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ADVANCES IN IMMUNOLOGY AND AUTOIMMUNE DISEASES: NEW INSIGHTS AND THERAPIES IN THE TREATMENT OF AUTOIMMUNE CONDITIONS

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Abstract: Autoimmune diseases represent a heterogeneous set of more than 80 chronic conditions characterized by an aberrant immune response against self-antigens, resulting in persistent inflammation and tissue damage. Given this, the present study aims to develop a study on the main advances in immunology and autoimmune diseases, identifying new insights and therapies in the treatment of autoimmune conditions. The methodology applied was based on a literature review, using books and scientific articles from databases on the subject, between 2020 and 205. The results identified a broad spectrum of therapeutic modalities, ranging from the most contemporary and disruptive advances in the field, such as metabolic glycoengineering, gene therapies with CAR T cells supported by messenger RNA technology, and the application of mesenchymal stem cells. The synthesis of such evidence provides substantive insights of considerable relevance to clinical practice and scientific research. In conclusion, it should be noted that recent advances reposition the therapeutic goal of not only controlling inflammation but also reprogramming the immune response toward tolerance, preserving defense against infections and neoplasms and reducing the burden of adverse effects. The challenge now is to transform this potential into reproducible, safe, and accessible clinical routines.
Keywords: Immunology. Autoimmune Disease. Immunomodulation

INTRODUCTION

Autoimmune diseases represent a heterogeneous group of more than 80 chronic conditions characterized by an aberrant immune response against self-antigens, resulting in persistent inflammation and tissue damage . Their global prevalence is estimated to be on the rise, affecting between 5% and 8% of the world's population, with a significant impact on morbidity and mortality, patients' quality of life, and costs to healthcare systems (Schäfer *et al.*, 2024).

These conditions range from systemic diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), to organ-specific diseases, such as type 1 diabetes (T1D), celiac disease, and multiple sclerosis (MS) (Kenison *et al.,* 2023).

Historically, the therapeutic management of these diseases has been based on nonspecific immunosuppression using corticosteroids, cytotoxic agents, and, more recently, broad-spectrum biologics such as anti-TNF and anti-CD20. Although effective in reducing inflammatory activity, these approaches have important limitations, including a high risk of opportunistic infections, secondary malignancies, and loss of response over time. These limitations reinforce the need for more targeted therapies capable of controlling the disease with less compromise of protective immunity (Sármay, 2021).

Over the past two decades, but particularly intensely in recent years, immunology has undergone a conceptual and technological revolution. Advances in single-cell *omics* (*single-cell RNA-seq*, *spatial transcriptomics*, and high-resolution proteomics) have enabled the identification of pathogenic cell subpopulations, differential activation trajectories, and immune profiles associated with prognosis and therapeutic response. These resources have brought new perspectives on the intra- and interindividual heterogeneity of autoimmune diseases, highlighting the importance of thinking about clinical-immunological endotypes rather than broad categories based solely on clinical manifestations (Ellebrecht *et al.*, 2020).

At the same time, microbiome studies have reinforced the idea that commensal microorganisms modulate immune tolerance and can act as triggers of autoimmunity, either throu-

gh molecular mimicry or by inducing chronic inflammatory states, which has expanded the traditional view of autoimmunity as an exclusively genetic and immunological , adding the dimension of the environment and host-microbiota interaction to autoimmunity (Rojas *et al.*, 2024).

From a therapeutic point of view, there have been notable advances in the last half-decade. Key cytokine blockers, such as IL-17, IL-23, and type I IFN, have demonstrated sustained efficacy in phase 3 clinical trials, with deeper and longer-lasting responses than those obtained with conventional immunosuppressants. The introduction of selective JAK and TYK2 inhibitors represented an important pharmacological innovation, allowing interference in critical intracellular pathways with increasing selectivity, albeit with challenges related to long-term safety (Rojas *et al.*, 2024).

More recently, cell therapies, such as chimeric antigen receptor T cells (CAR-T) targeting B cells, have shown potential to induce sustained remission in severe and refractory diseases such as SLE, approaching the concept of "immune *reset*" (Berry *et al.*, 2025).

