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RECENT TRENDS IN IMMUNOTHERAPHY FOR AUTOIMMUNE DISEASES

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ABSTRACT

Autoimmune diseases arise from a breakdown of immune tolerance, leading to chronic inflammation and progressive tissue damage. Conventional immunosuppressive therapies, although effective in symptom control, are limited by poor specificity, long-term toxicity, and increased susceptibility to infections. Advances in immunology have led to the development of targeted immunotherapies that selectively modulate pathogenic immune pathways while preserving protective immune functions. This review highlights recent trends in immunotherapy for autoimmune diseases, focusing on monoclonal antibodies, cytokine-targeted therapies, immune checkpoint modulators, and emerging cellular therapies such as chimeric antigen receptor (CAR) T-cell and chimeric autoantibody receptor (CAAR) T-cell therapies. Novel approaches including CAR-NK cells, regulatory T-cell therapy, mesenchymal stem cell therapy, gene editing using CRISPR/Cas9, and artificial intelligence-driven personalized immunotherapy are also discussed. In addition, key challenges such as cytokine release syndrome, infection risk, high cost, variable therapeutic response, and ethical concerns are addressed. Overall, immunotherapy represents a paradigm shift from broad immunosuppression toward precision immune modulation, offering the potential for durable remission and immune tolerance restoration in autoimmune diseases.

KEYWORD: Auto-Immune, Immuno Therapy, Immunosuppressive, Gene.

1. INTRODUCTION

Autoimmune diseases constitute a heterogeneous group of chronic disorders in which the immune system erroneously recognizes self-antigens as foreign, resulting in persistent inflammation and progressive tissue damage. Collectively, these conditions affect approximately 5–10% of the global

population and impose a substantial burden on patients as well as healthcare systems worldwide. Common autoimmune diseases such as systemic lupus erythematous (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and type 1 diabetes (T1D) involve multiple organs and physiological systems, including the skin, joints, kidneys, lungs, heart, and hematological components. The complex and multifactorial pathogenesis of autoimmune diseases is driven by genetic susceptibility, environmental triggers, immune dysregulation, and alterations in immune tolerance mechanisms.

For decades, the cornerstone of autoimmune disease management has relied on broad immunosuppressive therapies, including glucocorticoids, conventional immunosuppressants, and disease-modifying antirheumatic drugs. While these approaches are effective in controlling inflammation and alleviating symptoms, they are limited by poor specificity, long-term toxicity, and an increased risk of infections and malignancies due to generalized immune suppression. Moreover, conventional therapies often fail to address the underlying immune dysregulation, resulting in incomplete disease control and frequent relapses in many patients.

Advances in immunology and molecular medicine have led to the emergence of immunotherapy as a transformative strategy for autoimmune disease treatment. Unlike traditional therapies, immunotherapeutic approaches aim to selectively modulate pathogenic immune pathways while preserving protective immune functions. The introduction of biological agents, particularly monoclonal antibodies and receptor-fusion proteins, has revolutionized the treatment landscape by targeting specific cytokines, immune cell surface markers, and co-stimulatory pathways involved in disease pathogenesis. These targeted therapies have demonstrated improved efficacy, better safety profiles, and enhanced disease control across several autoimmune conditions.

More recently, innovative immunotherapeutic strategies such as bispecific antibodies, small-molecule kinase inhibitors, and cell-based therapies have expanded treatment possibilities. Among these, chimeric antigen receptor T (CAR-T) cell therapy, initially developed for oncology, has shown promising results in severe and refractory autoimmune diseases by selectively eliminating autoreactive immune cells. In parallel, growing evidence highlights the role of the gut microbiota and tissue-specific immune regulation in autoimmune pathogenesis, opening new avenues for combination therapies aimed at restoring immune tolerance.

This review focuses on recent trends in immunotherapy for autoimmune diseases, highlighting emerging therapeutic approaches, their mechanisms of action, and future directions in this rapidly evolving field.

2. PATHOGENESIS OF AUTOIMMUNE DISEASES

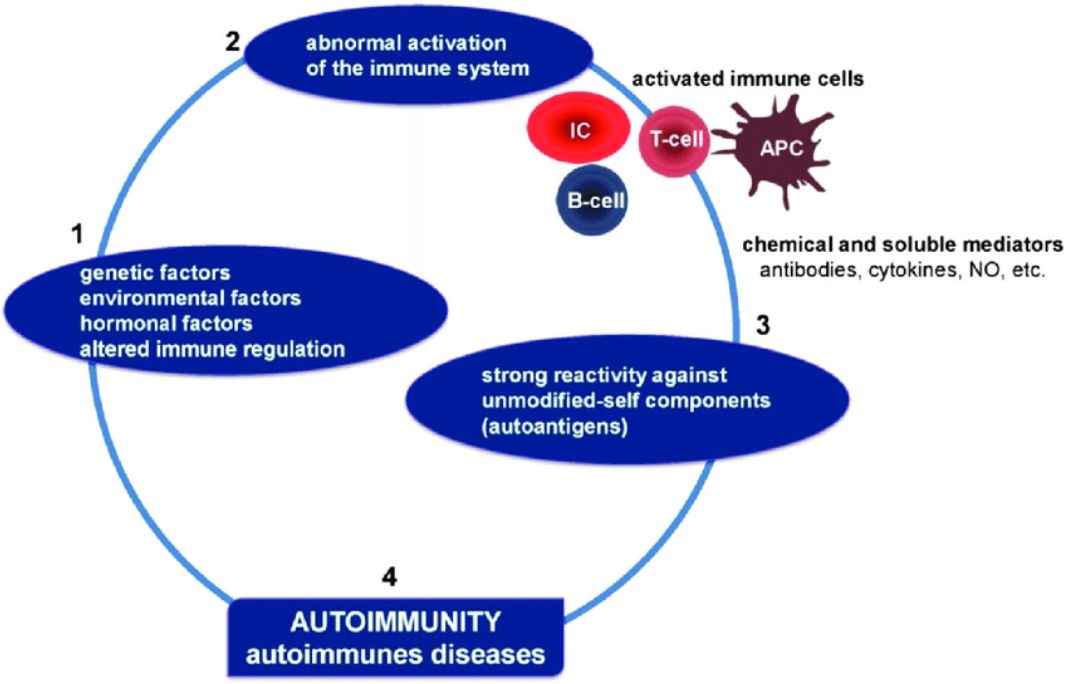

Fig: 1 Pathogenesis of Autoimmune Disease.

Loss of Immune Tolerance: Autoimmune diseases arise primarily due to a breakdown of immune tolerance, a process by which the immune system normally distinguishes self-antigens from foreign antigens. Under physiological conditions, central and peripheral tolerance mechanisms eliminate or inactivate autoreactive lymphocytes. Failure of these regulatory checkpoints results in the survival and activation of self-reactive immune cells that target host tissues. This loss of tolerance ultimately leads to chronic inflammation, tissue injury, and progressive organ dysfunction.

Role of Autoreactive B Cells and T Cells: Autoreactive B and T lymphocytes play a central role in the initiation and propagation of autoimmune pathology. B cells contribute not only through the production of pathogenic autoantibodies but also by functioning as antigen-presenting cells and by secreting pro-inflammatory cytokines. They promote the activation and differentiation of autoreactive T cells, thereby amplifying immune responses against self-antigens. T cells, particularly $CD4^+$ helper T cells, further exacerbate disease by releasing cytokines such as interleukin-17 (IL-17), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). These cytokines sustain inflammatory cascades and recruit additional immune cells to affected tissues. Impaired regulatory T cell (Treg) function also contributes to disease progression, as reduced Treg activity weakens immune suppression and tolerance maintenance.

