

Information of New Immunomodulators for Autoimmune Disease – A Review

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Abstract: Autoimmune diseases happen when the immune system mistakenly attacks the body's own cells, leading to long-term inflammation and tissue damage. Traditional medicines mainly suppress the whole immune system, which often causes many side effects and does not work for all patients. Because of this, new immunomodulators are being developed to target specific immune pathways, cells, or signals involved in autoimmune conditions. These new therapies include small-molecule inhibitors, biologic drugs, SIP receptor modulators, CAR-T cell therapy, tolerogenic vaccines, and microbiome-based approaches. They aim to control the disease more safely and effectively by correcting abnormal immune responses rather than blocking the entire immune system. This review explains the latest immunomodulators, their mechanisms, clinical progress, advantages, limitations, and future potential in treating autoimmune diseases.

Keywords: Immunomodulators; Autoimmune diseases; Targeted therapy; Biologics; Novel therapeutic approaches

I. INTRODUCTION

Autoimmune diseases are chronic conditions in which the immune system mistakenly identifies the body's own tissues as harmful and attacks them. Normally, the immune system protects the body from infections and foreign substances by recognizing "self" and "non-self" antigens. However, in autoimmune disorders, this balance breaks down due to a combination of genetic susceptibility, environmental triggers, hormonal influences, and alterations in immune regulation. As a result, patients experience long-lasting inflammation, pain, tissue destruction, and progressive functional impairment. Autoimmune diseases can affect almost any organ system, including joints in rheumatoid arthritis, skin in psoriasis, the nervous system in multiple sclerosis, and multiple organs in systemic lupus erythematosus. Due to their chronic nature, these illnesses significantly reduce quality of life, increase healthcare burden, and often require lifelong treatment [1]. The global prevalence of autoimmune disorders has been rising in recent decades, which is linked to changes in lifestyle, dietary habits, pollution, stress, and improved diagnostic technologies. Although each autoimmune disease has unique features, they share common immunological pathways such as loss of immune tolerance, overactivation of T cells and B cells, excessive cytokine production, and failure of regulatory mechanisms. Conventional therapies aim to reduce symptoms by providing broad immunosuppression. Examples include corticosteroids, methotrexate, azathioprine, and cyclophosphamide. While these medicines offer relief, they also suppress immunity widely, making patients more vulnerable to infections, metabolic problems, liver toxicity, and organ damage when used long-term. Moreover, many patients do not achieve complete remission, and some develop resistance or intolerance to these older drugs. This highlights the need for safer and more targeted therapeutic approaches [2]. In the past two decades, scientific understanding of immune mechanisms has advanced rapidly. Researchers have identified specific molecular pathways, cell receptors, and cytokine networks that drive autoimmunity. This knowledge has led to the development of new immunomodulators, which do not suppress the entire immune system but instead modify only the abnormal immune responses. These newer therapies include small-molecule inhibitors such as Janus kinase (JAK) inhibitors and Bruton's tyrosine kinase (BTK) inhibitors, biologic drugs like monoclonal antibodies, sphingosine-1-phosphate (S1P) receptor modulators, and novel strategies like CAR-T cell



therapy and tolerogenic vaccines. Because these treatments are more selective, they offer improved disease control with fewer systemic side effects. They also provide more personalized treatment options because different patients may have different immune pathways involved in their disease [3]. Another important reason for the development of newer immunomodulators is the unmet clinical need in severe and treatment-resistant autoimmune diseases. A significant number of patients fail to respond adequately to conventional therapies or experience frequent relapses. For example, some patients with lupus or multiple sclerosis continue to show disease progression despite taking multiple medicines. Newer immunomodulators aim to address this gap by targeting deeper levels of immune dysfunction, such as autoreactive B cell survival, cytokine amplification loops, or abnormal lymphocyte trafficking. These approaches help in achieving stable remission, reducing disease flares, and preventing long-term organ damage. Furthermore, some modern immunotherapies act faster, have predictable pharmacokinetics, and offer more convenient dosing options, which improves patient compliance and overall outcomes [4]. The introduction of biologics and targeted small molecules has also transformed the treatment landscape by improving our understanding of specific immune checkpoints. Biologics like anti-TNF, anti-IL-6, and anti-IL-17 antibodies have shown excellent efficacy in many autoimmune diseases. However, newer generations of immunomodulators are being designed to overcome limitations of earlier biologics, such as loss of efficacy due to antibody formation or incomplete pathway inhibition. Advanced technologies have led to the creation of bispecific antibodies, Fc-engineered molecules, and oral targeted drugs that provide longer duration of action with improved safety. Additionally, regenerative approaches like tolerogenic dendritic cell therapy and nanoparticle-based tolerance induction are emerging as promising alternatives to restore immune balance instead of merely suppressing inflammation [5]. Overall, autoimmune diseases represent a major global health challenge, and managing them requires continuous innovation in therapeutic strategies. New immunomodulators offer precise and effective ways to treat autoimmune disorders by focusing on disease-specific immune pathways. These advancements are expected to improve long-term disease control, minimize complications, and provide more personalized care. Therefore, understanding the mechanisms, advantages, and limitations of these new immunomodulators is essential for developing better therapeutic approaches and improving patient outcomes. This review summarizes the latest developments in new immunomodulators, their clinical applications, and future directions in autoimmune disease management [6].

