out using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) databases. The search terms were used in combination with the Boolean terms "AND", "OR", using the following search strategy: ((Autoimmune Diseases) OR ("autoimmune disease"[Title/Abstract])) AND (("Cellular Therapies"[Title/Abstract]) OR ("Hematopoietic Stem Cell Transplantation"[MeSH]) OR ("CAR-T Cells"[Title/Abstract])) AND ((Efficacy) OR (Safety)). From this search, 193 articles were found, which were then submitted to the selection criteria. The inclusion criteria were: articles in English; published between 2021 and 2025 and which addressed the themes proposed for this research, review-type studies, observational studies, experimental studies. The exclusion cri-

teria were: duplicate articles, articles available in abstract form, articles that did not directly address the proposal studied and articles that did not meet the other inclusion criteria. After applying the search strategy to the database, a total of 45 articles were found. After applying the inclusion and exclusion criteria, 30 articles were selected from the PubMed database to make up this study's collection.

## DISCUSSION

### MECHANISMS OF ACTION AND EFFICACY OF CELL THERAPIES IN AUTOIMMUNE DISEASES

Cell therapies have emerged as an innovative alternative in the treatment of refractory autoimmune diseases, acting to modulate the immune response and reduce chronic inflammation. For Alsuliman *et al.* (2024), CAR-T cells demonstrate high efficacy in the selective depletion of autoreactive B lymphocytes, restoring immunological tolerance and reducing the production of autoantibodies, promoting sustained remission in patients with systemic lupus erythematosus. Similarly, Ohno and Nakamura (2024) highlight the role of mesenchymal stem cells (MSCs) in suppressing the inflammatory response, reducing the progression of diseases such as multiple sclerosis and rheumatoid arthritis.

Immune modulation can also be achieved through regulatory T cells (Tregs), which suppress immune hyperactivity and minimize the progression of severe autoimmune diseases (Callegari; Derfuss; Galli, 2021). In addition, Loretelli *et al.* (2021) highlight the ability of cell therapies to offer personalized treatment, adapted to the patient's immune profile. Among these approaches, modified NK cells have emerged as a promising alternative, eliminating overactive antigen-presenting cells without compromising overall immunity.

Mariottini *et al.* (2023) discuss the sustained immune remodeling provided by the infusion of CAR-T cells, allowing a reduction in the need for conventional immunosuppressants. However, Komura (2024) points out that challenges remain, such as the cytokine release syndrome, requiring technological advances to minimize risks, such as the development of new generation CAR-T receptors.

Therefore, the mechanisms of action of cell therapies encompass the elimination of pathogenic cells and the reprogramming of the immune response, offering an innovative treatment for refractory autoimmune diseases (Mariottini *et al.,* 2023; Komura, 2024). Future prospects point to the combination of different cellular approaches, improving the safety and efficacy of these treatments (Loretelli *et al.,* 2021).

### CHALLENGES, LIMITATIONS AND SAFETY OF CELL THERAPIES

Cell therapies offer innovative potential for the treatment of autoimmune diseases, but face significant challenges in terms of safety and efficacy. According to Jin *et al.* (2021), the variability in patients' immune response and the risk of cell rejection represent substantial barriers to the widespread clinical implementation of these therapies. In addition, modified cells can trigger unexpected adverse reactions, such as cytokine release syndrome and immune toxicity.

The phenotypic stability of the cells used in therapies is also a point of concern. According to Farge *et al.* (2021), the ability of therapeutic cells to maintain their immunomodulatory characteristics over the long term has not yet been fully established, which may impact the durability of therapeutic effects. To minimize these risks, technological advances such as precise gene editing and the use of predictive biomarkers are being explored to improve the safety of these treatments.

Another critical challenge lies in the immunogenicity of the transplanted cells. According to Zhou *et al.* (2024), the susceptibility of cell therapies to individual variations in the immune system can impact their efficacy and safety, making it necessary to develop personalized strategies for each patient. According to Bailey *et al.* (2023), even with advanced strategies to reduce rejection, unwanted activation of the immune system can compromise the effectiveness of the treatment. The use of autologous cells, although promising, does not completely eliminate immunological risks and can make the process more expensive and time-consuming.