Autoantibodies and Cytokine Dysregulation: Autoantibody production is a hallmark of many systemic autoimmune diseases, including systemic lupus erythematosus (SLE). These antibodies form immune complexes with self-antigens, deposit in tissues, and activate complement pathways, resulting in inflammation and organ damage. Elevated titers of anti-nuclear and anti-double-stranded DNA antibodies are closely associated with disease severity in SLE. Cytokine imbalance further contributes to immune dysregulation. Increased levels of pro-inflammatory cytokines such as IL-6, IL-17, TNF-α, and type I interferons sustain immune activation and tissue injury. In SLE, type I interferon signaling driven by plasmacytoid dendritic cells enhances B-cell survival and autoantibody production. Collectively, cytokine overproduction creates a self-perpetuating inflammatory microenvironment.

Genetic and Environmental Factors: The development of autoimmune diseases is strongly influenced by a combination of genetic susceptibility and environmental triggers. Polymorphisms in human leukocyte antigen (HLA) genes and immune regulatory genes increase the likelihood of autoreactive lymphocyte survival and activation. These genetic predispositions create a permissive immune background for disease initiation. Environmental factors such as infections, toxins, ultraviolet radiation, and alterations in the gut microbiota can precipitate autoimmunity in genetically predisposed individuals. Infections may induce molecular mimicry or bystander activation, leading to cross-reactive immune responses against self-antigens. Additionally, hormonal factors and industrialization-related environmental changes have been associated with rising autoimmune disease prevalence.

3. CAR T-CELL THERAPY AS AN EMERGING IMMUNOTHERAPY FOR AUTOIMMUNE DISEASES

Chimeric antigen receptor (CAR) T-cell therapy has recently emerged as a transformative immunotherapeutic strategy beyond oncology, offering a novel disease-modifying approach for refractory autoimmune disorders. This technology involves the genetic engineering of a patient's autologous T lymphocytes to express synthetic receptors that recognize specific antigens on pathogenic immune cells. Once reinfused, these CAR-T cells selectively eliminate autoreactive immune populations, thereby restoring immune tolerance and reprogramming dysregulated immune responses rather than merely suppressing inflammation.

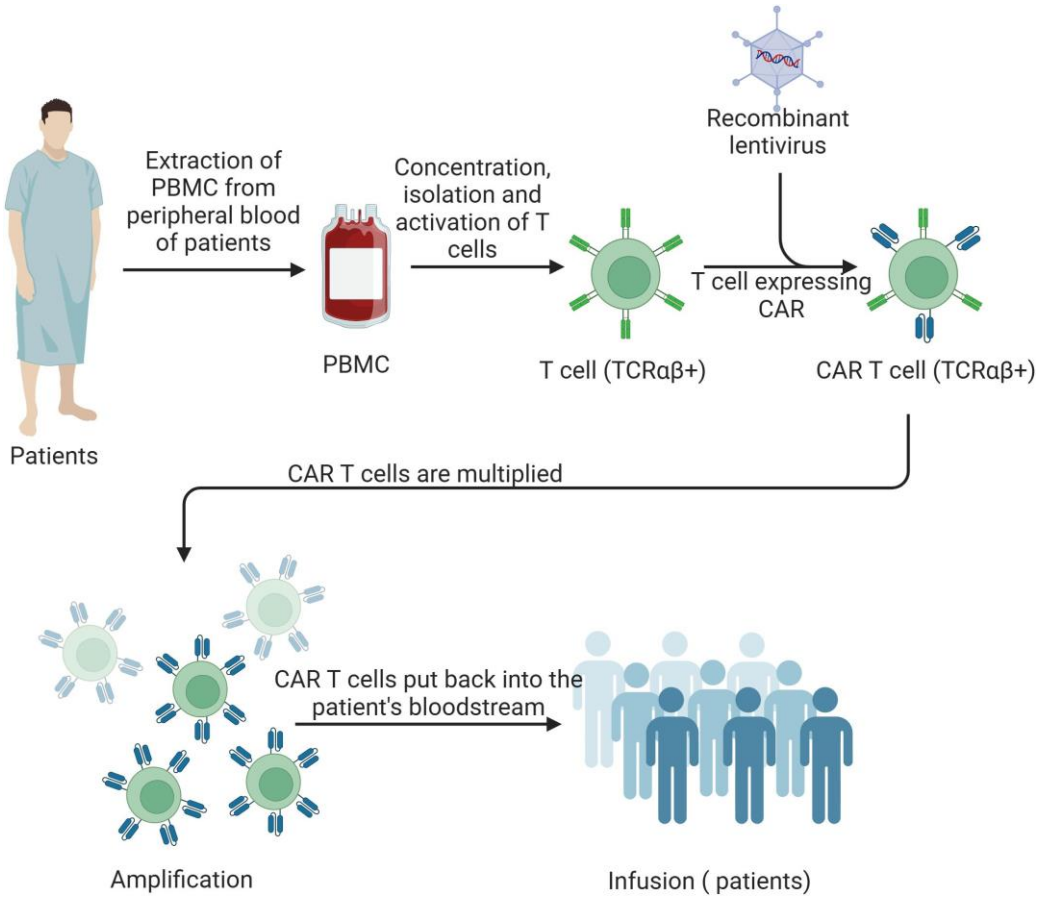

Fig: 2 Manufacturing and administration process of CAR T-cell therapy.

This figure illustrates the step-by-step process involved in the generation and administration of chimeric antigen receptor (CAR) T-cell therapy. Peripheral blood mononuclear cells (PBMCs) are first collected from the patient through peripheral blood extraction. T lymphocytes are then isolated, concentrated, and activated in vitro. Using a recombinant lentiviral vector, T cells are genetically engineered to express a specific chimeric antigen receptor on their surface. The modified CAR T cells are subsequently expanded to achieve adequate cell numbers. Finally, the amplified CAR T cells are reinfused into the patient's bloodstream, where they recognize and eliminate target antigen-expressing pathogenic cells, leading to therapeutic immune modulation.

Rationale and Target Selection in Autoimmunity: Autoreactive B cells play a central pathogenic role in many systemic autoimmune diseases, particularly systemic lupus erythematosus (SLE), by producing pathogenic autoantibodies and sustaining chronic immune activation. CAR-T therapy has therefore been primarily designed to target B-cell surface antigens. Among these, CD19 has emerged as the most widely studied and clinically validated target, as it is expressed across multiple stages of B-cell development, including naïve and memory B cells as well as plasmablasts. Other potential targets such as CD20 and B-cell maturation antigen (BCMA) are also under investigation, depending on disease phenotype and dominant pathogenic cell populations.

Clinical Evidence and Therapeutic Impact: The most compelling clinical evidence has come from patients with severe, treatment-resistant SLE. Early-phase trials and case reports demonstrated that CD19-directed CAR-T cells induced deep and sustained, drug-free remission. Treated patients exhibited marked reductions in anti-double-stranded DNA antibodies, normalization of complement levels, improvement in disease activity indices (SLEDAI), and prolonged absence of disease flares during long-term follow-up. These outcomes confirmed the pivotal role of autoreactive B cells in lupus pathogenesis and established CAR-T-mediated B-cell depletion as a potentially curative, disease-modifying intervention. Subsequent studies extended these findings to other autoimmune conditions. CD19 CAR-T therapy induced remission in refractory idiopathic inflammatory myopathies and showed clinical benefit in systemic sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, pemphigus vulgaris, and experimental models of multiple sclerosis. Notably, CAR-T cells rapidly eliminated plasmablasts responsible for autoantibody production. Even after B-cell reconstitution, patients maintained long-term remission, with repopulated B-cell compartments skewed toward naïve, non-class-switched phenotypes, suggesting immune system “resetting” and restoration of tolerance.

Advantages Over Conventional Therapies: Compared with existing B-cell-targeted biologics such as rituximab and belimumab, CAR-T therapy provides deeper and more sustained depletion of autoreactive B-cell populations. Unlike chronic immunosuppressive regimens, CAR-T therapy offers the possibility of long-term remission following a single treatment course. This approach may reduce long-term dependency on glucocorticoids and immunosuppressants and limit cumulative drug toxicity. Importantly, CAR-T therapy targets the immunological root of disease rather than providing only symptomatic control.

