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Immunotherapy for Autoimmune Disorders: Current Status and Future Perspectives

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ABSTRACT

Autoimmune disorders affect over 5-8% of the global population, arising from loss of immune tolerance and attack on self-antigens. Conventional treatments rely on broad immunosuppression with corticosteroids and DMARDs, which offer symptomatic relief but carry significant toxicity and incomplete remission. Immunotherapy has emerged as a targeted paradigm, aiming to restore immune homeostasis rather than suppress it globally. Understanding its evolution is critical for advancing precision medicine in autoimmunity. To review examines the current status, mechanisms, clinical applications, and future directions of immunotherapeutic approaches for autoimmune disorders. Findings from this study revealed that current immunotherapies include anti-TNF (infliximab, adalimumab), anti-CD20 (rituximab), anti-IL-17 (secukinumab), and anti-BAFF (belimumab) agents, showing 50-70% response rates in RA and SLE. Novel cell-based approaches, particularly CAR-Tregs, low-dose IL-2 therapy, and mesenchymal stem cell transplantation, demonstrate ability to restore regulatory T-cell function and durable tolerance in early-phase trials. Tolerogenic dendritic cell vaccines and antigen-specific immunotherapies are emerging for MS and T1D with reduced off-target effects. However, challenges persist including cytokine release syndrome, high costs, loss of efficacy over time, and risk of opportunistic infections. Biomarker-driven stratification and combination therapies are improving outcomes, with JAK inhibitors and checkpoint agonists showing promise in refractory cases. Immunotherapy is transforming autoimmune disease management from broad suppression to precise immune rebalancing. While biologics remain the mainstay, next-generation cell-based and antigen-specific therapies offer potential for long-term remission and cure. Future progress hinges on identifying predictive biomarkers, reducing costs, and conducting large-scale trials. Integration of omics, AI-driven drug discovery, and personalized tolerance induction will define the next era of autoimmune therapeutics.

Keywords: *Immunotherapy; Autoimmune disorders; Biologics; CAR-Treg; and Immune tolerance.*

Introduction

Autoimmunity arises when T cells, B cells, or both become inappropriately activated and cause damage to one or more organs [1].

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Under normal conditions, the immune system distinguishes self-components from foreign pathogens through immune-tolerance mechanisms that eliminate or silence self-reactive lymphocytes [2]. However, genetic susceptibility and environmental influences can disrupt the balance between immune effector and regulatory components, thereby promoting autoimmune disease [3]. Immune tolerance is maintained through complementary central and peripheral mechanisms, with central tolerance eliminating developing self-reactive T cells in the thymus and removing or editing self-reactive B cells in the bone marrow, while peripheral mechanisms, including anergy, inhibitory signalling, regulatory T-cell activity, and immunoregulatory cytokines, prevent activation of autoreactive cells [4]. Failure of these mechanisms can permit autoreactive lymphocytes to expand and produce inflammatory mediators that sustain tissue injury [5].

The development of immunotherapy has been guided by increasing understanding of these tolerance pathways. Conventional treatment has relied largely on corticosteroids, antiproliferative drugs, and other broad immunosuppressive agents, which can reduce inflammation but are limited by toxicity and incomplete efficacy [6].

More targeted biologic therapies, including monoclonal antibodies and engineered fusion proteins, have subsequently been developed to block inflammatory cytokines, deplete pathogenic lymphocytes, or modify co-stimulatory signaling. Agents directed against tumour necrosis factor, CD20, CD80/86, interleukin-6 receptors, and B-cell activating factor have demonstrated the potential of targeted immunotherapy in conditions such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and systemic lupus erythematosus [7]. Despite these advances, many biologic therapies suppress disease activity without permanently restoring immune tolerance; in type 1 diabetes, anti-CD3 therapy, rituximab, and abatacept have produced temporary preservation of β-cell function, but progressive β-cell loss has commonly recurred after treatment [8-10].