2. Need for New Immunomodulators

The treatment of autoimmune diseases has traditionally depended on broad immunosuppressive drugs such as corticosteroids, methotrexate, azathioprine, and cyclophosphamide. While these medicines help reduce inflammation, they suppress the entire immune system instead of targeting only the harmful immune activity. This leads to several problems, including increased risk of infections, delayed wound healing, metabolic disturbances, and organ toxicity during long-term use. Many patients also experience inadequate symptom control or frequent disease flare-ups even after regular treatment. These limitations clearly show the urgent need for more selective, safer, and efficient therapeutic agents capable of regulating specific immune pathways without affecting normal immunity [7]. Another major reason new immunomodulators are needed is the rise in the number of patients who develop resistance or intolerance to existing therapies. In some autoimmune diseases, such as systemic lupus erythematosus or multiple sclerosis, patients may respond initially but later lose responsiveness due to drug resistance or antibody formation against biologic drugs. Additionally, some patients suffer from severe side effects that force them to discontinue treatment. These issues highlight the necessity to discover and develop immunomodulators that can work on new molecular targets, provide sustained benefits, and minimize unwanted effects. Modern research has identified several important immune checkpoints, cytokines, signaling molecules, and cell-based pathways that can be precisely regulated by newer therapies to provide better disease management [8]. New immunomodulators are also needed to improve long-term outcomes and prevent irreversible organ damage. Many autoimmune disorders cause progressive damage to joints, nerves, kidneys, or the gastrointestinal tract if not treated early with effective therapy. Traditional drugs may help control symptoms but often fail to offer long-term protection against disease progression. Newer targeted



immunomodulators such as JAK inhibitors, BTK inhibitors, SIP receptor modulators, monoclonal antibodies, and tolerogenic cell-based therapies aim to interrupt the disease at its root by modifying the underlying immune dysfunction instead of only suppressing inflammation. These advanced therapies provide improved remission rates, reduced organ damage, and better quality of life, making them essential for modern autoimmune disease management [9].

3. Classification of New Immunomodulators

New immunomodulators can be classified based on their mechanism of action, molecular target, or therapeutic approach. Understanding this classification helps clinicians select appropriate therapies and researchers design better drugs. Broadly, these agents are divided into small molecule inhibitors, biologics, cell-based therapies, tolerogenic vaccines, and microbiome-based therapies [10].

1. Small-molecule inhibitors are orally administered drugs that target intracellular signalling pathways essential for immune cell activation. Examples include JAK inhibitors (tofacitinib, baricitinib, upadacitinib) and BTK inhibitors (ibrutinib, neratinib). JAK inhibitors block the JAK–STAT pathway, reducing the production of inflammatory cytokines, while BTK inhibitors suppress B-cell receptor signalling, decreasing autoantibody production. These drugs offer rapid action, oral dosing convenience, and reversible effects compared to traditional immunosuppressants [11].

2. Biologics are protein-based therapies, usually monoclonal antibodies or fusion proteins, that target specific immune molecules. Examples include anti-cytokine antibodies (anti-TNF, anti-IL-6, anti-IL-17), B-cell–targeting antibodies (rituximab, ocrelizumab), and co-stimulation modulators (abatacept, CD40–CD40L blockers). Biologics selectively neutralize disease causing cytokines or deplete specific immune cells, offering targeted immunomodulation with reduced systemic toxicity. Advances in engineering, such as bispecific antibodies and Fc modifications, have improved efficacy, half-life, and safety [12].

3. Cell-based therapies include CAR-T regulatory cells (CAR-Tregs) and tolerogenic dendritic cells. CAR-Tregs are genetically engineered T-cells designed to suppress autoreactive immune responses, while tolerogenic dendritic cells present antigens in a way that induces immune tolerance. These therapies can provide long-term disease control by reprogramming the immune system rather than broadly suppressing it [13].