For Riet and Chmielewski (2022), an alternative approach consists of developing regulatory CAR-T cells, which have a more stable profile and less immunogenic potential. According to Li *et al.* (2024), recent studies have explored the use of fourth-generation CAR--T cells, which incorporate additional safety mechanisms to minimize adverse events such as immune toxicity and excessive activation of the inflammatory system. However, clinical studies are needed to validate their safety and applicability on a large scale. According to Zhou *et al.* (2024), although cell therapies have a more stable immunogenic profile, the need for strict monitoring and standardized protocols to avoid adverse reactions still persists. According to Li *et al.* (2024), the implementation of new generations of CAR-T cells seeks to improve the specificity of therapy, reducing adverse events without compromising efficacy. Thus, although cell therapies represent a revolution in the management of autoimmune diseases, overcoming these limitations is essential to ensure their clinical viability and widespread acceptance.

## INNOVATIONS AND TECHNOLOGICAL ADVANCES IN CELL THERAPIES

Cell therapies have undergone significant advances in recent years, driven by improvements in cell engineering techniques and the integration of innovative technologies. According to Genchi *et al*. (2023), one of the main recent developments has been the application of nanotechnology to optimize the delivery and stability of therapeutic cells. This approach improves treatment efficacy by ensuring greater precision in the release of cells into target tissues, reducing the risk of adverse effects. In addition, biomimetic systems are being developed to improve the interaction of transplanted cells with the patient's immune microenvironment.

For Brittain *et al.* (2024), the incorporation of gene editing using CRISPR-Cas9 technology represents a milestone in the evolution of cell therapies. This tool enables the precise modification of genes involved in the pathogenesis of autoimmune diseases, allowing for the development of modified immune cells with a greater capacity for immune regulation and a lower risk of rejection. This approach has been explored to enhance the functionality of CAR-T and regulatory T cells , broadening their clinical applications.

According to Bruera *et al.* (2022), another important innovation is the use of machine learning platforms to improve the selection and personalization of cell therapies. Artificial intelligence has been used to analyze large volumes of genomic and immunological data, allowing the identification of cell profiles that are more responsive to treatment and the prediction of potential adverse events. These strategies contribute to making treatments more effective and safer by reducing variability in patient responses.

These advances reinforce the promise of cell therapies as a revolutionary approach to refractory autoimmune diseases. For Cheever *et al.* (2024), the development of platforms based on induced pluripotent stem cells (iPSCs) allows the creation of personalized and less immunogenic cell lines, increasing therapeutic efficacy without compromising safety. In addition, Fischbach *et al.* (2024) highlight the potential of CAR-T cells adapted for autoimmune diseases, demonstrating safety and positive clinical impact in multiple sclerosis. The development of new strategies, combining nanotechnology, gene editing and machine learning, has the potential to transform regenerative medicine and provide increasingly effective and personalized therapeutic alternatives. However, additional clinical studies are needed to validate the safety and feasibility of these approaches on a large scale (Genchi *et al.,* 2023; Brittain *et al*., 2024; Bruera *et al.,* 2022).

## FUTURE PERSPECTIVES AND CLINICAL APPLICATIONS OF CELL THERAPIES

Cell therapies continue to evolve, presenting promising advances for the treatment of refractory autoimmune diseases. According to Dingfelder *et al.* (2024), new approaches, such as genetic modification of immune cells, are being explored to increase the efficacy and safety of these therapies. In addition, an in-depth understanding of the interaction between immune cells and target tissues enables more targeted and personalized treatments, minimizing the risk of adverse reactions.

According to Bailey *et al.* (2023), one of the critical challenges for the expansion of cell therapies is to ensure their accessibility to a greater number of patients. Advances in the engineering of induced pluripotent stem cells (iPSCs) have enabled the creation of immune--compatible cell lines, reducing the need for immunosuppressants and increasing therapeutic efficiency. This technology has the potential to revolutionize regenerative medicine and significantly expand clinical applications.