Consequently, current immunotherapeutic research is increasingly exploring strategies that restore the balance between pathogenic effector cells and regulatory immune compartments. Regulatory T cells are central to peripheral tolerance, and their absence or dysfunction is associated with severe systemic autoimmunity [11,12]. Ex vivo expansion and transfer of regulatory T cells have suppressed autoimmune diseases in animal models, although their persistence and phenotypic stability remain important challenges for clinical translation [13,14]. Antigen-specific immunotherapy can selectively suppress pathogenic immune responses while preserving protective immunity by promoting mechanisms such as regulatory T-cell induction, anergy, inhibitory signalling, and apoptotic-cell clearance; however, clinical effectiveness has been inconsistent [15,16]. These limitations provide a rationale for combining immunotherapeutic interventions that act through complementary mechanisms, although combination therapy may increase immunosuppression and infection risk and requires consideration of treatment sequence, disease stage, safety, and patient-specific immune characteristics [17,18]. This review examines the immunological basis of tolerance, principal biologic and cell-based approaches, antigen-specific immunotherapy, and rational combination strategies for achieving more durable immune tolerance.

Immune Dysregulation and the Loss of Self-Tolerance

The pathogenesis of autoimmune disease is fundamentally rooted in the failure of self-tolerance, involving defects in central and peripheral regulatory checkpoints that normally prevent immune responses against host antigens. Genetic predispositions can interact with environmental triggers to permit autoreactive clones to enter the periphery, while tissue injury, generation of neo-self antigens, and molecular mimicry can further promote autoreactive responses. Once self-tolerance is breached, autoreactive T and B cells drive disease progression; T cells can differentiate into inflammatory subsets such as Th1 and Th17, while deficiencies in FOXP3+ regulatory T cells impair suppression of these responses [20,21]. Autoreactive B cells contribute through autoantibody production, antigen presentation, cytokine secretion, and maintenance of local immune activation.

Cytokine networks further amplify inflammation, with the JAK-STAT pathway integrating signals from cytokines such as IL-6, IFN-γ, IL-12, and IL-23 to regulate genes involved in immune-cell proliferation, survival, and inflammatory mediator production [22,23].