Safety Concerns and Practical Limitations: Despite its promise, CAR-T therapy in autoimmune diseases is associated with significant challenges. Cytokine release syndrome (CRS) and neurotoxicity, well-recognized complications in oncology, remain potential risks, although reported cases in autoimmune cohorts have generally been mild and transient. Prolonged B-cell aplasia raises concerns about infection risk and over-immunosuppression, particularly in patients who are already immunocompromised. Additional barriers include manufacturing complexity, individualized production timelines, logistical constraints, and high costs, all of which limit large-scale clinical deployment.

Biomarkers and Patient Stratification: The identification of predictive biomarkers has enhanced the clinical refinement of CAR-T therapy. Elevated endothelial activation markers, inflammatory cytokines such as interleukin-6, immune exhaustion markers including PD-1 and CTLA-4, and acute-phase reactants such as C-reactive protein have been associated with adverse outcomes or severe CRS. In contrast, higher expression of cytotoxic mediators such as granzyme and perforin correlates with improved therapeutic efficacy. These biomarkers offer valuable tools for patient stratification, risk prediction, and individualized treatment planning.

Future Directions and Next-Generation Approaches: Ongoing research aims to overcome current limitations through several innovative strategies. These include the development of next-generation CAR-T cells incorporating safety "suicide switches" to control toxicity, and universal off-the-shelf CAR-T products using CRISPR-based genome editing to reduce cost and production time. Alternative platforms such as CAR-engineered natural killer (CAR-NK) cells and CAR macrophages are being explored for broader immune modulation with improved safety profiles. Additionally, CAR-engineered regulatory T cells represent a promising suppressive approach to dampen pathological immune activation. Combination strategies integrating CAR-T therapy with biologics such as BAFF or APRIL inhibitors may further enhance durability and reduce relapse risk. Machine-learning-driven personalization and larger controlled trials are expected to define optimal patient selection, long-term safety, and clinical durability.

4. CHIMERIC AUTOANTIBODY RECEPTOR (CAAR) T-CELL THERAPY IN AUTOIMMUNE DISEASES

- Certain autoimmune diseases are directly driven by pathogenic autoantibodies that bind self-antigens and cause tissue injury.
- CAAR-T therapy is a modified CAR-T strategy designed to selectively eliminate autoreactive B cells while preserving normal B cells required for protective immunity.
- In CAAR-T cells, the antigen-binding scFv domain is replaced with the extracellular domain of the target autoantigen.

- This enables CAAR-T cells to recognize and kill only those B cells producing disease-causing autoantibodies.
- The first CAAR construct used desmoglein-3 (Dsg3) to treat pemphigus vulgaris, an autoimmune blistering disorder.
- Dsg3 CAAR-T cells selectively depleted anti-Dsg3 B cells, reduced autoantibody titers, and improved blistering in mouse models.
- A muscle-specific tyrosine kinase (MuSK) CAAR-T was later developed for MuSK myasthenia gravis.
- MuSK CAAR-T cells specifically eliminated anti-MuSK B cells and improved disease features in experimental models.
- Clinical trials are currently evaluating CAAR-T therapy in pemphigus vulgaris and MuSK myasthenia gravis.

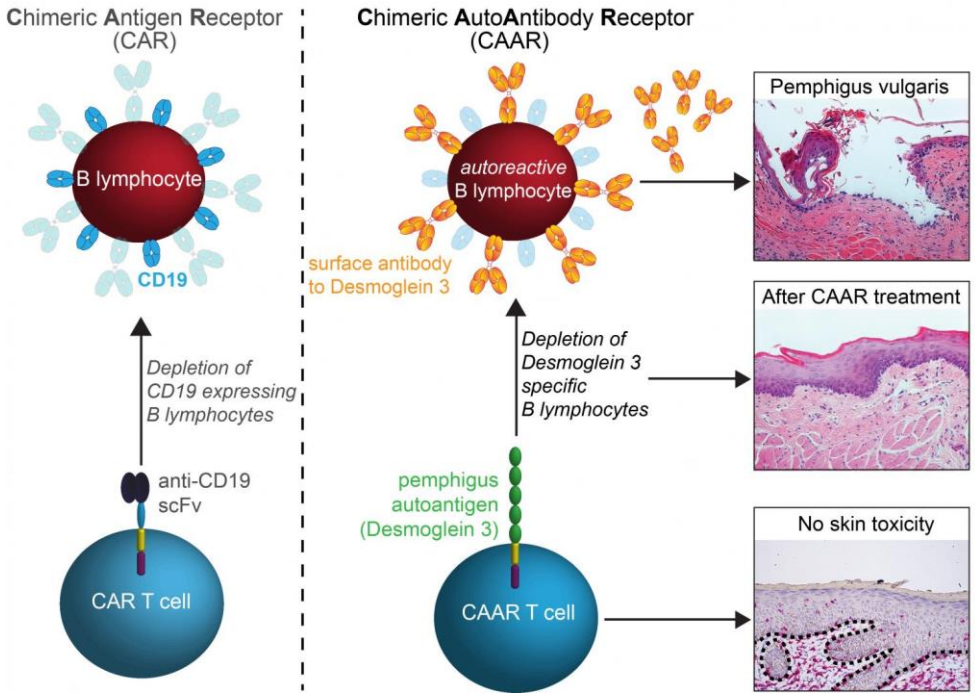

Fig: 3 Comparison of CAR-T and CAAR-T cell therapy in autoimmune diseases.

This figure compares conventional chimeric antigen receptor (CAR) T-cell therapy with chimeric autoantibody receptor (CAAR) T-cell therapy. CAR-T cells target broadly expressed B-cell antigens such as CD19, resulting in depletion of all CD19-positive B lymphocytes. In contrast, CAAR-T cells express specific autoantigens, such as desmoglein-3, on their surface, allowing selective recognition and elimination of autoreactive B cells. In pemphigus vulgaris, CAAR-T therapy specifically removes pathogenic B cells producing anti-desmoglein antibodies, leading to disease resolution without skin toxicity and preserving normal immune function.

5. MONOCLONAL ANTIBODIES (mAbs) – FIRST-GENERATION TARGETED THERAPY:

Monoclonal antibodies (mAbs) represent the earliest form of targeted immunotherapy that significantly transformed the management of autoimmune diseases. Unlike conventional immunosuppressants, which broadly suppress immune function, mAbs are designed to bind specific cytokines, immune cell surface antigens, or signaling molecules involved in disease pathogenesis. By selectively modulating defined immune pathways, mAbs offer improved therapeutic precision and reduced off-target toxicity. These biologics laid the foundation for modern precision immunotherapy and remain widely used in clinical practice for multiple autoimmune disorders.

Mechanism of Action of Monoclonal Antibodies: Monoclonal antibodies exert their therapeutic effects by binding to defined molecular targets that drive autoimmune inflammation. These targets include pro-inflammatory cytokines, cytokine receptors, and surface antigens on immune cells. Upon binding, mAbs either neutralize cytokine activity, block receptor-ligand interactions, or induce immune cell depletion through antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated lysis. By interrupting these pathogenic immune circuits, mAbs reduce immune activation, suppress inflammatory cascades, and limit tissue injury. This targeted mode of action enables modulation of disease-specific pathways while preserving large portions of protective immune function.

Anti-TNF Therapy (Infliximab, Adalimumab): Tumor necrosis factor-α (TNF-α) is a central pro-inflammatory cytokine involved in synovial inflammation, leukocyte recruitment, and tissue destruction. Anti-TNF monoclonal antibodies such as infliximab and adalimumab bind soluble and membrane-bound TNF-α, thereby neutralizing its biological activity. These agents were among the first biologics approved for autoimmune diseases and demonstrated remarkable clinical efficacy in rheumatoid arthritis (RA), Crohn's disease, and ulcerative colitis. Anti-TNF therapy significantly reduces disease activity, prevents joint erosion, and improves quality of life in patients unresponsive to conventional therapies.