For Haghikia, Schett and Mougiakakos (2024), the improvement of gene editing techniques, such as CRISPR-Cas9, has been one of the most important factors in optimizing cell therapies. The combination of these approaches with immunomodulatory therapies has demonstrated clinical benefits, allowing greater control over the course of autoimmune diseases and reducing the chances of relapses. According to Qin *et al*. (2020), hematopoietic stem cell transplantation (HSCT) has also been shown to be effective in restoring immune tolerance in patients with autoimmune neuropathies, reinforcing its role as a viable alternative for severe diseases.

According to Blache *et al*. (2023), the implementation of these therapies on a large scale still faces challenges, such as high costs and complex regulations. However, the continuous evolution of clinical research and the standardization of protocols are fundamental to guaranteeing the safety and efficacy of these approaches. With advances in biotechnology and improved therapeutic strategies, cell therapies have the potential to transform the treatment of autoimmune diseases, becoming an increasingly viable option in clinical practice.

## FINAL CONSIDERATIONS

Cell therapies represent a promising approach to the treatment of refractory autoimmune diseases, offering more targeted and potentially effective alternatives. Approaches such as CAR-T cells, mesenchymal stem cells and regulatory T cells have demonstrated the ability to modulate the immune response and reduce the need for conventional immunosuppressants. However, challenges such as safety, costs and standardization of protocols still limit their clinical application. Technolo-

gical advances, including CRISPR-Cas9 and artificial intelligence, have been explored to optimize these therapies and minimize risks. Future studies should focus on personalizing treatment and improving long-term efficacy. Despite their limitations, cell therapies have the potential to transform the management of autoimmune diseases, providing innovative and personalized alternatives for patients unresponsive to traditional approaches.

## REFERENCES


ALSULIMAN, Tamim *et al.* **Harnessing the potential of CAR-T cell in lupus treatment: From theory to practice.** Autoimmunity Reviews, p. 103687, 2024.

BAILEY, Stefanie R. *et al.* **Four challenges to CAR T cells breaking the glass ceiling.** European Journal of Immunology, v. 53, n. 11, p. 2250039, 2023.

BLACHE, Ulrich *et al.* **CAR T cells for treating autoimmune diseases.** RMD open, v. 9, n. 4, p. e002907, 2023.

BRITTAIN, Gavin *et al.* **Efficacy and safety of autologous haematopoietic stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine in relapsing remitting multiple sclerosis (StarMS): protocol for a randomised controlled trial.** BMJ open, v. 14, n. 2, p. e083582, 2024.

BRUERA, Sebastian *et al.* **Stem cell transplantation for systemic sclerosis.** Cochrane Database of Systematic Reviews, n. 7, 2022.

CALLEGARI, Ilaria; DERFUSS, Tobias; GALLI, Edoardo. **Update on treatment in multiple sclerosis**. La Presse Médicale, v. 50, n. 2, p. 104068, 2021.

CHEEVER, Abigail *et al.* **Application of novel CAR technologies to improve treatment of autoimmune disease**. Frontiers in Immunology, v. 15, p. 1465191, 2024.

CINGIREDDY, Ananya Reddy *et al.* **CD19 chimeric antigen receptor (CAR) T-cell therapy for systemic autoimmune diseases**. Cureus, v. 16, n. 5, p. e60924, 2024.

DINGFELDER, Janin *et al.* **Fully Human Anti-CD19 CAR T Cells Derived from Systemic Lupus Erythematosus Patients Exhibit Cytotoxicity with Reduced Inflammatory Cytokine Production.** Transplantation and Cellular Therapy, 2024.

FARGE, Dominique *et al.* A**utologous stem cell transplantation in scleroderma**. La Presse Médicale, v. 50, n. 1, p. 104065, 2021.

FISCHBACH, Felix *et al.* **CD19-targeted chimeric antigen receptor T cell therapy in two patients with multiple sclerosis**. Med, 2024.

GENCHI, Angela *et al.* **Neural stem cell transplantation in patients with progressive multiple sclerosis: an open-label, phase 1 study**. Nature medicine, v. 29, n. 1, p. 75-85, 2023.