4. Tolerogenic vaccines and antigen-specific immunotherapies aim to retrain the immune system to recognize self-antigens as harmless. These include peptide-based vaccines, mRNA vaccines, or nanoparticle-delivered antigens. By inducing antigen-specific regulatory T-cells, these vaccines reduce autoimmune responses without compromising overall immunity. They are being studied for multiple sclerosis, type 1 diabetes, and other autoimmune disorders [14].

5. Microbiome-based therapies manipulate the gut microbiota or use microbial metabolites to influence immune regulation. Dysbiosis, an imbalance in gut bacteria, is associated with increased autoimmune activity. Interventions such as probiotics, engineered microbial strains, or faecal microbiota transplantation (FMT) aim to restore a healthy microbial balance, thereby modulating systemic immunity and reducing inflammation. These therapies are experimental but show promise in diseases like inflammatory bowel disease and rheumatoid arthritis [15]. In summary, the classification of new immunomodulators reflects the increasing precision in autoimmune therapy, ranging from targeted small molecules to advanced cellular and microbiome-based strategies. Each class has unique mechanisms, advantages, and clinical applications, providing multiple options for individualized treatment [10–15].

4. Mechanism of Action of New Immunomodulators

New immunomodulators act by selectively targeting immune pathways that are dysregulated in autoimmune diseases. Unlike conventional immunosuppressants, which broadly suppress immune function, these therapies aim to correct abnormal immune responses while leaving normal immunity largely intact. The main mechanisms include cytokine inhibition, blockade of intracellular signalling pathways, B-cell modulation, lymphocyte trafficking control, stimulation blockade, and induction of immune tolerance [16].

1. Cytokine inhibition is one of the most widely used mechanisms. In autoimmune disorders, proinflammatory cytokines such as TNF- α , IL-6, IL-17, and IL-23 play a key role in mediating tissue inflammation and damage.



Monoclonal antibodies like infliximab (anti-TNF), tocilizumab (anti-IL-6), and eculizumab (anti-IL-17) selectively bind to these cytokines or their receptors, neutralizing their effects. By doing this, immune cells receive fewer inflammatory signals, which reduces swelling, pain, and tissue destruction in conditions such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease [17].

2. JAK–STAT pathway inhibition is another critical mechanism. Small-molecule drugs like tofacitinib, baricitinib, and upadacitinib inhibit Janus kinase (JAK) enzymes, preventing cytokine mediated signal transmission into the nucleus. Overactive JAK–STAT signalling contributes to excessive production of inflammatory molecules. By blocking this pathway, JAK inhibitors can suppress multiple inflammatory signals simultaneously, offering a broader but controlled anti-inflammatory effect [18].

3. B-cell targeted therapy focuses on reducing autoantibody production and B-cell activity. B-cells are responsible for producing antibodies that attack self-tissues in autoimmune diseases. Therapies such as rituximab (anti-CD20), ocrelizumab, and BAFF inhibitors (e.g., belimumab) either deplete B-cells or inhibit their survival. This mechanism is particularly effective in systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis, as it reduces disease flare-ups and slows progression [19].

4. Lymphocyte trafficking modulation prevents pathogenic immune cells from reaching target tissues. Sphingosine-1-phosphate (S1P) receptor modulators, such as fingolimod, trap lymphocytes within lymph nodes, reducing the number of T-cells entering inflamed organs. This targeted control of immune cell movement is especially beneficial in multiple sclerosis and inflammatory bowel disease, as it limits local inflammation while preserving systemic immunity [20].

5. Co-stimulation blockade is an emerging approach that interferes with T-cell activation. Drugs like abatacept (CTLA-4-Ig) and CD40–CD40L blockers prevent antigen-presenting cells from fully activating T-cells. Without co-stimulation, autoreactive T-cells remain inactive, reducing immune-mediated tissue damage. This mechanism is more physiological than broad immunosuppression and is under investigation for rheumatoid arthritis, systemic lupus erythematosus, and other autoimmune disorders [21].

6. Induction of immune tolerance is a novel mechanism employed by cellular therapies and tolerogenic vaccines. CAR-T regulatory cells (CAR-Tregs) and tolerogenic dendritic cells help re-educate the immune system to tolerate self-antigens. By enhancing regulatory T-cell activity or presenting antigens in a tolerogenic context, these therapies aim to restore immune balance and achieve long-term remission without general immune suppression [22]. In conclusion, new immunomodulators use a variety of precise mechanisms to target the key drivers of autoimmunity. Their selective action allows for improved efficacy, fewer side effects, and personalized therapy compared with traditional immunosuppressive drugs. Understanding these mechanisms is essential for designing new therapies and improving outcomes in autoimmune diseases [16–22].