Anti-IL-6 Therapy (Tocilizumab): Interleukin-6 (IL-6) is a pleiotropic cytokine that promotes B-cell maturation, T-cell differentiation, and acute-phase inflammatory responses. Tocilizumab, a humanized monoclonal antibody targeting the IL-6 receptor, blocks IL-6-mediated signaling pathways. Clinical trials have shown that IL-6 receptor blockade is highly effective in reducing disease activity and systemic inflammation in rheumatoid arthritis, particularly in patients refractory to anti-TNF agents. Tocilizumab has also demonstrated benefit in juvenile idiopathic arthritis and other inflammatory conditions.

Anti-CD20 Therapy (Rituximab): B cells play a critical pathogenic role in autoimmunity through autoantibody production, antigen presentation, and cytokine secretion. Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen expressed on mature B cells. Binding of rituximab to CD20 results in B-cell depletion via antibody-dependent cytotoxicity and complement activation. This therapy has shown clinical benefit in multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis by reducing autoantibody titers and dampening inflammatory immune responses.

Anti-BAFF Therapy (Belimumab): B-cell activating factor (BAFF) is a key survival cytokine that supports B-cell maturation and persistence. Elevated BAFF levels correlate with disease activity in systemic lupus erythematosus. Belimumab is a fully human monoclonal antibody that binds soluble BAFF, thereby preventing its interaction with B-cell receptors. Belimumab became the first FDA-approved biologic specifically indicated for SLE. Clinical trials demonstrated that BAFF inhibition reduces disease activity, flare frequency, and autoantibody levels, particularly in patients with active, refractory disease.

Clinical Applications in Autoimmune Diseases: Monoclonal antibody therapies have been successfully applied across a wide range of autoimmune disorders. In rheumatoid arthritis, anti-TNF agents and IL-6 receptor blockers significantly reduce synovial inflammation and prevent structural joint damage. In multiple sclerosis, mAbs such as rituximab and natalizumab reduce relapse rates and slow disease progression by targeting B cells and leukocyte trafficking. In systemic lupus erythematosus, belimumab and rituximab reduce disease activity by suppressing pathogenic B-cell responses. In inflammatory bowel disease, anti-TNF antibodies such as infliximab and adalimumab induce and maintain remission by suppressing mucosal inflammation. Collectively, these biologics have become central components of standard care for moderate-to-severe autoimmune diseases.

Limitations of Monoclonal Antibody Therapy: Despite their success, monoclonal antibodies possess several limitations. Immunogenicity remains a major challenge, as patients may develop anti-drug antibodies that reduce therapeutic efficacy and increase adverse reactions.Long-term B-cell depletion and cytokine blockade can predispose patients to opportunistic infections and malignancies. Infusion reactions and immune-related adverse events have also been reported. Furthermore, the high cost of biologic therapies limits accessibility, particularly in low- and middle-income regions. Variable patient responses further complicate treatment selection and highlight the need for predictive biomarkers to guide therapy optimization.

6. CYTOKINE-TARGETED THERAPIES IN AUTOIMMUNE DISEASES

Cytokines play a central role in the initiation and perpetuation of autoimmune inflammation by regulating immune cell activation, differentiation, and survival. Dysregulated production of pro-

inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-17 (IL-17), and type I interferons contributes to chronic immune activation, tissue injury, and organ dysfunction. Based on this pathogenic understanding, therapeutic strategies that selectively block cytokines or their receptors have emerged as a major pillar of modern immunotherapy for autoimmune diseases. These agents provide a more targeted alternative to broad immunosuppression and represent a key transition toward precision immune modulation.

Mechanism of Action of Cytokine Blockers: Cytokine-targeted therapies function by neutralizing circulating cytokines, blocking cytokine receptors, or inhibiting downstream signaling pathways. Monoclonal antibodies or receptor-fusion proteins bind specific cytokines such as TNF-α, IL-6, IL-17, or interferon-α, thereby preventing their interaction with cognate receptors on immune and stromal cells. By interrupting cytokine-driven signaling cascades, these agents suppress inflammatory gene transcription, reduce immune cell recruitment, and limit activation of autoreactive lymphocytes. This targeted inhibition dampens pathogenic immune circuits while preserving a substantial portion of protective immune function.

TNF-α Blockade: TNF-α is a master pro-inflammatory cytokine involved in leukocyte recruitment, synovial inflammation, and tissue destruction. Excessive TNF-α signaling contributes to the pathogenesis of rheumatoid arthritis, inflammatory bowel disease, psoriasis, and ankylosing spondylitis. Monoclonal antibodies such as infliximab and adalimumab bind soluble and membrane-bound TNF-α, neutralizing its biological activity. TNF-α blockade significantly reduces inflammatory burden, prevents joint erosion in rheumatoid arthritis, and induces remission in inflammatory bowel disease. These agents were among the first biologics to demonstrate that selective cytokine inhibition could profoundly alter disease trajectories.

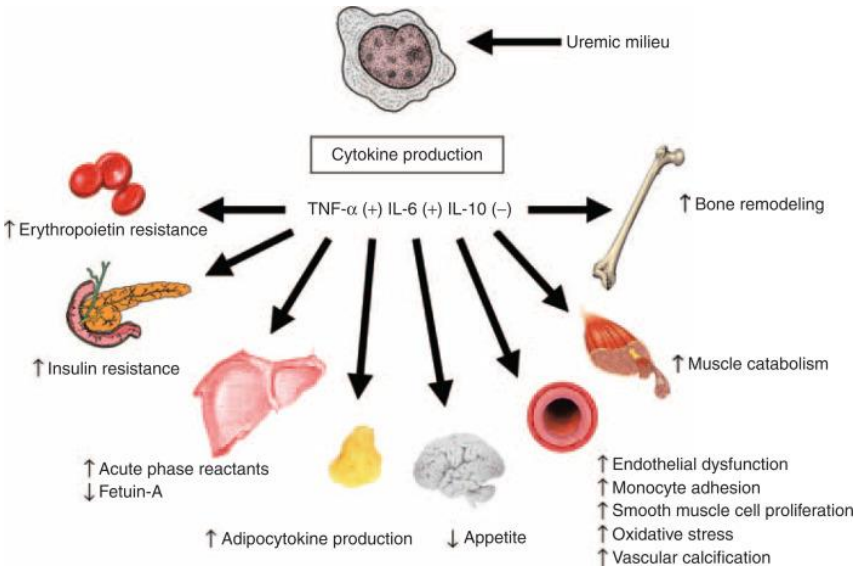

Fig: 4 Systemic effects of cytokine dysregulation in inflammatory and autoimmune conditions.

This figure demonstrates the systemic consequences of chronic cytokine imbalance characterized by increased levels of pro-inflammatory cytokines such as TNF-α and IL-6, along with reduced anti-inflammatory IL-10. Cytokine dysregulation leads to erythropoietin resistance, insulin resistance, muscle catabolism, bone remodeling, endothelial dysfunction, oxidative stress, vascular calcification, reduced appetite, and altered adipocytokine production. These widespread effects explain the multisystem involvement observed in autoimmune and chronic inflammatory diseases and highlight the therapeutic importance of cytokine-targeted interventions.

IL-6 Blockade: IL-6 is a pleiotropic cytokine that promotes B-cell differentiation, T-cell activation, acute-phase responses, and osteoclast-mediated bone resorption. Elevated IL-6 levels correlate with disease activity and joint damage in rheumatoid arthritis and contribute to systemic inflammation in multiple autoimmune disorders. Tocilizumab and sarilumab, monoclonal antibodies targeting the IL-6 receptor, inhibit IL-6-mediated signaling pathways. Clinical studies have shown that IL-6 blockade effectively reduces disease activity, suppresses systemic inflammation, and slows radiographic progression in rheumatoid arthritis, particularly in patients refractory to TNF-α inhibitors.

IL-17 Blockade: IL-17, produced predominantly by Th17 cells, plays a critical role in neutrophil recruitment, epithelial inflammation, and tissue remodeling. IL-17-driven immune responses are strongly implicated in the pathogenesis of psoriasis, psoriatic arthritis, and ankylosing spondylitis. Secukinumab and other IL-17-neutralizing antibodies inhibit IL-17-mediated inflammatory signaling. These agents have demonstrated high efficacy in treating plaque psoriasis and psoriatic arthritis, leading to sustained skin clearance and reduced joint inflammation. Compared with broad cytokine inhibition, IL-17-specific blockade offers a more selective and often better-tolerated therapeutic approach.

