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Research Progress and Clinical Challenges of Precision Targeted Therapy for Autoimmune Diseases

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Abstract

The treatment of autoimmune diseases is undergoing a paradigm shift from "broad-spectrum immunosuppression" toward "precision targeted intervention." Although conventional synthetic disease-modifying antirheumatic drugs (such as methotrexate) remain the cornerstone of therapy, their efficacy ceiling and cumulative toxicity limit long-term use, and clinical practice still has safety gaps, such as inadequate folic acid supplementation. The advent of targeted biologic agents (e.g., TNF-α inhibitors, IL-6R antagonists) and JAK inhibitors has enabled precise blockade of specific inflammatory pathways. However, studies such as ORAL Surveillance have revealed a "safety paradox" of JAK inhibitors regarding cardiovascular and thrombotic risks, highlighting the need for a careful balance between efficacy and risk in clinical practice. To address the clinical challenge of secondary loss of response, precision-switching strategies grounded in immunogenicity theory and therapeutic drug monitoring—including same-target cycling and cross-pathway switching—have emerged as core approaches to optimize efficacy. Meanwhile, bispecific antibodies and CAR-T cell therapies have demonstrated potential breakthrough value in refractory autoimmune diseases; however, their long-term safety, suitability for specific patient populations, and accessibility require further validation through larger-scale clinical studies.

Keywords

targeted therapy, autoimmune diseases, JAK inhibitors, immunogenicity, CAR-T therapy, precision medicine

1. Introduction

Autoimmune diseases (ADs) are a group of chronic inflammatory disorders caused by the breakdown of immune tolerance mechanisms and subsequent aberrant attacks of the immune system on self-tissues, with their prevalence showing a continuous upward trend [1]. In China alone, the number of patients with rheumatoid arthritis (RA) has exceeded 5 million [2]. These diseases are characterized by a protracted course, recurrent episodes, and a high disability rate, severely impairing patients' physical and mental health as well as their quality of life.

For a long time, the treatment of autoimmune diseases has relied primarily on glucocorticoids and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Although glucocorticoids can rapidly control acute-phase inflammation, their long-term use may lead to multisystem adverse effects such as osteoporosis and an increased risk of infections, placing patients in a therapeutic dilemma. The efficacy of

csDMARDs, represented by methotrexate (MTX), has a clear "ceiling effect"—approximately 30%–40% of RA patients have an inadequate response to MTX monotherapy [3], Moreover, it has limitations such as slow onset of action, hepatotoxicity, and bone marrow suppression. More critically, the core of traditional therapeutic strategies is "broad-spectrum immunosuppression," which achieves symptom relief by non-selectively suppressing overall immune function—acting as a blunt instrument—without fundamentally correcting the imbalance in the immune regulatory network.

It is this clinical dilemma that has spurred the introduction of the "treat-to-target" (T2T) strategy, which requires clinicians to control disease activity more quickly and precisely. The advent of targeted biologic agents and oral small-molecule targeted drugs has ushered the treatment of autoimmune diseases into a new era of "precision guidance." This article focuses primarily on rheumatoid arthritis (RA) as the representative disease, while also covering systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and others, systematically reviewing the therapeutic landscape, core challenges, and future directions of targeted therapy, to provide a reference for precise drug selection and strategy switching in clinical practice.

2. Therapeutic Landscape and Mechanistic Insights of Targeted Therapy

2.1 TNF-α Inhibitors: Cornerstone Status and Differential Selection

Tumor necrosis factor-alpha (TNF-α) is a core pro-inflammatory cytokine in the inflammatory cascade of autoimmune diseases. TNF-α inhibitors (TNFi), as the first approved biologic agents, remain a first-line choice for RA and AS. The TNFi commonly used in clinical practice mainly fall into three categories: infliximab (a chimeric monoclonal antibody), adalimumab (a fully human monoclonal antibody), and etanercept (a receptor fusion protein).

The most critical difference among the three lies in their ability to act on transmembrane TNF-α. Infliximab and adalimumab can induce complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) in immune cells expressing transmembrane TNF, thereby inducing apoptosis. In contrast, etanercept lacks this capacity. This mechanistic difference is particularly evident in the risk of *Mycobacterium tuberculosis* reactivation. Because transmembrane TNF signaling is essential for maintaining granuloma integrity, drugs that induce apoptosis are more likely to disrupt established tuberculosis granulomas, thereby reactivating latent infection. Data show that the incidence of tuberculosis reactivation in patients treated with infliximab is significantly higher than in those treated with etanercept [4].

Regarding disease alignment, TNFi play an irreplaceable role in improving the axial symptoms of AS, with 40–60% of patients achieving a ≥50% improvement in the BASDAI score [5], whereas approximately 30%–40% of patients with RA exhibit primary nonresponse [6].