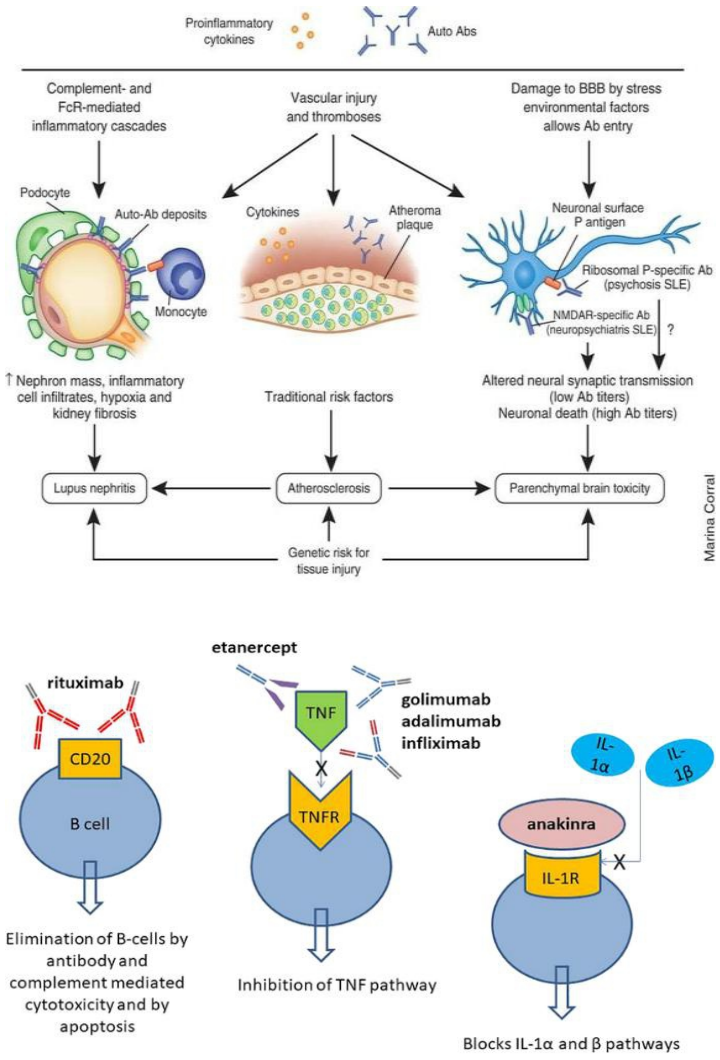

Figure 1. Immune dysregulation and therapeutic targets in autoimmune disease
Sources: *Sakano & Harris (2019)*

The shift towards targeted immunotherapy reflects the limitations of broad-spectrum immunosuppressive drugs, which can suppress protective immunity and produce metabolic complications [24]. In contrast, targeted immunotherapies inhibit specific inflammatory signals or immune-cell populations involved in disease [25]. This strategic targeting reflects the heterogeneity of autoimmune diseases, as different disorders may be driven by distinct inflammatory pathways; for example, TNF-α inhibitors are effective in rheumatoid arthritis and ankylosing spondylitis but have limited efficacy in systemic lupus erythematosus [24]. Understanding these differences is therefore important for the continued development and application of biological and small-molecule immunotherapies [25].

Table 1: Major autoimmune disorders and their immunotherapeutic targets

Disease	Immune Target / Pathway	Representative Therapy
Rheumatoid Arthritis (RA)	TNF-α, IL-6, JAKs	Etanercept, Tocilizumab, Tofacitinib
Systemic Lupus Erythematosus (SLE)	Type 1 Interferon, BAFF	Anifrolumab, Belimumab
Psoriasis / Psoriatic Arthritis	IL-17, IL-23, TYK2	Secukinumab, Ustekinumab, Deucravacitinib
Ankylosing Spondylitis (AS)	TNF-α, IL-17	Infliximab, Ixekizumab
Juvenile Idiopathic Arthritis (JIA)	IL-1, IL-6, T-cell costimulation	Anakinra, Tocilizumab, Abatacept
Multiple Sclerosis (MS)	CD20+ B cells	Ocrelizumab, Rituximab
Neuromyelitis Optica (NMOSD)	CD19+ B cells / Plasmablasts	Inebilizumab
Inflammatory Bowel Disease (CD/UC)	TNF-α, IL-23, JAKs	Adalimumab, Risankizumab, Upadacitinib

Source: *Fischer et al. (2020)*

Current Immunotherapeutic Approaches

Targeted biological therapies and selective small-molecule inhibitors that act at particular stages of the immune cascade are becoming more and more prevalent in the current pharmacopeia for autoimmune diseases [26,27]. The main types of these treatments include monoclonal antibodies, cytokine inhibitors, B-cell and T-cell targeted agents, and JAK inhibitors. TNF inhibitors like infliximab, adalimumab, golimumab, certolizumab, and etanercept decrease TNF-α-mediated inflammatory signaling, though TNF blockade can occasionally result in paradoxical immune responses. Monoclonal antibodies can target soluble molecules or cell-surface receptors. Agents like anakinra, canakinumab, tocilizumab, sarilumab, secukinumab, ixekizumab, ustekinumab, and anifrolumab are used in various autoimmune and autoinflammatory conditions, and cytokine-targeted therapies have extended to IL-1, IL-6, IL-17, IL-23, and type 1 interferon pathways [29, 30]. Immune-cell populations are directly altered by cell-targeted treatments. Rituximab, ocrelizumab, or ofatumumab are frequently used to target CD20 in B-cell depletion, whereas inebilizumab targets CD19 to provide broader B-cell lineage depletion; belimumab, on the other hand, inhibits BAFF-dependent B-cell survival [31,32,33]. Co-stimulation blockade, in which abatacept binds CD80/CD86 and limits the secondary signal necessary for complete T-cell activation, can be used to modulate T cells [34, 35]. While deucravacitinib specifically targets TYK2-dependent signaling, JAK inhibitors, such as tofacitinib, baricitinib, upadacitinib, and filgotinib, act intracellularly to disrupt cytokine signaling [36,28].