5. Therapeutic Applications of New Immunomodulators

New immunomodulators have dramatically transformed the management of autoimmune diseases by offering targeted therapies that address the underlying immune dysregulation. Unlike conventional immunosuppressants, which broadly inhibit immune function and often cause systemic side effects, these novel agents act on specific immune pathways, allowing precise control over disease activity while preserving normal immune responses. They are increasingly applied in a variety of autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis, inflammatory bowel disease, and type 1 diabetes, each with unique mechanisms and therapeutic considerations [23]. In rheumatoid arthritis, a chronic autoimmune condition characterized by synovial inflammation, joint pain, and progressive cartilage and bone destruction, new immunomodulators have improved disease outcomes substantially. JAK inhibitors such as tofacitinib, baricitinib, and upadacitinib suppress the JAK–STAT signalling pathway, reducing the production of pro-inflammatory cytokines and limiting synovial inflammation. Biologic agents like anti-TNF monoclonal antibodies, including infliximab and adalimumab, neutralize tumour necrosis factor-alpha, a central mediator of inflammation, resulting in reduced joint swelling, pain, and damage. B-cell targeted therapies, including rituximab, deplete autoreactive B-cells, which are responsible for the production of pathogenic



autoantibodies. Clinical studies have shown that these therapies not only reduce disease activity and flares but also improve physical function and quality of life for RA patients [24]. Systemic lupus erythematosus is a complex autoimmune disease affecting multiple organ systems, including the kidneys, skin, joints, and hematologic compartments. B-cell modulating agents such as BAFF inhibitors (belimumab) selectively decrease the survival of autoreactive B-cells, reducing autoantibody formation and systemic inflammation. Type I interferon inhibitors, such as alirocumab, suppress the overactive interferon pathway, which plays a pivotal role in SLE pathogenesis. Co-stimulation blockers like abatacept prevent T-cell activation, thereby reducing immune-mediated tissue damage. These targeted approaches have been shown to achieve better disease remission, decrease the reliance on corticosteroids, and improve long-term organ protection [25]. Multiple sclerosis, a demyelinating autoimmune disorder of the central nervous system, has also benefited from advanced immunomodulatory therapies. Sphingosine-1-phosphate receptor modulators, including fingolimod and ozanimod, prevent autoreactive lymphocytes from leaving lymph nodes, reducing their infiltration into the central nervous system and limiting neuroinflammation. B-cell depleting antibodies such as ocrelizumab reduce pathogenic B-cell populations that contribute to myelin destruction. Emerging cellular therapies, including CAR-T regulatory cells, show promise in inducing immune tolerance and potentially achieving long-term disease remission by directly modulating autoreactive immune responses [26]. Psoriasis and psoriatic arthritis are autoimmune conditions characterized by hyperactive Th17 responses, leading to skin lesions, joint inflammation, and systemic comorbidities. Monoclonal antibodies targeting IL-17 (eculizumab) and IL-23 (rusalka) effectively reduce inflammatory signalling and improve both cutaneous and joint symptoms. Small-molecule inhibitors like apremilast, a phosphodiesterase 4 inhibitor, modulate intracellular signalling pathways, resulting in reduced cytokine production. These therapies are associated with rapid clinical improvements, decreased flare frequency, and enhanced quality of life for patients with moderate-to-severe disease [27]. Inflammatory bowel disease, including Crohn's disease and ulcerative colitis, involves chronic gastrointestinal inflammation driven by dysregulated immune responses. Anti-TNF agents and IL12/23 inhibitors such as ustekinumab neutralize inflammatory cytokines, mitigating intestinal damage. S1P receptor modulators restrict lymphocyte trafficking to inflamed gut tissue, decreasing local inflammation. Microbiome-based therapies, including faecal microbiota transplantation and engineered probiotics, are being investigated as novel approaches to restore immune homeostasis via gut microbial modulation [28]. Type 1 diabetes, caused by autoimmune destruction of pancreatic β - cells, is another area where immunomodulators are being explored. Antigen-specific tolerogenic vaccines aim to retrain the immune system to tolerate pancreatic antigens, preventing or slowing β -cell destruction. Early-phase studies using CAR-T regulatory cells and peptide-based vaccines have demonstrated potential in preserving residual β -cell function, delaying disease progression, and reducing insulin dependency. These approaches offer hope for long-term disease control without global immunosuppression. Overall, the therapeutic application of new immunomodulators highlights the shift toward precision medicine in autoimmune disease management. By selectively targeting disease-relevant immune pathways, these therapies provide more effective control, reduced adverse effects, and improved patient quality of life. Ongoing research continues to expand their indications, optimize dosing regimens, and explore combination strategies, making them central to the future of autoimmune therapy [23–28].