At the same time, tolerogenic immunotherapy strategies—including nanoparticle--based vaccines, low-dose IL-2, and ex vivo expanded Tregs—seek to restore immune tolerance in an antigen-specific manner, representing one of the most promising fields for the next decade (Berry *et al.*, 2025).

Therefore, this work is justified by the need to synthesize the new mechanistic insights brought about by high-resolution technologies, recent therapeutic advances that have already transformed clinical practice, and future perspectives focused on specific tolerance and personalized medicine. This overview contributes to understanding not only the current state of the art, but also the challenges that still need to be overcome to ensure more effective, safe, and equitable treatments for patients with autoimmune diseases.

Therefore, this study aims to identify the main advances in immunology and autoimmune diseases, identifying new insights and therapies in the treatment of autoimmune conditions.

METHODOLOGY

This is an integrative literature review study with a qualitative approach, whose objective is to identify, analyze, and synthesize scientific evidence published between 2020 and 2025 on advances in Immunology and Autoimmune Diseases and new insights and therapies in the treatment of autoimmune conditions. The integrative review was chosen because it allows the inclusion of studies with different designs (clinical trials, cohorts, case series, and systematic reviews), enabling a comprehensive analysis of the topic.

The articles were searched in the following scientific databases: PubMed/MEDLINE; LILACS (Latin American and Caribbean Health Sciences Literature) and SciELO (Scientific Electronic Library Online). Health science descriptors (Decs) in Portuguese and English were used, combined by Boolean operators (AND, OR).

Thus, the main descriptors used were: *"Immunology," "Autoimmune Diseases," "Therapeutics," "Immunotherapy," "Biological Therapy," "Stem Cell Therapy," "Janus Kinase Inhibitors," "Microbiome," "Single-Cell Transcriptomics," "Biomarkers," "Immune Tolerance," "Cytokines," "Immunomodulation," and "Translational Medical Research."*

The inclusion criteria were articles published between 2020 and 2025; original studies, systematic reviews, narrative reviews, and *meta-analyses* that directly address immunology applied to autoimmune diseases, including new mechanistic insights, biomarkers, and innovative therapies; Texts available in English, Spanish, or Portuguese, in order

to broaden the scope without compromising comprehension; and studies that describe or analyze new immunomodulatory therapies, cell therapies, selective small molecules (e.g., tyk2 inhibitors, jak), and tolerance induction strategies.

Exclusion criteria included articles published before 2020, as they did not fall within the temporal scope of the research; works not available in full text, restricting the analysis to abstracts only; opinion articles, editorials, letters to the editor, and comments, as they did not present robust scientific evidence; and duplicate works between databases (only the most complete and updated version will be considered).

The screening was carried out in three stages: reading titles and abstracts for initial exclusion of articles outside the scope; reading potentially eligible articles in full to confirm inclusion criteria; and standardized data extraction.

Given this, a comparative analysis was performed between the studies to identify trends, benefits, limitations, and gaps in evidence. Whenever possible, differences in results between older studies were highlighted to assess technical evolution and the consolidation of practices.

As this study was based exclusively on data publicly available in the scientific literature, there was no need to submit it to the Research Ethics Committee, following the guidelines of CNS Resolution No. 510/2016 (Brazil, 2016). Therefore, in order to illustrate the article search process, Figure 1 shows the research flowchart.

RESULTS AND DISCUSSION

The management of autoimmune diseases intrinsically requires a multidisciplinary approach, bringing together the collaborative expertise of various specialists, including rheumatologists, immunologists, physical therapists, psychologists, and nurses. This comprehensive strategy aims not only to control physical symptoms, but also to comprehensively address the emotional and psychosocial aspects inherent in these chronic conditions (Milhomem; Almeida, 2023).

At the same time, advances in basic and translational research have outlined increasingly sophisticated and targeted therapeutic perspectives. In this context, the crucial role of the PD-L1 (Programmed Death-Ligand 1) molecule as a central regulator of immune tolerance stands out. Innovative *in situ* immobilization strategies, combining principles of covalent and non-covalent modification, have demonstrated remarkable potential. Through the sequential application of metabolic glycoengineering and bioorthogonal click chemistry, it has been possible to achieve efficient decoration of the surface of target cells with PD-L1, resulting in significantly prolonged retention (Wang *et al.*, 2023).