Table 2: Major immunotherapeutic classes in autoimmune disorders

Therapy Class	Target/Mechanism	Representative Drugs	Major Applications
TNF Inhibitors	Neutralization of TNF-α (Choy *et al.*, 2020)	Infliximab, Etanercept, Adalimumab	RA, AS, Psoriasis, PsA, UC, CD
Cytokine Inhibitors	IL-1, IL-6, IL-17, IL-23 blockade (Choy *et al.*, 2020)	Anakinra, Tocilizumab, Secukinumab, Ustekinumab	RA, JIA, Psoriasis, PsA, AS, CD, UC
B-cell Depletion	Anti-CD20, Anti-CD19, Anti-BAFF (Parodis *et al.*, 2017; Crickx *et al.*, 2020)	Rituximab, Inebilizumab, Belimumab	RA, MS, NMOSD, SLE, GPA, MPA
Co-stimulation Blockade	CD80/CD86 inhibition (CTLA4-Ig) (Liu *et al.*, 2021)	Abatacept	RA, JIA
JAK Inhibitors	Intracellular JAK-STAT signaling (McLornan *et al.*, 2021)	Tofacitinib, Baricitinib, Upadacitinib	RA, PsA, UC
TYK2 Inhibitors	Selective TYK2 signaling (Papp *et al.*, 2018)	Deucravacitinib	Psoriasis

These targeted therapies modify pathological immune responses by interrupting molecular pathways that sustain chronic inflammation [26,25]. Their development has provided a more selective approach to autoimmune disease management and supports continued investigation of therapies matched to disease-specific immune pathways.

Clinical Applications Across Autoimmune Disorders

The clinical landscape of autoimmune disease management has been transformed by targeted immunotherapies that modulate specific pathological pathways rather than inducing global immune suppression [27]. In rheumatoid arthritis (RA), therapeutic strategies include TNF-α and IL-6 blockade and inhibition of the JAK pathway, with agents such as infliximab and tocilizumab reducing inflammation, improving clinical outcomes, and limiting structural damage [28,29]. However, increased susceptibility to serious infections, including tuberculosis reactivation, remains an important limitation. In systemic lupus erythematosus (SLE), targeting B-cell survival with belimumab and type I interferon signaling with anifrolumab has reduced disease activity and severe flares, although molecular and clinical heterogeneity contributes to variable treatment responses. Rituximab has also shown mixed results, potentially because long-lived plasma cells lack CD20 and may continue producing autoantibodies [30].

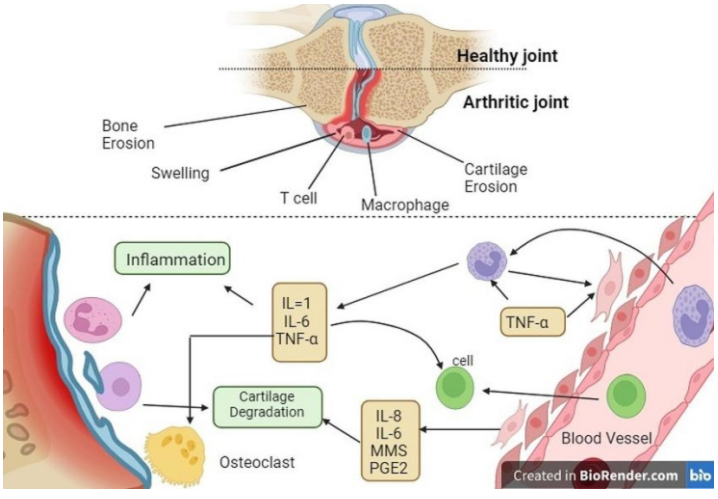

Figure 2. Disease-specific targets and immunotherapeutic interventions
Source: *Liu & Davidson (2012)*