6. Advantages and Limitations of New Immunomodulators

New immunomodulators have revolutionized autoimmune disease therapy by offering precise targeting of pathological immune pathways, minimizing systemic immunosuppression, and improving patient outcomes. One of the primary advantages is specificity. Unlike conventional immunosuppressants, which broadly suppress the immune system, these agents act selectively on cytokines, immune cells, or signalling pathways that drive autoimmune pathology. This selective action reduces the risk of infections, malignancies, and other systemic side effects that are commonly seen with older therapies [29]. Another significant advantage is the ability to achieve faster disease control. Small-molecule inhibitors, such as JAK inhibitors, and biologics, including anti-TNF and anti-IL-17 antibodies, can rapidly reduce inflammation, alleviate symptoms, and improve quality of life. Many patients experience improvements within weeks,



which is substantially faster than conventional disease-modifying therapies [30]. Additionally, the availability of multiple drug classes allows for personalized therapy, enabling clinicians to select the most appropriate treatment based on the specific disease mechanism, severity, and patient characteristics. This individualized approach increases efficacy and reduces unnecessary exposure to less effective treatments [31]. New immunomodulators also provide long-term disease management by not only suppressing active inflammation but also modulating immune tolerance. Cellular therapies, such as CAR-T regulatory cells and tolerogenic dendritic cells, aim to reprogram the immune system to tolerate self-antigens, offering the potential for sustained remission and reduced relapse frequency. Furthermore, some therapies, like microbiome-based interventions, may improve systemic immune homeostasis and overall health beyond disease specific outcomes [32]. Despite these advantages, new immunomodulators also have limitations. One key challenge is high cost, which can limit accessibility, particularly in low- and middle- income countries. Biologics and cellular therapies often require complex manufacturing processes, specialized storage, and hospital-based administration, adding to the financial burden. Another limitation is the risk of immunogenicity, where the body generates antibodies against biologic agents, reducing their efficacy over time and sometimes causing adverse reactions [33].

7. Future Perspectives and Emerging Therapies

The field of immunomodulation is moving toward precision-targeted and potentially curative therapies, building on the successes of small molecules, biologics, and cellular treatments. One of the most promising avenues is the development of next-generation biologics, including bispecific and Mult specific antibodies. Unlike traditional monoclonal antibodies, which target a single cytokine or receptor, bispecific antibodies can simultaneously bind two different immune molecules, enhancing therapeutic efficacy. For example, a bispecific antibody targeting both TNF α and IL-17 could more effectively control inflammation in severe rheumatoid arthritis or psoriatic arthritis, particularly in patients who do not respond to single-target therapies. The design of these molecules also allows for tuning their pharmacokinetics and tissue specificity, potentially reducing systemic side effects while maximizing local disease control [34]. Cell-based therapies are rapidly advancing as an area of transformative potential. Beyond conventional CAR-T regulatory cells, researchers are developing engineered Tregs, mesenchymal stem cells, and tolerogenic dendritic cells that can actively restore immune tolerance. These therapies work by suppressing autoreactive T-cells, promoting regulatory immune responses, and even enhancing tissue repair in damaged organs such as the kidneys in lupus nephritis or the CNS in multiple sclerosis. Gene-editing technologies, particularly CRISPR-Cas9, allow precise modifications in immune cells to enhance their specificity, persistence, and safety, opening the possibility of creating patient-specific cellular therapies that are both highly effective and durable [35]. Antigen-specific tolerogenic vaccines represent another exciting frontier. These vaccines aim to selectively educate the immune system to tolerate disease-specific autoantigens without impairing global immunity. Advances in nanoparticle delivery systems, mRNA platforms, and peptide-based vaccines allow for precise antigen presentation that promotes regulatory T-cell activation while minimizing inflammatory responses. Early-stage trials in conditions like type 1 diabetes and multiple sclerosis have shown that these vaccines can reduce autoimmune attack on target tissues, preserving function while limiting side effects compared to systemic immunosuppression [36]. The human microbiome is increasingly recognized as a critical factor in autoimmunity, and future therapies may harness its immunomodulatory potential. Dysbiosis, an imbalance in gut microbial communities, can drive aberrant immune activation. Therapies targeting the microbiome include engineered probiotic strains, prebiotics, and fecal microbiota transplantation (FMT). These approaches aim to restore microbial balance, enhance regulatory immune cell populations, and reduce systemic inflammation. Combining microbiome-based interventions with traditional immunomodulators could provide synergistic effects, improving clinical outcomes in diseases such as inflammatory bowel disease and systemic lupus erythematosus [37]. Finally, precision medicine and biomarker guided therapy are poised to revolutionize autoimmune disease management. Advances in genomics, proteomics, single-cell RNA sequencing, and metabolomics enable the identification of patient-specific disease mechanisms and immune signatures. Clinicians can use these biomarkers to tailor therapy selection,