2.2 Non-TNF Pathways: Precision Targeting and Salvage Strategies

For patients who fail TNFi therapy, non-TNF targeted agents provide effective alternative options, with different drugs demonstrating unique advantages in specific subgroups.

Anti-IL-6R monoclonal antibody (tocilizumab) exerts its anti-inflammatory effects by blocking IL-6 signaling. Its two unique features are: first, it suppresses CRP rapidly (returning to normal levels within 24-48 hours) [7], providing an objective basis for early clinical decision-making; second, it offers a distinct benefit for RA-associated anemia—by blocking IL-6-induced hepcidin elevation, iron utilization efficiency is restored. Tocilizumab is primarily indicated for RA patients with a high inflammatory response or anemia after TNFi failure, and it is also the only biologic agent approved for giant cell arteritis (GCA).

T cell co-stimulation modulator (abatacept) inhibits complete T cell activation by blocking the interaction between CD80/CD86 and CD28. Its advantages are particularly prominent in two RA subgroups: first, patients with high ACPA titers (mechanistic studies suggest that ACPA-positive RA is highly dependent on T-B cell collaboration); second, RA patients with comorbid interstitial lung disease (ILD)—while both TNFi and IL-6 inhibitors are associated with worsening of ILD, abatacept has demonstrated a significantly superior safety profile in this setting.

Rituximab works by eliminating CD20-positive B cells, thereby blocking autoantibody production and antigen presentation. Although its use in RA has been gradually replaced by TNFi, its role as a salvage therapy in refractory SLE (particularly lupus nephritis) and ANCA-associated vasculitis (AAV) remains irreplaceable. Real-world studies have shown that rituximab enables a ≥4-point reduction in the SLEDAI score in 60-70% of patients with severe SLE [8], and it has become a first-line option for remission induction in AAV.

2.3 JAK Inhibitors: Balancing Oral Convenience and Safety

JAK inhibitors exert their effects by competitively binding to the ATP-binding site of JAK kinases, thereby simultaneously blocking the intracellular signaling of multiple pro-inflammatory cytokines (including IL-2, IL-6, IL-12, and IL-23). Compared with biologic agents, their advantages include oral administration, a short half-life, and a lack of immunogenicity, which greatly improve treatment adherence. In RA, the efficacy of JAK inhibitors is comparable to that of TNFi, with an ACR20 response rate of approximately 60–70% [1], and they are also effective in patients who have failed TNF-α inhibitor therapy.

However, safety concerns regarding JAK inhibitors have significantly shifted their clinical positioning. The large post-marketing safety study ORAL Surveillance, which enrolled RA patients aged 50 years or older with at least one cardiovascular risk factor, showed that the tofacitinib group had a significantly higher incidence of major adverse cardiovascular events (MACE) compared with the TNF-α inhibitor group (HR 1.33), as well as a higher incidence of malignancies (particularly lung cancer and lymphoma) (HR 1.48) [1]. In addition, venous thromboembolism (VTE), serious infections, and dose-dependent elevations in blood lipids have also been reported.

It should be noted that ORAL Surveillance primarily focused on tofacitinib, and whether its conclusions can be fully extrapolated to other JAK inhibitors remains unclear. Different JAK inhibitors exhibit selectivity for different JAK isoforms: tofacitinib is a non-selective JAK inhibitor (mainly inhibiting JAK1/JAK3), baricitinib is a JAK1/JAK2 inhibitor, upadacitinib is a JAK1-selective inhibitor, and filgotinib is also a JAK1-selective inhibitor. These differences in selectivity may lead to variations in cardiovascular safety profiles among different JAK inhibitors, but comparative studies are currently lacking.

Behind the safety controversy lies a profound biological mechanism: the JAK-STAT pathway is involved not only in transmitting inflammatory signals but also in hematopoiesis, vascular repair, and lipid metabolism homeostasis. Complete blockade of this pathway may disrupt the balance between tissue repair and inflammation. Based on the above evidence, the FDA and EMA have issued black box warnings for JAK inhibitors, explicitly recommending that they be used in elderly patients, smokers, and those with cardiovascular risk factors only when no alternative treatment options are available. The positioning of JAK inhibitors is shifting from “suitable for the general population” to “targeted use in specific populations”—younger patients without risk factors who require rapid symptom control or prefer oral administration remain reasonable candidates. In contrast, TNFi have a better safety profile in high-risk populations.