In multiple sclerosis (MS), anti-CD20 therapies such as rituximab and ocrelizumab reduce clinical relapses and new brain lesions, highlighting the important contribution of B cells to neuroinflammation [31]. In inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, TNF-α, IL-23, and integrin pathways are important therapeutic targets, with agents such as adalimumab and vedolizumab supporting clinical remission and mucosal healing.

However, secondary loss of response and development of anti-drug antibodies remain important limitations [32]. Psoriasis and psoriatic arthritis have similarly benefited from therapies targeting the IL-23/Th17 axis, including IL-17 and IL-23 inhibitors, while TYK2 inhibition provides an additional targeted approach. High treatment costs and concerns regarding long-term safety remain challenges [33].

Table 3: Clinical applications of immunotherapy in major autoimmune disorders

Disease	Therapeutic Approach	Major Benefit	Important Limitation
Rheumatoid Arthritis	TNF or IL-6 blockade	Prevention of joint destruction	Increased risk of serious infections
Systemic Lupus Erythematosus	BAFF or IFNAR inhibition	Reduction in systemic disease activity	High degree of patient heterogeneity
Multiple Sclerosis	B-cell depletion (Anti-CD20)	Reduction in relapses and new lesions	Risk of infusion reactions and PML
Inflammatory Bowel Disease	TNF, IL-23, or Integrin inhibition	Achievement of mucosal healing	Secondary loss of response (ADA)
Psoriasis	IL-17 or IL-23 inhibition	Near-complete skin clearance	High economic burden and cost

Safety, Adverse Effects and Treatment Limitations

Although targeted immunotherapies provide greater specificity, they remain associated with important safety and practical limitations. Increased susceptibility to infections is a major concern, particularly tuberculosis reactivation with TNF inhibitors and herpes zoster with JAK inhibitors [3, 10]. Biological therapies may also cause infusion or hypersensitivity reactions, while anti-drug antibodies can reduce therapeutic effectiveness and contribute to loss of clinical response. Long-term concerns include malignancy and cardiovascular events, while certain JAK inhibitors have been associated with warnings concerning serious cardiovascular events, cancer, thrombosis, and death in specific patient populations [11,12]. High manufacturing costs, cold-chain requirements, and specialized administration further limit access, particularly in low-resource settings, although biosimilars may help reduce some economic barriers.