Validation in preclinical models of type 1 diabetes mellitus and rheumatoid arthritis attested to the efficacy of this "double anchor" platform in immune modulation, with a pronounced reduction in cytotoxic T lymphocyte infiltration concomitant with an increase in the regulatory T cell population (Wang *et al.*, 2023).

Additionally, the elucidation of epigenetic mechanisms, particularly the post-transcriptional modification of RNA known as N6-methyladenosine (m6A), emerges as a fundamental axis in the pathogenesis and treatment of diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Recent evidence indicates that compounds such as Triptolide and Sarsasapogenin exert their therapeutic effects in RA by modulating key targets, including IGF2BP3 and TGM2, which are closely linked to the m6A machinery (Huang *et al.,* 2023).

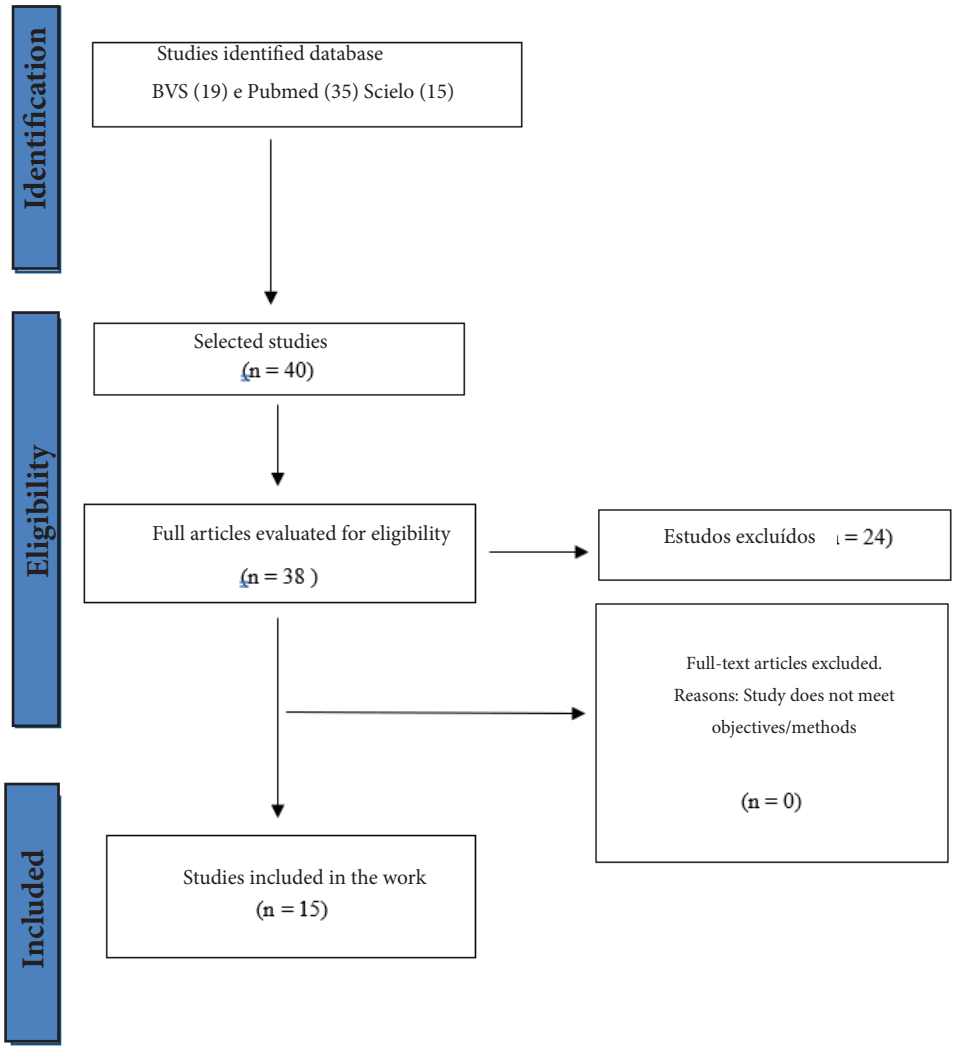

Figure 1 – Prisma Flowchart

Source: Authors' data (2025)

In the context of SLE, RNA methylation profiles show significant correlations with autoantibody production, gene expression patterns, and T-cell dysfunction, in which processes such as DNA hypomethylation and fine-tuning of long non-coding RNAs (lncRNAs), exemplified by Xist and PSMB8-AS1, reveal considerable translational potential for both accurate diagnosis and the development of new interventions (Souza, 2024). These findings underscore the premise that the integration of genetic, epigenetic, and immunological approaches is an indispensable paradigm for advancing the management of these complex pathologies (Huang *et al.*, 2023).