IFN-α Blockade in Systemic Lupus Erythematosus: Type I interferons, particularly interferon-α (IFN-α), are key drivers of immune dysregulation in systemic lupus erythematosus. IFN-α promotes B-cell survival, enhances autoantibody production, and induces transcription of interferon-stimulated genes associated with disease severity. Anifrolumab, a monoclonal antibody targeting the type I interferon receptor, blocks IFN-α-mediated signaling. Clinical trials have demonstrated that IFN-α blockade reduces disease activity, flare frequency, and corticosteroid dependence in patients with moderate-to-severe SLE. This therapy represents the first successful clinical translation of interferon pathway inhibition in lupus.

Disease Relevance and Clinical Applications: Cytokine-targeted therapies have transformed the management of several autoimmune diseases. TNF-α and IL-6 inhibitors are now integral components of rheumatoid arthritis therapy. IL-17 inhibitors are frontline agents for psoriasis and psoriatic arthritis. IFN-α blockade has emerged as a disease-specific targeted strategy for SLE. These therapies highlight the concept that distinct autoimmune diseases are driven by dominant cytokine pathways and that selective cytokine inhibition can provide disease-tailored therapeutic benefit.

Benefits of Cytokine-Targeted Therapies: Cytokine blockers offer multiple clinical advantages over conventional immunosuppressants. They provide targeted inhibition of defined inflammatory pathways, resulting in superior disease control and reduced off-target toxicity. These agents improve symptom burden, reduce flare frequency, and slow structural damage in chronic autoimmune diseases. Additionally, cytokine-targeted therapies have validated pathogenic immune pathways, thereby guiding further drug development and biomarker discovery.

Limitations and Drawbacks: Despite their success, cytokine-targeted therapies have important limitations. Long-term cytokine inhibition increases susceptibility to opportunistic infections, including tuberculosis and fungal infections. Secondary loss of response and immunogenicity due to anti-drug antibody formation may compromise long-term efficacy. Furthermore, not all patients respond to cytokine blockade, reflecting disease heterogeneity and redundant inflammatory pathways. High treatment costs and the need for parenteral administration also limit accessibility, particularly in resource-limited settings.

7. IMMUNE CHECKPOINT MODULATORS IN AUTOIMMUNE DISEASES

Immune checkpoints are critical regulatory pathways that maintain immune homeostasis by controlling the magnitude and duration of T-cell responses. Molecules such as cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) and programmed death-1 (PD-1) function as inhibitory receptors that act as physiological “brakes” on immune activation. In autoimmune diseases, dysregulation of these checkpoint pathways contributes to excessive T-cell activation, loss of immune tolerance, and chronic tissue inflammation. Unlike cancer immunotherapy, where checkpoint inhibition is used to enhance immune responses, the therapeutic goal in autoimmunity is immune re-balancing. This involves restoring inhibitory checkpoint signaling to suppress autoreactive T cells and re-establish immune tolerance.

CTLA-4 and PD-1 Pathways in Immune Regulation: CTLA-4 and PD-1 are key negative regulators of T-cell activation. CTLA-4 is expressed on activated T cells and regulatory T cells (Tregs) and competes with the co-stimulatory receptor CD28 for binding to CD80 and CD86 on antigen-presenting cells. Engagement of CTLA-4 delivers inhibitory signals that reduce T-cell proliferation and cytokine production. PD-1, expressed on activated T cells, binds to its ligands PD-L1 and PD-L2 on immune and tissue cells. This interaction suppresses T-cell receptor signaling, limits effector T-cell function, and promotes immune tolerance. In autoimmune diseases, impaired checkpoint signaling results in persistent activation of autoreactive T cells, enhanced inflammatory cytokine production, and progressive tissue damage.

T-Cell Co-Stimulation Control

Full activation of naïve T cells requires two signals:

1. Antigen recognition through the T-cell receptor
2. A co-stimulatory signal mediated by CD28 binding to CD80/CD86

Checkpoint pathways regulate this co-stimulatory process. CTLA-4 acts as a dominant negative regulator of CD28-mediated activation, thereby preventing excessive immune responses. Modulation of this pathway enables selective suppression of pathogenic T-cell activation without inducing global immunosuppression. This principle forms the basis for therapeutic strategies aimed at dampening autoreactive T-cell responses while preserving protective immunity.

Abatacept (CTLA-4-Ig): Abatacept is a recombinant fusion protein consisting of the extracellular domain of CTLA-4 linked to an immunoglobulin Fc fragment. It binds with high affinity to CD80 and CD86 on antigen-presenting cells, thereby blocking their interaction with CD28 on T cells. By inhibiting co-stimulatory signaling, abatacept prevents full T-cell activation, reduces inflammatory cytokine production, and suppresses autoreactive immune responses. Clinically, abatacept has demonstrated efficacy in rheumatoid arthritis and has shown benefit in systemic lupus erythematosus and other immune-mediated disorders. It improves disease activity, reduces joint inflammation, and slows structural damage, particularly in patients refractory to conventional therapies.

PD-1 Pathway Modulation: The PD-1 pathway plays a complementary role in maintaining peripheral immune tolerance. Augmentation of PD-1 signaling induces functional exhaustion or anergy in autoreactive T cells, thereby limiting tissue inflammation. Preclinical models of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis have shown that enhancing PD-1/PD-L1 signaling can suppress disease activity and reduce autoreactive T-cell responses. Unlike cancer therapy, where PD-1 blockade enhances immunity, autoimmune applications aim to strengthen inhibitory signaling to promote immune tolerance and restore homeostasis.

Concept of Immune Re-Balancing: Immune checkpoint modulation in autoimmunity is based on the concept of immune re-balancing rather than immune suppression. Instead of eliminating immune cells or broadly inhibiting inflammatory pathways, checkpoint-based therapies aim to restore physiological regulatory mechanisms that naturally restrain immune activation.

This strategy promotes:

- Suppression of autoreactive T cells
- Enhancement of regulatory T-cell activity
- Restoration of peripheral immune tolerance

By recalibrating immune signaling thresholds, checkpoint modulators offer a more physiological and potentially safer approach to long-term disease control.

Therapeutic Potential and Limitations: Immune checkpoint modulators represent a promising therapeutic class for autoimmune diseases due to their ability to selectively regulate T-cell activation. Abatacept has already been successfully integrated into clinical practice, validating the feasibility of co-stimulation blockade. However, checkpoint modulation requires precise dosing and careful patient selection. Excessive inhibition of immune responses may increase susceptibility to infections and malignancies. Conversely, incomplete suppression may fail to adequately control disease activity. Furthermore, the complexity of checkpoint signaling networks and inter-individual variability in immune profiles pose challenges for predicting therapeutic responses.

8. CELLULAR THERAPIES BEYOND CAR-T IN AUTOIMMUNE DISEASES:

While CAR-T cell therapy has demonstrated transformative potential in refractory autoimmune diseases, its limitations, including toxicity, manufacturing complexity, and cost, have driven the exploration of alternative cellular immunotherapies. Emerging strategies such as CAR-engineered natural killer (CAR-NK) cells, regulatory T-cell (Treg) therapy, and mesenchymal stem cell (MSC) transplantation aim to restore immune tolerance and rebalance dysregulated immune responses rather than merely eliminating pathogenic cells. These next-generation cellular therapies represent a paradigm shift toward durable immune modulation and tolerance restoration.

CAR-NK Cells: Natural killer (NK) cells are innate immune effector cells capable of recognizing and eliminating abnormal or stressed cells without prior antigen sensitization. Unlike T cells, NK cells exhibit reduced alloreactivity and a lower propensity to induce cytokine release syndrome (CRS), making them attractive candidates for adoptive cellular therapy.