GRANIT, Volkan *et al.* **Safety and Efficacy of Autologous RNA Chimeric Antigen Receptor T-cell (rCAR-T) Therapy in Myasthenia Gravis: a prospective, multicenter, open-label, non-randomised phase 1b/2a study.** The Lancet. Neurology, v. 22, n. 7, p. 578, 2023.

GUFFROY, Aurélien *et al.* **CAR-T cells for treating systemic lupus erythematosus: A promising emerging therapy**. Joint Bone Spine, v. 91, n. 5, p. 105702, 2024.

HAGHIKIA, Aiden; SCHETT, Georg; MOUGIAKAKOS, Dimitrios. **B cell-targeting chimeric antigen receptor T cells as an emerging therapy in neuroimmunological diseases**. The Lancet Neurology, v. 23, n. 6, p. 615-624, 2024.

JIN, Xuexiao *et al*. **Therapeutic efficacy of anti-CD19 CAR-T cells in a mouse model of systemic lupus erythematosus**. Cellular & molecular immunology, v. 18, n. 8, p. 1896-1903, 2021.

KOMURA, Kazuhiro. **CD19: a promising target for systemic sclerosis**. Frontiers in Immunology, v. 15, p. 1454913, 2024.

KONEN, Franz Felix *et al*. **Stem cell therapy in neuroimmunological diseases and its potential neuroimmunological complications**. Cells, v. 11, n. 14, p. 2165, 2022.

LI, Yan-Ruide *et al*. **Frontiers in CAR-T cell therapy for autoimmune diseases**. Trends in Pharmacological Sciences, 2024.

LORETELLI, Cristian *et al*. **Cell therapy for type 1 diabetes.** Expert opinion on biological therapy, v. 20, n. 8, p. 887-897, 2020.

MARIOTTINI, Alice *et al*. **Haematopoietic stem cell transplantation for the treatment of multiple sclerosis: Recent advances**. Current Neurology and Neuroscience Reports, v. 23, n. 9, p. 507-520, 2023.

OHNO, Ryunosuke; NAKAMURA, Akihiro. **Advancing Autoimmune Rheumatic Disease Treatment: CAR-T Cell Therapies-Evidence, Safety, and Future Directions. In: Seminars in Arthritis and Rheumatism**. WB Saunders, 2024. p. 152479.

ORVAIN, Cindy *et al*. **Is there a place for chimeric antigen receptor–T cells in the treatment of chronic autoimmune rheumatic diseases?**. Arthritis & rheumatology, v. 73, n. 11, p. 1954-1965, 2021.

QIN, Zhen *et al*. **Progress in hematopoietic stem cell transplantation for CIDP**. International Journal of Medical Sciences, v. 17, n. 2, p. 234, 2020.

RIET, Tobias; CHMIELEWSKI, Markus. **Regulatory CAR-T cells in autoimmune diseases: Progress and current challenges**. Frontiers in Immunology, v. 13, p. 934343, 2022.

TIAN, Dai-Shi *et al*. **B cell lineage reconstitution underlies CAR-T cell therapeutic efficacy in patients with refractory myasthenia gravis**. EMBO Molecular Medicine, v. 16, n. 4, p. 966-987, 2024.

WANG, Jia-Yi; WANG, Liang. **CAR-T cell therapy: Where are we now, and where are we heading?**. Blood Science, v. 5, n. 04, p. 237-248, 2023.

YANG, Zhibo; LIU, Yingfeng; ZHAO, Hai. **CAR T treatment beyond cancer: Hope for immunomodulatory therapy of non-cancerous diseases**. Life Sciences, p. 122556, 2024.

YU, Jingjing *et al.* **CAR immunotherapy in autoimmune diseases: promises and challenges**. Frontiers in Immunology, v. 15, p. 1461102, 2024.

ZHOU, Jincai *et al*. **CAR T-cell therapy for systemic lupus erythematosus: current status and future perspectives**. Frontiers in Immunology, v. 15, p. 1476859, 2024.