dosing, and monitoring, optimizing efficacy and minimizing adverse effects. This approach could allow for stratification of patients, identifying which individuals are most likely to respond to a particular immunomodulator, which may also guide early interventions to prevent disease progression [38]. In summary, the future of immunomodulation lies in highly targeted, personalized, and potentially curative therapies. Next-generation biologics, cellular therapies, antigen-specific vaccines, microbiome-based interventions, and precision medicine strategies collectively promise to redefine the management of autoimmune diseases. By integrating these approaches, future treatment paradigms may achieve sustained remission, reduced reliance on chronic immunosuppression, and improved patient quality of life, while minimizing long-term adverse effects. As research progresses, clinical translation of these therapies will likely transform autoimmune care, moving from symptom management toward restoring immune balance and long-term disease control [34–38].

8. Drug Development and Clinical Trials

The development of new immunomodulators for autoimmune diseases is a complex and rigorous process that integrates basic research, preclinical studies, and clinical trials. Drug discovery begins with identifying novel molecular targets, such as specific cytokines, receptors, or immune cell subsets, that play critical roles in disease pathogenesis. High-throughput screening, bioinformatics, and molecular modelling are commonly used to design small molecules or biologics that can selectively modulate these targets. Preclinical studies in cell cultures and animal models help to assess efficacy, safety, pharmacokinetics, and potential toxicities before moving to human trials [39]. Once a promising candidate is identified, it enters the clinical trial phase, which typically consists of three stages. Phase I trials involve a small group of healthy volunteers or patients to evaluate safety, tolerability, and pharmacokinetics. These trials help determine the appropriate dose range and identify early adverse effects. Phase II trials are conducted in a larger patient population to assess efficacy, dose-response relationships, and further evaluate safety. In autoimmune diseases, these trials often measure clinical endpoints such as reduction in disease activity scores, improvement in organ function, or biomarker modulation [40]. Phase III trials involve large-scale, multicentre studies to confirm therapeutic efficacy and monitor long-term safety. They are critical for regulatory approval and often compare the new immunomodulator with standard-of-care treatments. Randomized, double-blind, placebo-controlled designs are considered the gold standard to minimize bias. Examples of recent Phase III trials include studies evaluating JAK inhibitors in rheumatoid arthritis, IL-17 inhibitors in psoriasis, and B-cell depleting therapies in systemic lupus erythematosus, demonstrating significant improvement in clinical outcomes compared to conventional therapies [41]. Beyond Phase III, post-marketing surveillance (Phase IV) is essential to monitor rare adverse effects, long-term safety, and effectiveness in broader patient populations. Real-world data from registries and observational studies provide valuable insights into long-term treatment adherence, durability of response, and potential drug interactions. Adaptive trial designs and biomarker-driven studies are increasingly being implemented to optimize dosing and patient selection, reflecting the growing trend toward precision medicine in autoimmune therapy [42]. Recent advances in innovative trial designs have accelerated drug development. For instance, umbrella trials allow multiple therapies to be tested simultaneously in patients stratified by molecular biomarkers, while basket trials test a single therapy across multiple autoimmune disorders with shared pathogenic pathways. Such approaches reduce development time and cost, while increasing the likelihood of identifying effective therapies for specific patient subgroups. Additionally, artificial intelligence and machine learning are being applied to predict drug responses, identify adverse effects, and optimize trial design, further streamlining the path from discovery to clinical application [43].

9. Pharmacokinetics and Pharmacodynamics

Understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of new immunomodulators is crucial for optimizing therapy in autoimmune diseases. Pharmacokinetics refers to how the body absorbs, distributes, metabolizes, and excretes a drug, while pharmacodynamics describes how the drug interacts with its molecular targets to produce therapeutic effects. Both PK and PD determine the efficacy, safety, and dosing regimen of immunomodulators [44].