CAR-NK cells are genetically engineered to express chimeric antigen receptors that enable targeted recognition of autoreactive immune cells. Compared with CAR-T cells, CAR-NK cells demonstrate a safer toxicity profile, reduced neurotoxicity, and a lower risk of prolonged cytopenias. Preclinical and early clinical studies suggest that CAR-NK cells can selectively eliminate pathogenic immune cell populations while preserving broader immune competence. These properties position CAR-NK cells as a promising off-the-shelf cellular therapy platform for autoimmune diseases, with potential applications in systemic lupus erythematosus and multiple sclerosis.

Regulatory T-Cell (Treg) Therapy: Regulatory T cells (Tregs) play a central role in maintaining peripheral immune tolerance by suppressing excessive immune activation and inhibiting autoreactive T and B cells. Dysfunction or numerical deficiency of Tregs is a hallmark of many autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus. Adoptive Treg therapy involves ex vivo expansion or genetic engineering of autologous Tregs followed by reinfusion into patients. These infused Tregs suppress pathogenic effector T-cell responses through cytokine secretion (e.g., IL-10, TGF-β), metabolic disruption, and direct cell-to-cell contact. Preclinical and early-phase clinical studies indicate that Treg-based therapies can reduce inflammation, prevent disease progression, and promote long-term immune tolerance. Unlike depletion-based strategies, Treg therapy aims to re-establish physiological immune regulation rather than eliminate immune cell populations.

Mesenchymal Stem Cell (MSC) Therapy: Mesenchymal stem cells are multipotent stromal cells with potent immunomodulatory properties. MSCs suppress immune activation by inhibiting T-cell proliferation, modulating dendritic cell maturation, and promoting the generation of regulatory immune subsets. In autoimmune diseases, MSCs exert anti-inflammatory effects by secreting immunoregulatory cytokines, inducing Treg expansion, and suppressing autoreactive lymphocyte responses. Clinical studies in systemic lupus erythematosus, multiple sclerosis, and inflammatory bowel disease have demonstrated that MSC therapy can reduce disease activity, improve organ function, and decrease autoantibody titers. MSC-based therapies offer a cell-mediated approach to immune tolerance induction with relatively favorable safety profiles and minimal immunogenicity.

Immune Tolerance Restoration: A central objective of next-generation cellular therapies is immune tolerance restoration rather than broad immunosuppression. Unlike monoclonal antibodies and cytokine blockers, which suppress discrete inflammatory pathways, cellular therapies aim to recalibrate immune homeostasis by correcting regulatory deficits. CAR-NK cells eliminate pathogenic immune cells with reduced collateral damage.

Treg therapy restores regulatory dominance over autoreactive effector cells. MSC therapy promotes an immunosuppressive microenvironment that favors tolerance induction. Together, these approaches converge on the shared therapeutic goal of re-educating the immune system, suppressing autoreactivity, and establishing durable remission without continuous pharmacologic suppression.

Therapeutic Potential and Challenges: Cellular therapies beyond CAR-T hold immense promise for long-term disease modification in autoimmune disorders. Their ability to restore immune balance, minimize systemic immunosuppression, and induce tolerance distinguishes them from conventional biologics. However, several challenges remain. These include limited scalability, variability in cell product quality, high manufacturing costs, and incomplete understanding of long-term safety. Moreover, optimal dosing, timing of administration, and patient selection criteria remain to be defined. Despite these limitations, ongoing advances in cell engineering, gene editing, and biomaterial-based delivery platforms are expected to accelerate clinical translation and improve therapeutic feasibility.

9. GENE EDITING AND PERSONALIZED IMMUNOTHERAPY IN AUTOIMMUNE DISEASES

Recent advances in immunotherapy have extended beyond biologics and cellular therapies toward precision-based strategies that integrate gene editing, biomarker profiling, and artificial intelligence. These emerging approaches aim to correct immune dysregulation at a molecular level and tailor therapies to individual immune signatures. Technologies such as CRISPR/Cas9 genome editing, biomarker-guided treatment selection, and AI-driven patient stratification represent a paradigm shift toward truly personalized immunotherapy in autoimmune diseases.

CRISPR-Based Gene Editing in Immunotherapy: Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 technology has emerged as a powerful genome-editing tool capable of precisely modifying immune cell genomes. In the context of autoimmune diseases, CRISPR is being explored to engineer immune cells with enhanced therapeutic properties or reduced pathogenic potential. One major application involves CRISPR-mediated editing of CAR-T cells to generate “off-the-shelf” allogeneic products. By deleting endogenous T-cell receptors and human leukocyte antigen (HLA) molecules, gene-edited CAR-T cells can evade host immune rejection and minimize graft-versus-host disease. This approach enables scalable manufacturing and broader accessibility of CAR-based therapies. CRISPR is also being investigated to inactivate genes associated with autoreactive T-cell or B-cell receptors, thereby reducing the generation of pathogenic immune clones. Additionally, gene editing can be used to enhance the suppressive capacity of regulatory T cells (Tregs) by modifying transcription factors or cytokine signaling pathways that promote immune tolerance. These strategies aim to reprogram immune cells toward a tolerogenic phenotype rather than eliminating them.

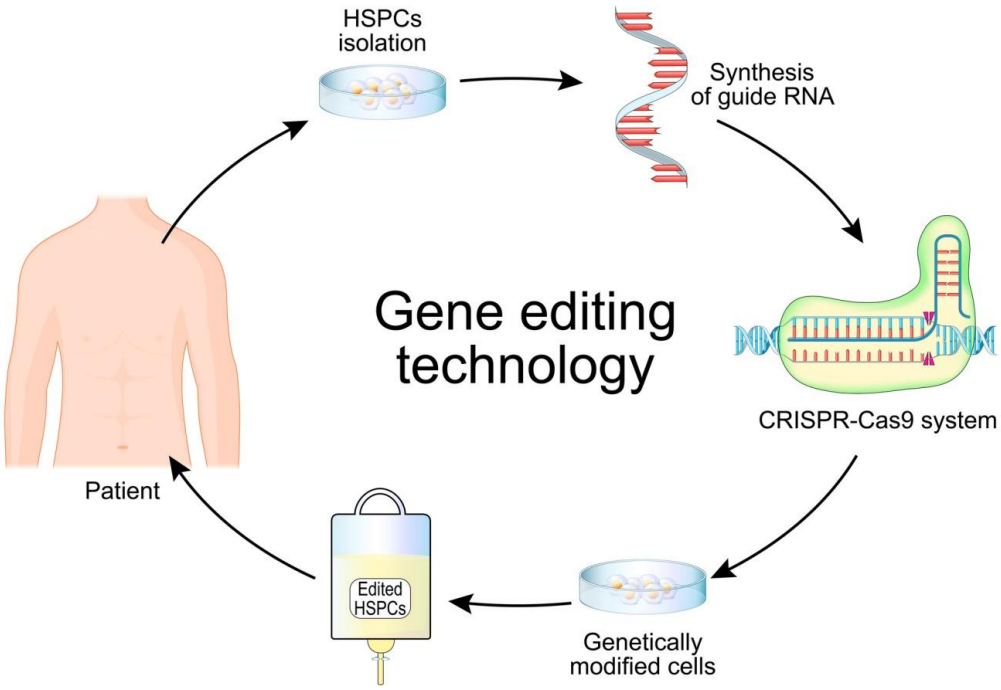

Fig: 5 CRISPR–Cas9–based gene editing technology in immunotherapy.

This figure illustrates the workflow of CRISPR–Cas9–based gene editing used in immunotherapy. Hematopoietic stem and progenitor cells (HSPCs) are first isolated from the patient. Guide RNA specific to the target gene is synthesized and combined with the CRISPR–Cas9 system to induce precise genome editing. The genetically modified cells are expanded in vitro and reinfused into the patient. This approach enables accurate modification of disease-associated genes and forms the basis of personalized and precision immunotherapy for autoimmune diseases.