It is worth highlighting the role of fine and balanced regulation of the cytokine IL-17, with special emphasis on its isoform IL-17A. These molecules play a critical role in the innate and adaptive immune defense mechanisms of the host; however, their unregulated and excessive production is closely associated with the pathogenesis of a diverse spectrum of autoimmune and inflammatory diseases, such as multiple sclerosis, Hashimoto's thyroiditis, and systemic lupus erythematosus (Huang *et al.*, 2023).

In this regard, Pinto (2021) corroborates this association by demonstrating that serum levels of the proinflammatory inter-

leukin IL-17A are directly and positively correlated with disease activity indices in several autoimmune entities, including systemic myopathies. Complementarily, Silva's (2020) research advances by specifically proposing IL-17A as a potential robust serum biomarker for monitoring the activity and progression of systemic autoimmune diseases.

In parallel with the targeting of specific cytokine pathways, cellular therapeutic modalities are gaining prominence, in which mesenchymal stem cells (MSCs) stand out in the therapeutic scenario due to their intrinsic immunomodulatory properties and remarkable regenerative capacities. Evidence indicates that MSCs have the ability to suppress aberrant immune responses, attenuate chronic inflammatory processes, and promote the regeneration of damaged tissues (Zaripova *et al.,* 2023).

Cavalcante's (2020) research goes further by emphasizing the substantial translational potential of this approach, highlighting the feasibility of its large-scale production. Given the global impact of autoimmune diseases, the use of MSCs is therefore consolidating itself as a deeply innovative and promising theranostic perspective.

Transcending conventional cellular approaches, cutting-edge research explores transient genetic platforms. For example, Blache *et al*. (2023) contrast conventional symptomatic management strategies, often dependent on broad-spectrum immunosuppressants, with the emerging alternative of mRNA-based CAR T-cell therapy.

This technology offers pharmacological control over chimeric antigen receptor (CAR) expression, enabling precision immune modulation that is simultaneously controlled, dosable, and reversible. This pharmacodynamic profile confers significant advantages, notably a reduced risk of off-target events and the possibility of repeated administrations to optimize the therapeutic response (Blache *et al.*, 2023).

Along the same lines, Junior *et al*. (2022) detail that this transient approach consists of administering genetically reprogrammed T lymphocytes, via mRNA gene transfer, to temporarily express a CAR. This enables an acute and highly targeted immune response, giving clinicians unprecedented control over the duration and intensity of the intervention, which translates into a new paradigm for the treatment of autoimmune diseases with significant improvement in the symptom profile.

Di Filippo *et al.* (2024) describe that intra-disease heterogeneity is one of the main obstacles for clinical trials and daily practice, as studies on systemic lupus erythematosus and multiple sclerosis have highlighted multiomic panels and light neurofilament as promising tools for (i) predicting activity/relapse; (ii) therapy selection (e.g., IFN-high endotypes for anifrolumab); and (iii) response and toxicity monitoring. The goal is to abandon broad categories and migrate to actionable endotypes with validated cut-offs and composites (Di Filippo et al., 2024).

According to Gjurgjaj *et al*. (2025), over the last decade, advances in immunology have reshaped the diagnosis and treatment of autoimmune diseases, the fine-grained reading of pathogenic immune states (via single-cell and spatial omics), the consolidation of biologics (IL-17/23, IFN) and selective small molecules (TYK2), the emergence of cell therapies (anti-CD19 CAR-T in refractory SLE), and the decisive move toward antigen-specific tolerance comprise a more precise and potentially safer therapeutic ecosystem.

A ccording to Li *et al.* (2024), when analyzing clinical risks and immunosuppression, CAR-T for autoimmune diseases, especially anti-CD19, presents risks similar to those observed in oncology, such as cytokine release syndrome (CRS), neurotoxicity (ICANS), and

prolonged cytopenias with opportunistic infections. Studies in lupus show mild to moderate CRS (grades 1-2), usually controlled, but with rare cases of ICANS and upper respiratory tract infections (Sayed *et al.*, 2025).