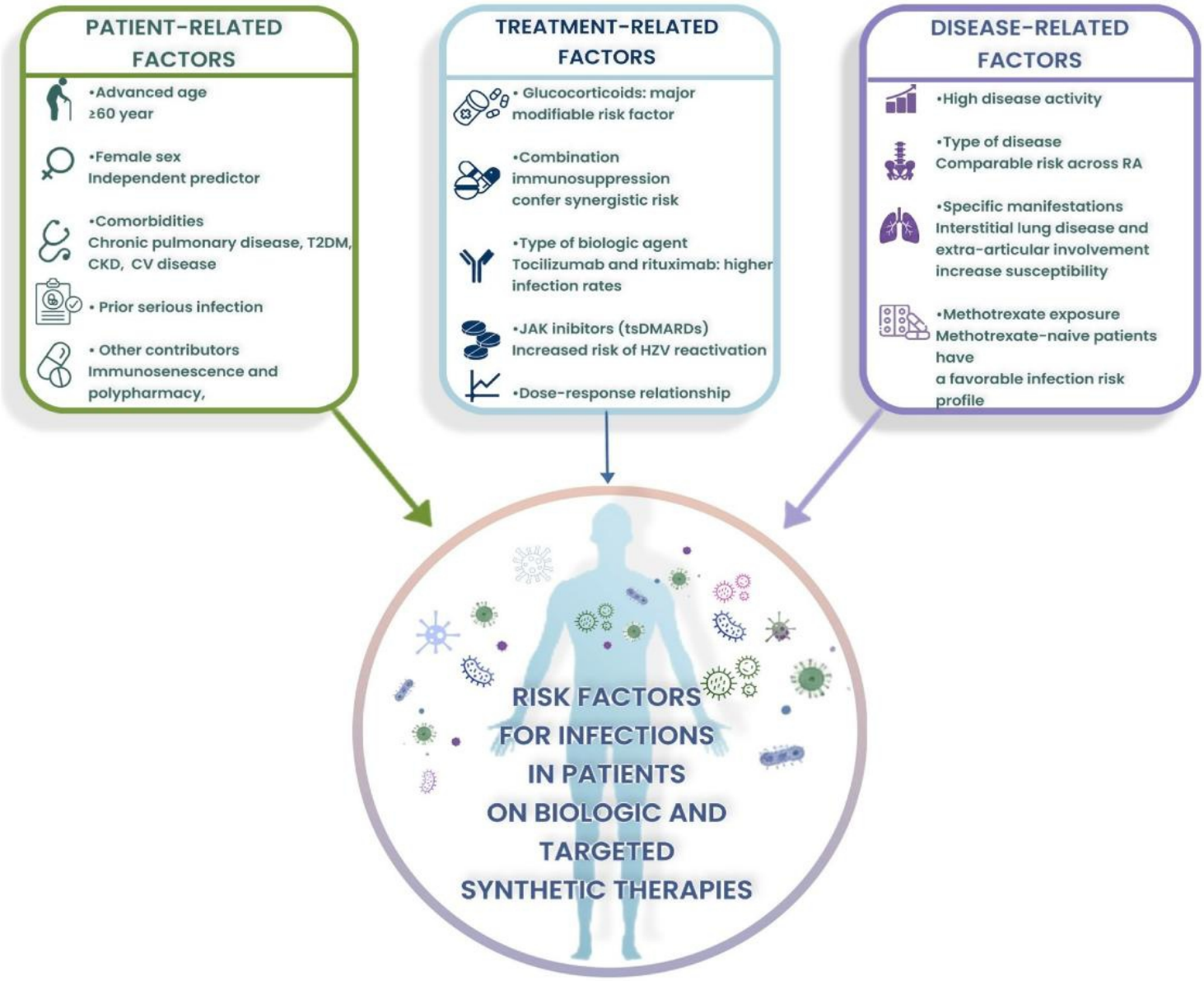

Figure 3. Major safety risks of immunotherapy in autoimmune disease
Source: *Capuccio et al. (2026)*

Treatment resistance represents another major limitation, with primary non-response and secondary loss of response occurring in patients receiving biological therapies. These limitations are partly related to molecular heterogeneity and immunogenicity, emphasizing the need for better treatment selection and biomarker-guided approaches [5,13].

Table 4: Major limitations of current autoimmune immunotherapy

Limitation	Clinical Consequence	Potential Response
Increased Infection Risk	Reactivation of TB, Zoster, or opportunistic infections	Pre-treatment screening, vaccination, and monitoring
Immunogenicity (ADA)	Neutralization of drug and loss of therapeutic response	Switch to different agent or add methotrexate
Serious Adverse Events	Cardiovascular events, thrombosis, or malignancy	Careful patient stratification and risk assessment
High Treatment Costs	Limited patient access and health inequality	Development of biosimilars and oral small molecules
Treatment Resistance	Persistent disease activity and joint/organ damage	Biomarker-guided therapy selection and switching

Comparative Treatment Trends and Clinical Decision-Making

The management of autoimmune diseases is shifting from broad-spectrum immunosuppression toward targeted and individualized treatment strategies [11]. Conventional treatments such as corticosteroids and methotrexate remain widely used but are associated with systemic toxicity and non-specific immune suppression. Targeted therapies instead interrupt specific molecular drivers of inflammation, although treatment response varies considerably between patients because of underlying biological heterogeneity [13]. Biomarkers such as gene-expression signatures, cytokine profiles, and cell-surface markers are therefore being investigated to improve treatment selection. For example, a high interferon signature may help identify SLE patients who could benefit from anifrolumab, while disease-associated immune markers may contribute to treatment selection in RA [14]. However, standardized assays, cost, and prospective clinical validation remain barriers to routine biomarker-guided treatment. Single-cell sequencing and multi-omics approaches may further support patient stratification and precision immunotherapy [15].