Absorption and bioavailability are key PK factors, particularly for biologics and small molecules. Most biologics, such as monoclonal antibodies, are administered via subcutaneous or intravenous routes due to poor oral absorption. Their large molecular size prevents effective gastrointestinal uptake. In contrast, small molecules like JAK inhibitors are orally bioavailable, making them more convenient for chronic therapy. Factors such as drug formulation, patient age, gastrointestinal conditions, and concomitant medications can influence absorption and systemic availability [45]. Distribution describes how immunomodulators are dispersed throughout the body. Biologics primarily remain in the vascular and interstitial spaces due to their large size, whereas small molecules can penetrate tissues more readily, including inflamed synovium or the central nervous system. Protein binding and tissue affinity also play a role in drug distribution. Understanding distribution is important for predicting therapeutic concentrations at disease sites and for evaluating potential off-target effects [46]. Metabolism and elimination are critical for drug clearance. Biologics are metabolized by proteolytic degradation in the reticuloendothelial system, whereas small molecules undergo hepatic metabolism through cytochrome P450 enzymes. Renal and biliary excretion can also affect drug clearance. Impaired liver or kidney function can lead to drug accumulation, increasing the risk of toxicity. Therefore, PK studies guide dose adjustments in patients with organ dysfunction [45,46]. Pharmacodynamics focuses on the drug's interaction with immune targets and the resulting biological effects. For instance, JAK inhibitors block the JAK-STAT signalling pathway, reducing the transcription of proinflammatory cytokines, while monoclonal antibodies like anti-TNF agents neutralize TNF- α to prevent tissue inflammation. PD studies often measure biomarkers such as cytokine levels, autoantibody titers, or cell population changes to correlate drug exposure with clinical efficacy. Dose-response relationships are essential for determining the optimal balance between efficacy and safety [44,47]. Therapeutic drug monitoring (TDM) is increasingly applied to immunomodulators to ensure effective drug concentrations while minimizing adverse effects. For biologics, measuring serum trough levels and anti-drug antibodies helps predict treatment response and guide dose adjustments. For small molecules, PK/PD modelling can optimize dosing schedules, reduce toxicity, and personalize therapy. TDM is particularly important in autoimmune diseases where individual variability in drug metabolism, immune response, and disease severity can affect outcomes [47].

10. Safety and Adverse Effects

The safety of new immunomodulators is a critical consideration in autoimmune disease management. Although these therapies provide targeted suppression of pathogenic immune responses, they can also disrupt normal immunity, resulting in adverse effects that range from mild to severe. Careful monitoring and preventive strategies are essential to minimize risks [48]. Infections are among the most significant adverse effects. Biologics such as anti-TNF, anti-IL-6, and B-cell depleting agents impair the body's ability to fight infections, leading to opportunistic infections like tuberculosis, pneumocystis pneumonia, viral hepatitis, and systemic fungal infections. The risk is higher in patients receiving combination therapies, elderly patients, or those with comorbidities. Preventive measures include screening for latent infections, vaccination prior to therapy initiation, and patient education for early detection of symptoms [49]. Immunogenicity, or the formation of anti-drug antibodies (ADAs), is another key safety concern for biologics. ADAs can neutralize therapeutic effects, shorten drug half-life, or trigger hypersensitivity reactions ranging from rashes and fever to severe anaphylaxis. Repeated dosing of agents like infliximab or adalimumab increases the likelihood of ADA development. Regular therapeutic drug monitoring can detect ADAs and guide dose adjustment or switching to alternative therapies [50]. Organ specific toxicities have been observed with small-molecule inhibitors. JAK inhibitors may cause hematologic abnormalities, including anaemia, neutropenia, and thrombocytopenia. Hepatotoxicity is also reported, necessitating routine liver function monitoring. Certain JAK inhibitors are associated with cardiovascular events, such as thromboembolism and myocardial infarction, especially in patients with pre-existing cardiovascular risk factors. These risks emphasize careful patient selection and individualized therapy [51]. Long-term safety concerns include the risk of malignancy and chronic immunosuppression. Although clinical trials have not shown a substantial increase in cancer incidence, long-term observational studies are critical to identify late-onset adverse effects. Chronic immunosuppression may also reduce vaccine efficacy and delay wound healing. Patients on long-term combination



therapy with multiple immunosuppressants require close follow-up and risk assessment [52]. Management strategies focus on minimizing adverse effects while maintaining therapeutic efficacy. Approaches include dose adjustment, temporary discontinuation, switching to alternative agents, and supportive care. Proactive measures such as vaccination, infection screening, patient education, and monitoring biomarkers or drug levels improve safety outcomes [53].