Yang *et al.* (2025) point out that non-viral methods such as mRNA induce transient CAR expression, avoiding genomic integration and potential oncogenesis associated with lentiviral vectors. In contrast, viral DNA CAR-T allows prolonged expression, but with the risk of random insertion and possible development of secondary malignancies.

It should be noted that, in terms of costs, a study by Li *et al.* (2024) showed that the cost is between US$373,000 and US$475,000 per dose, with complex and time-consuming autologous production (2-4 weeks), limited to specialized centers. According to the authors, in one example, with lupus, as in Germany, the cost reached US$ 530,000, in addition to logistical challenges of production and rapid delivery.

Regarding the risks of secondary neoplasms, there are documented cases (at least 22 by 2023) of secondary T-cell malignancies where the CAR transgene was found in the malignant clone, suggesting possible causality with retroviral viral vectors (Huang *et al.*, 2025). Furthermore, the FDA issued boxed warnings for several CAR-T products in April 2024 regarding this risk, therefore, prolonged surveillance and are recommended (Huang *et al.*, 2025).

Although CAR-T and MSCs have been discussed independently, an emerging perspective in the literature points to the possibility of biomarker-guided combination therapies. In refractory SLE, for example, deep B-cell depletion mediated by anti-CD19 CAR-T could potentially be synergized with the subsequent use of JAK inhibitors to modulate persistent inflammatory pathways, particularly in patients with a high interferon signature (Di Filippo *et al.,* 2024; Berry *et al.*, 2025).

The integration of biomarkers, such as serum IFN-α levels, light neurofilament, or multiomic expression profiles, can guide not only the selection of candidates for these strategies but also the optimal timing of intervention, maximizing efficacy and reducing toxicity (Gjurgjaj *et al.*, 2025). This combinatorial approach, still in the conceptual and experimental stage, aligns with the paradigm of precision medicine, in which different therapeutic modalities are applied in a complementary and personalized way, representing a promising frontier for future clinical trials (Gjurgjaj *et al.*, 2025).

Therefore, for Gjurgjaj *et al.* (2025), the next decade will likely be marked by biomarker-guided adaptive trials, combination therapies (biological + tolerogenic), and, in niche areas, personalized clonotypic approaches. The promise is to reduce dependence on global immunosuppression and deliver deep and sustainable remissions with better quality of life, without losing sight of safety surveillance and equity of access.

CONCLUSION

Over the last decade, immunology has consolidated a turning point in the care of autoimmune diseases. Instead of considering them as homogeneous entities treated only with nonspecific immunosuppression, they have come to be understood as syndromes of mechanisms, consisting of mosaics of pathogenic cellular states, immuno-tissue circuits, and environmental modulators. This paradigm shift, supported by advances in omics technologies and the integration of the microbiome and epigenetics, paves the way for precision medicine based on clinical-immunological endotypes.

The integrative review presented here highlighted a wide spectrum of emerging therapeutic modalities, ranging from cytokine blockers and selective small molecules to

advanced cell therapies, such as CAR-T and mesenchymal stem cells. However, crucial challenges remain. From a methodological point of view, the absence of flowcharts and comparative syntheses in the reviews limits reproducibility.

In the translational field, cell therapies such as CAR-T require deeper critical analysis, considering risks (prolonged cytopenias, cytokine release syndrome, insertion mutagenesis), differences between transient and stable platforms, and cost and access barriers. Additionally, the integration between genetics and therapies remains a link to be strengthened: epigenomic and genomic profiles must evolve into robust predictive biomarkers capable of guiding the selection of patients who are candidates for advanced therapies.

The ethical and social implications, especially those related to equity of access, cannot be overlooked. Finally, the discussion of combined strategies (such as CAR-T s associated with JAK inhibitors) represents a promising but still largely unexplored frontier that deserves attention in future clinical trials.

Therefore, recent advances reposition the therapeutic goal of not only controlling inflammation but also reprogramming the immune response toward tolerance. The challenge is to transform this potential into safe, reproducible, accessible, and equitable clinical routines, guided by biomarkers that enable the application of precision medicine in a fair and sustainable manner.

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