Biomarker-Guided Personalized Therapy: The heterogeneity of autoimmune diseases results in substantial inter-individual variability in treatment responses. Biomarker-guided therapy has therefore emerged as a cornerstone of personalized immunotherapy. Molecular biomarkers, cytokine profiles, genetic polymorphisms, and immune cell signatures are increasingly used to predict therapeutic efficacy, disease progression, and adverse events. For example, cytokine profiling can identify dominant inflammatory pathways, enabling clinicians to select appropriate cytokine blockers such as TNF-α, IL-6, or IL-17 inhibitors. Genetic markers, including HLA genotypes, can predict susceptibility to specific autoimmune conditions and guide therapy selection. Single-cell sequencing and multi-omics technologies now allow high-resolution characterization of immune cell populations and signaling networks. These tools facilitate identification of disease-driving immune subsets and enable rational matching of patients with targeted therapies such as B-cell–depleting agents, checkpoint modulators, or CAR-based interventions.

Artificial Intelligence–Based Patient Stratification: Artificial intelligence (AI) and machine learning have introduced transformative capabilities for analyzing complex immunological datasets. By integrating clinical parameters, genomic data, transcriptomics, proteomics, and cytokine profiles, AI models can identify patterns associated with therapeutic response or treatment failure. Machine learning algorithms are being developed to stratify patients into responder and non-responder subgroups, predict toxicity risk, and optimize dosing regimens. These tools can assist clinicians in selecting the most appropriate immunotherapy for each patient based on individualized immune signatures. AI is also being applied in drug discovery to identify novel therapeutic targets and predict molecular interactions. By mapping immune signaling networks and disease-associated pathways, AI-driven platforms accelerate the development of next-generation immunotherapies with improved safety and efficacy profiles.

Concept of Precision Immunotherapy: Gene editing and personalized approaches collectively contribute to the broader concept of precision immunotherapy. Rather than applying uniform treatment regimens, precision strategies tailor interventions to each patient's immunological and genetic landscape.

This approach enables:

- Targeted elimination or reprogramming of autoreactive immune cells
- Selection of therapies based on dominant pathogenic pathways
- Reduction of unnecessary immunosuppression
- Optimization of therapeutic benefit–risk ratios

Precision immunotherapy aims not only to control disease activity but also to induce long-term immune tolerance and durable remission.

Therapeutic Potential and Challenges: Gene editing and personalized immunotherapy offer unprecedented opportunities to transform autoimmune disease management. These approaches promise highly specific, durable, and patient-centered therapies capable of correcting immune dysregulation at its root. However, several challenges remain. Gene-editing technologies are still in experimental stages and raise concerns regarding off-target effects, genomic instability, and long-term safety. High costs, regulatory complexity, and ethical considerations further limit clinical translation. Similarly, biomarker discovery and AI-driven stratification require large, high-quality datasets and standardized analytical pipelines. Validation of predictive models in diverse patient populations remains essential before widespread clinical adoption.

10. CHALLENGES AND LIMITATIONS OF IMMUNOTHERAPY IN AUTOIMMUNE DISEASES

Despite the remarkable progress achieved with biologics, cellular therapies, and precision immunotherapy, several critical challenges continue to limit the widespread clinical translation of these advanced interventions. Treatment-related toxicities, infection risk, high economic burden, inter-individual variability in therapeutic response, and ethical as well as logistical constraints remain major barriers to long-term success. Addressing these limitations is essential for the sustainable and equitable implementation of next-generation immunotherapies in autoimmune diseases.

Cytokine Release Syndrome (CRS) and Neurotoxicity: One of the most serious complications associated with advanced cellular therapies, particularly CAR-T cell therapy, is cytokine release syndrome (CRS). CRS results from excessive immune activation and massive cytokine secretion following immune cell engagement with target antigens. Clinically, CRS manifests as fever, hypotension, hypoxia, and multiorgan dysfunction. Immune effector cell-associated neurotoxicity syndrome (ICANS) represents another potentially life-threatening adverse effect. It is characterized by confusion, seizures, cerebral edema, and altered consciousness. Although CRS and neurotoxicity are better characterized in oncology, similar toxicities remain a concern in autoimmune applications, especially given that many patients are already immunologically fragile. These toxicities highlight the need for improved safety switches, dose optimization, and predictive biomarkers to identify high-risk individuals prior to therapy initiation.

Increased Risk of Infections and Over-Immunosuppression: Most immunotherapies suppress key immune pathways involved in host defense. Monoclonal antibodies targeting TNF-α, IL-6, IL-17, BAFF, or CD20 impair immune surveillance and increase susceptibility to opportunistic infections such as tuberculosis, fungal infections, and viral reactivations. Cell-based therapies that induce prolonged B-cell aplasia or deep lymphocyte depletion further exacerbate immunodeficiency, increasing long-term infection risk. This is particularly problematic in autoimmune patients who may already be receiving corticosteroids or conventional immunosuppressants. Thus, maintaining a delicate balance between therapeutic efficacy and immune competence remains a major clinical challenge.

High Cost and Limited Accessibility: The economic burden of modern immunotherapies is substantial. Biologic agents, including monoclonal antibodies and fusion proteins, are expensive and require long-term administration. CAR-T cell therapy and other advanced cellular interventions involve complex manufacturing processes, including leukapheresis, genetic modification, ex vivo expansion, and quality control testing. These logistical requirements translate into extremely high treatment costs and limited availability, particularly in low- and middle-income countries. The

financial toxicity associated with immunotherapy raises ethical concerns regarding equitable access and long-term sustainability of these treatments within public healthcare systems.

Variable Therapeutic Response and Loss of Efficacy: A major limitation of immunotherapy is the marked heterogeneity in patient responses. While some individuals achieve durable remission, others show partial or no response. This variability reflects differences in genetic background, immune signatures, disease stage, and dominant pathogenic pathways. Secondary loss of response is also common, particularly with monoclonal antibodies, due to immunogenicity and anti-drug antibody formation. These antibodies neutralize therapeutic agents and reduce long-term efficacy. The lack of robust predictive biomarkers currently limits the ability to prospectively identify patients most likely to benefit from a given immunotherapy.

Ethical and Logistical Challenges: Advanced immunotherapies raise important ethical and regulatory concerns. Gene-editing approaches and cellular therapies involve permanent or long-lasting immune modifications, the long-term consequences of which are not fully understood. Logistical complexity further limits scalability. CAR-T therapy requires individualized manufacturing, making rapid treatment deployment difficult for critically ill patients. Cold-chain storage, specialized facilities, and highly trained personnel are essential for safe delivery. In addition, patient selection, informed consent, and long-term monitoring impose significant clinical and ethical responsibilities on healthcare providers.

DISCUSSION

The present review highlights the rapid evolution of immunotherapy as a transformative approach for the management of autoimmune diseases. Unlike conventional immunosuppressive therapies, which broadly suppress immune function and are associated with significant long-term adverse effects, modern immunotherapeutic strategies aim to selectively target disease-specific immune pathways while preserving protective immunity. This shift from generalized immunosuppression to precision immune modulation represents a major advancement in autoimmune disease treatment.

A key finding of this review is the growing success of targeted biological therapies, particularly monoclonal antibodies and cytokine inhibitors. Agents targeting TNF-α, IL-6, IL-17, BAFF, and type I interferons have demonstrated significant clinical benefits across various autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and inflammatory bowel disease. These therapies have improved disease control, reduced relapse rates, and minimized tissue damage compared with traditional treatments. However, variability in patient response and the development of anti-drug antibodies continue to limit their long-term effectiveness.

The review further emphasizes the emergence of cellular immunotherapies as promising disease-modifying interventions. CAR-T cell therapy has shown remarkable efficacy in refractory autoimmune diseases, particularly systemic lupus erythematosus, by selectively eliminating

autoreactive B cells and restoring immune tolerance. Similarly, CAAR-T cell therapy offers a highly specific approach by targeting only pathogenic autoantibody-producing B cells while preserving normal immune function. These innovative therapies have demonstrated the potential to achieve durable remission following a single treatment course, representing a significant departure from lifelong immunosuppressive treatment strategies.