11. Challenges and Research Gaps

Despite the remarkable advances in immunomodulatory therapies, several challenges continue to hinder optimal treatment of autoimmune diseases. One of the primary obstacles is the heterogeneity of autoimmune disorders. Diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and psoriasis are highly variable in terms of clinical presentation, underlying pathophysiology, and immunological profiles. This heterogeneity makes it difficult to predict which patients will respond to a particular therapy, resulting in variable efficacy across patient populations. Genetic differences, variations in cytokine expression, and differences in immune cell composition further complicate patient stratification [54]. Long-term safety and tolerability remain major concerns. While most immunomodulators demonstrate favourable safety profiles in short-term trials, data on prolonged use over years or decades are limited. Chronic use can lead to cumulative adverse effects such as opportunistic infections, malignancy, organ toxicity, and cardiovascular events. For example, long-term anti-TNF therapy has been associated with increased susceptibility to tuberculosis and reactivation of latent viral infections. Similarly, prolonged JAK inhibitor therapy can increase the risk of thromboembolic events in susceptible individuals. There is a pressing need for long-term registries and postmarketing surveillance studies to better understand these risks and to develop monitoring guidelines [55]. Economic and accessibility barriers also restrict the global impact of new immunomodulators. Biologics require complex recombinant technology, strict cold-chain logistics, and specialized administration, all of which contribute to high costs. Patients in low- and middle-income countries often cannot access these therapies due to financial constraints or healthcare infrastructure limitations. Even in high-income countries, insurance coverage and reimbursement policies significantly influence treatment availability, creating healthcare disparities. Addressing these challenges requires cost-effective strategies such as biosimilars, generic alternatives, patient assistance programs, and government subsidies [56]. A major research gap lies in precision medicine and biomarker development. Currently, clinicians have limited tools to predict which patients will respond optimally to specific immunomodulators. Although some biomarkers such as autoantibody profiles, cytokine levels, and gene-expression signatures have been studied, most are not validated for routine clinical use. Without reliable predictive biomarkers, treatment often involves a trial-and-error approach, which can delay effective therapy and expose patients to unnecessary adverse effects. Research into multi-omics approaches, single cell analysis, and computational modelling may provide solutions to enable personalized immunomodulator therapy in the future [57]. Emerging therapies, including cellular and gene based immunomodulators, introduce new challenges in terms of technical feasibility, regulatory approval, immunogenicity, scalability, and ethical concerns. For example, CAR-T cell therapies and gene-editing approaches like CRISPR-Cas9 show promise in autoimmune disease management, but large-scale production, stability, cost, and long-term safety remain significant hurdles. Additionally, ethical considerations regarding genome manipulation and the potential for off-target effects must be addressed. These challenges highlight the need for robust preclinical models, standardized protocols, and extensive clinical trials before such therapies can be widely adopted [58]. Another important challenge is the integration of real-world evidence into clinical decision-making. Most current knowledge comes from controlled clinical trials, which often exclude patients with comorbidities or atypical disease presentations. Real-world data on effectiveness, adherence, and long-term safety in diverse patient populations are limited. Integrating electronic health records, patient registries, and pharmacovigilance data can provide valuable insights into treatment optimization and help bridge the gap between trial outcomes and routine clinical practice [54]. Finally, the rapid pace of therapeutic innovation creates a knowledge gap among clinicians. With new biologics, small molecules, and combination therapies constantly entering the market, staying updated on efficacy, safety profiles, drug interactions, and administration protocols is challenging. Continuous



medical education, clinical guidelines updates, and interdisciplinary collaboration are essential to ensure safe and effective use of these advanced therapies [55]. In conclusion, although new immunomodulators have significantly improved the management of autoimmune diseases, several challenges and research gaps remain. Addressing disease heterogeneity, ensuring long-term safety, improving cost-effectiveness and accessibility, validating biomarkers for precision therapy, evaluating emerging cellular and gene-based therapies, and integrating real-world data are critical for optimizing treatment outcomes.[56].

II. CONCLUSION

The development of new immunomodulators has revolutionized the treatment of autoimmune diseases, offering targeted therapies that can effectively modulate immune responses while minimizing systemic side effects. Biologics and small-molecule inhibitors have transformed disease management, reducing inflammation, preventing tissue damage, and improving patient quality of life. The integration of these therapies into clinical practice represents a significant advancement over traditional immunosuppressive drugs. Despite these advances, challenges such as disease heterogeneity, variable patient responses, long-term safety concerns, high cost, and limited accessibility remain. The lack of validated predictive biomarkers limits the ability to tailor therapy to individual patients, often requiring a trial-and-error approach. Emerging therapies, including cellular and gene-based immunomodulators, hold great promise but face hurdles related to safety, technical feasibility, ethical considerations, and large-scale clinical translation. Addressing these challenges requires a multi-faceted approach that includes long-term safety studies, cost-reduction strategies such as biosimilars, development of precision medicine tools, and the integration of real-world data into clinical decision-making. Collaborative efforts among researchers, clinicians, policymakers, and patient advocacy groups are essential to ensure equitable access and optimize treatment outcomes. In summary, while new immunomodulators have significantly improved the management of autoimmune diseases, ongoing research and innovation are essential to fully realize their potential. Personalized therapy, improved accessibility, and continued evaluation of long-term safety will be key factors in shaping the future of autoimmune disease management, ultimately enhancing patient care and quality of life.

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