Table 5: Conventional versus targeted immunotherapy

Approach	Major Strength	Major Limitation	Clinical Direction
Conventional (e.g. MTX)	Low cost and broad availability	Systemic toxicity and non-specific suppression	Used as baseline or induction therapy
Targeted (e.g. mAbs)	High potency and pathway specificity	High cost and risk of immunogenicity/ADA	Used for refractory, severe, or specific phenotypes
Precision (Biomarker-led)	Personalized to individual patient biology	Limited biomarker availability and validation	Emerging goal of modern clinical practice

Future Perspectives

The future of autoimmune therapy increasingly focuses on restoring immune tolerance and developing personalized cell-based technologies. CAR-T-cell therapy can target autoreactive B cells, with preliminary studies in severe SLE demonstrating deep clinical remission following CD19-targeted treatment [17,18]. CAAR-T cells may provide greater antigen-specificity by targeting disease-associated B cells while sparing non-pathogenic populations. Regulatory T-cell approaches are also being investigated, including low-dose IL-2 therapy to expand Tregs and restore immune regulation [20,21]. Antigen-specific approaches, including tolerogenic vaccines and autoantigen delivery, aim to induce long-lasting immune unresponsiveness [22,23].

Table 6: Emerging immunotherapeutic strategies and their potential

Strategy	Therapeutic Concept	Expected Benefit	Current Challenge
CAR-T / CAAR-T	Selective depletion of autoreactive cells	Deep remission in refractory cases	CRS and manufacturing complexity
Low-dose IL-2 / Tregs	Expansion of regulatory T-cell populations	Restoration of homeostatic immune balance	Maintaining long-term Treg stability
Antigen-Specific Tolerance	Re-education of the immune system to self-antigens	Prevention of disease without suppression	Identification of key autoantigens
Gene Editing (CRISPR)	Modification of genes involved in immune function	Potential long-term disease control	Off-target effects and ethical concerns
AI and Deep Learning	Precision drug discovery and stratification	Improved therapy selection	Data privacy and clinical integration

Gene-editing technologies such as CRISPR-Cas9 may further enable the development of engineered immune cells with therapeutic functions, while artificial intelligence and deep-learning approaches may support drug discovery and patient stratification. However, challenges including manufacturing complexity, potential long-term toxicity, cost, and clinical integration remain important barriers [24].

Conclusion

Targeted immunotherapy has substantially expanded the therapeutic options for autoimmune diseases by allowing specific cytokines, signaling pathways, and immune-cell populations to be modulated rather than broadly suppressing immune. However, treatment resistance, infections, immunogenicity, adverse effects, high costs, and the persistence of disease heterogeneity continue to limit durable treatment responses. Emerging approaches involving regulatory T cells, antigen-specific tolerance, CAR-T/CAAR-T cells, gene editing, biomarkers, and artificial intelligence may provide opportunities to move beyond chronic suppression toward restoration of immune tolerance.

Continued research will therefore be important for developing safer, more precise, and more durable immunotherapeutic strategies for autoimmune disease.

Authors' Contributions

The authors of this research have significantly contributed to the study's conception, data collection, and manuscript development. All authors were involved in writing the manuscript or critically reviewing it for its intellectual value. They have reviewed and approved the final version for submission and publication and accepted full responsibility for the content and integrity of the work.

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Conflict of Interest

The authors declared that there are no conflicts of interest.

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