Beyond CAR-based therapies, other cellular approaches such as CAR-NK cells, regulatory T-cell therapy, and mesenchymal stem cell therapy are gaining attention due to their ability to restore immune homeostasis with potentially improved safety profiles. These therapies focus on re-establishing immune tolerance rather than merely suppressing inflammatory responses, thereby addressing the underlying pathophysiology of autoimmune diseases.

Recent advances in gene-editing technologies and personalized immunotherapy further expand the therapeutic landscape. CRISPR/Cas9-based genome editing offers opportunities to modify pathogenic immune cells and generate next-generation cellular therapies with enhanced efficacy and safety. Additionally, biomarker-guided treatment selection and artificial intelligence-driven patient stratification are facilitating the development of precision immunotherapy, enabling individualized treatment strategies based on specific immune and genetic profiles.

Despite these promising developments, several challenges remain. Serious adverse effects such as cytokine release syndrome, neurotoxicity, infection risk, and prolonged immunosuppression continue to raise safety concerns, particularly with advanced cellular therapies. Furthermore, high treatment costs, manufacturing complexity, limited accessibility, and ethical considerations associated with gene editing and cellular engineering pose significant barriers to widespread clinical implementation. The identification of reliable predictive biomarkers and long-term safety data will be essential for optimizing patient selection and improving therapeutic outcomes.

Overall, the findings suggest that immunotherapy is reshaping the treatment paradigm for autoimmune diseases by offering more targeted, effective, and potentially curative approaches. Continued research, technological innovation, and carefully designed clinical trials will be critical for overcoming existing limitations and translating these advances into routine clinical practice.

11. CONCLUSION

Recent advances in immunotherapy have significantly transformed the management of autoimmune diseases by moving beyond conventional immunosuppression toward targeted and personalized treatment approaches. Monoclonal antibodies, cytokine-targeted therapies, immune checkpoint modulators, and emerging cellular therapies have demonstrated substantial potential in controlling disease activity, reducing tissue damage, and restoring immune tolerance.

Among these innovations, CAR-T and CAAR-T cell therapies represent groundbreaking developments with the ability to selectively eliminate pathogenic immune cells and induce durable remission in refractory autoimmune disorders. Furthermore, emerging strategies involving CAR-NK

cells, regulatory T cells, mesenchymal stem cells, CRISPR-based gene editing, and artificial intelligence-driven personalized immunotherapy offer exciting prospects for future disease management.

Despite these advancements, challenges related to safety, treatment accessibility, manufacturing complexity, cost, and long-term efficacy remain significant. Addressing these issues through continued research, biomarker development, regulatory support, and technological innovation will be essential for maximizing the clinical benefits of immunotherapy.

In conclusion, immunotherapy represents a paradigm shift in autoimmune disease treatment, offering the potential for precise immune modulation, long-term disease control, and restoration of immune tolerance. As scientific understanding and therapeutic technologies continue to advance, personalized immunotherapy is expected to become a cornerstone of future autoimmune disease management, improving patient outcomes and quality of life.

12. REFERENCES

1. Davidson A, Diamond B. Autoimmune diseases. *N Engl J Med*. 2001;345(5):340–350.
2. Rosenblum MD, Remedios KA, Abbas AK. Mechanisms of human autoimmunity. *J Clin Invest*. 2015;125(6):2228–2233.
3. Murphy K, Weaver C. *Janeway'sImmunobiology*. 9th ed. New York: Garland Science; 2017.
4. Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. *Immunity*. 2017;46(2):183–196.
5. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2011;365(22):2110–2121.
6. Dörner T, Furie R. Novel paradigms in systemic lupus erythematosus. *Lancet*. 2019;393(10188):2344–2358.
7. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023–2038.
8. Moulton VR, Tsokos GC. T cell signaling abnormalities in systemic lupus erythematosus. *CurrOpinRheumatol*. 2011;23(5):452–457.
9. Townsend MJ, Monroe JG, Chan AC. B-cell targeted therapies in autoimmune disease. *Immunity*. 2010;32(4):445–456.
10. Chan AC, Carter PJ. Therapeutic antibodies for autoimmunity. *Nat Rev Immunol*. 2010;10(5):301–316.
11. Feldmann M, Maini RN. TNF defined as a therapeutic target. *Nat Med*. 2003;9(10):1245–1250.
12. Keystone EC. IL-6 as a therapeutic target in rheumatoid arthritis. *Arthritis Res Ther*. 2008;10(Suppl 1):S2.
13. Genovese MC, et al. Tocilizumab in rheumatoid arthritis. *N Engl J Med*. 2008;359(7):677–688.
14. Edwards JCW, et al. Efficacy of B-cell depletion therapy with rituximab in RA. *N Engl J Med*. 2004;350(25):2572–2581.
15. Navarra SV, et al. Efficacy and safety of belimumab in SLE. *Lancet*. 2011;377(9767):721–731.

16. Furie R, et al. Anifrolumab in moderate-to-severe SLE. *N Engl J Med*. 2019;382(3):211–221.
17. Krueger JG, et al. IL-17 inhibition in autoimmune disease. *J Clin Invest*. 2012;122(4):1163–1170.
18. Bluestone JA, et al. Immune tolerance in autoimmune disease. *Nat Rev Immunol*. 2015;15(3):149–160.
19. Kremer JM, et al. Treatment of rheumatoid arthritis by blockade of T-cell costimulation with abatacept. *N Engl J Med*. 2003;349(20):1907–1915.
20. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252–264.
21. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. *Science*. 2018;359(6382):1361–1365.
22. Mackensen A, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat Med*. 2022;28(10):2124–2132.
23. Mougiakakos D, et al. Immune reconstitution after CAR-T therapy. *Nat Rev Rheumatol*. 2023;19(2):103–116.
24. Ellebrecht CT, et al. Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. *SciTransl Med*. 2016;8(333):333ra49.
25. Kansal R, Richardson N, Neeli I, et al. Sustained B cell depletion by CD19-targeted CAR T cells in autoimmunity. *Front Immunol*. 2019;10:1993.
26. Rezvani K, Rouce R, Liu E, Shpall E. Engineering natural killer cells for cancer immunotherapy. *Nat Rev ClinOncol*. 2020;17(7):425–440.
27. Bluestone JA, Tang Q. Therapeutic vaccination using regulatory T cells. *Nat Rev Immunol*. 2018;18(3):168–178.
28. Dazzi F, Ramasamy R, Glennie S, Jones SP, Roberts I. Mesenchymal stem cells and autoimmunity. *Nat Rev Rheumatol*. 2017;13(7):421–432.
29. Barrangou R, Doudna JA. Applications of CRISPR technologies in biology. *Science*. 2016;352(6290):aad4194.
30. Roth TL, et al. Reprogramming human T cell function with CRISPR/Cas9. *Nature*. 2018;559(7714):405–409.
31. Zhang Q, et al. Biomarkers in autoimmune diseases. *Clin Rev Allergy Immunol*. 2020;59(2):232–245.
32. Khatri P, et al. Ten years of systems immunology. *Nat Rev Immunol*. 2021;21(6):335–346.
33. Deeks ED. Anifrolumab: A review in systemic lupus erythematosus. *Drugs*. 2021;81(12):1371–1381.
34. Marshall HT, et al. Management of cytokine release syndrome. *Blood*. 2018;131(6):673–680.
35. Smolen JS, et al. Treat-to-target strategies in autoimmune disease. *Ann Rheum Dis*. 2020;79(6):685–699.

36. Liston A, Humblet-Baron S, Duffy D, Goris A. Human immune diversity. *Nat Immunol*. 2021;22(6):676–686.
37. Galli E, et al. Regulatory T cells in autoimmunity. *Autoimmun Rev*. 2019;18(6):558–565.
38. Selmi C. The worldwide gradient of autoimmune conditions. *Autoimmun Rev*. 2010;9(5):A247–A250.
39. Rose NR. Prediction and prevention of autoimmune disease. *Autoimmun Rev*. 2016;15(6):556–561.
40. Goodnow CC, Sprent J, Fazekas de St Groth B, Vinuesa CG. Cellular and genetic mechanisms of self tolerance. *Nat Rev Immunol*. 2005;5(3):241–252.