3. Breaking the Deadlock of Drug Resistance: Immunogenicity Theory and Switching Strategies

3.1 Immunological Basis of Secondary Loss of Response

Despite the remarkable efficacy of biologic agents, a challenging issue in clinical practice is the gradual loss of efficacy in patients who initially responded well after months or even years of continuous treatment—a phenomenon known as secondary loss of response (SLR). The primary mechanism underlying SLR is immunogenicity, whereby the patient's immune system recognizes therapeutic monoclonal antibodies as “foreign antigens” and subsequently generates anti-drug antibodies (ADAs).

ADAs lead to loss of efficacy through two pathways: neutralizing ADAs bind directly to the antigen-binding region of the drug, blocking the interaction between the drug and its target; non-neutralizing ADAs bind to the constant region of the drug, forming immune complexes that are rapidly cleared, resulting in a significant reduction in trough serum drug concentrations. Both mechanisms often coexist. Clinically, this manifests as a gradual increase in previously controlled disease activity metrics and a progressive shortening of the post-dose improvement period until it eventually disappears.

The incidence of ADA varies significantly among different biologic agents, which is closely related to their molecular structure and degree of humanization: the ADA positivity rate can reach 40–60% for infliximab (a chimeric antibody), approximately 15–30% for adalimumab (a fully human antibody), and less than 5% for etanercept (a fusion protein) [9]. Multiple pharmacokinetic and pharmacodynamic studies have confirmed that ADA-positive patients have trough serum drug concentrations that are 50–80% lower than those of ADA-negative patients [9], and this reduction is significantly negatively correlated with higher DAS28 scores and lower ACR response rates.

3.2 TDM-Based Precision Switching: A Two-Step Strategy

In clinical practice, when facing patients who have failed biologic therapy, it is first necessary to distinguish between primary nonresponse and secondary loss of response, and then select an appropriate switching strategy based on the underlying mechanism of failure.

Step 1: Identifying the type of treatment failure. Primary nonresponse typically occurs within 3–6 months after treatment initiation, with patients showing no significant improvement from the outset, suggesting that the chosen drug target is not the core driver of the inflammatory pathway in that patient. Secondary loss of response is characterized by "initial efficacy followed by subsequent loss of response," with ADA testing often positive and drug concentrations below the therapeutic window. Therapeutic drug monitoring (TDM)—the simultaneous measurement of drug concentrations and ADA levels—can effectively distinguish between "pharmacokinetic failure" (ADA-mediated) and "pharmacodynamic failure" (pathway-independent).

It should be noted, however, that although TDM has clear theoretical value, its routine clinical application in rheumatic diseases is not yet well established. Currently, TDM is widely used with robust evidence in inflammatory bowel disease, whereas in rheumatic diseases such as rheumatoid arthritis, the benefits of TDM-guided therapy have not yet been confirmed by high-quality prospective studies, and its use in clinical practice should be cautious.

Step 2: Mechanism-based strategy selection. There are three types of treatment failure. First, for primary nonresponse or pharmacodynamic failure, switching to a drug targeting a different pathway is recommended. Data have shown that in TNFi-primary nonresponders, switching to tocilizumab achieves an ACR20 response rate of 55–65%, whereas switching to another TNFi yields only 25–35%. Second, for secondary loss of response with ADA positivity, options include switching to a different molecular structure targeting the same pathway (e.g., infliximab to adalimumab) to circumvent the existing interference through ADA molecular specificity, or adding MTX to reduce immunogenicity—a systematic review showed that adding MTX reduces the ADA positivity rate by approximately 50% [9] and extends the median drug survival by 12–24 months. Third, for secondary loss of response with ADA negativity, other causes (such as concurrent infection or poor medication adherence) should be investigated, or cross-pathway switching may be considered.

4. Future Perspectives: From "Control" to "Cure"

4.1 Bispecific Antibodies: A 1+1>2 Synergistic Effect

Bispecific antibodies are a class of artificially engineered antibodies that simultaneously target two different antigens. In the field of autoimmune diseases, bispecific antibodies targeting both IL-17A and TNF-α (such as ABT-122) have completed early-stage clinical trials [6].

From a pathophysiological perspective, TNF-α and IL-17A are key nodes in the inflammatory cascade of RA, AS, and psoriatic arthritis (PsA), and they exert a synergistic amplification effect [10]. TNF-α promotes Th17 cell differentiation and induces IL-17A production, while IL-17A in turn amplifies TNF-α-mediated inflammatory signals. In RA, both cytokines contribute to synovial inflammation and bone erosion; in AS and PsA, IL-17A plays a particularly prominent role in spine pathology and enthesitis. Therefore, simultaneous blockade of these two targets may theoretically produce a synergistic therapeutic effect and potentially overcome the common problem of resistance to single-target agents.

Early-stage clinical trial data indicate that the ACR20 response rate with ABT-122 in RA patients is comparable to that with adalimumab (a TNF-α monoclonal antibody). Still, statistical superiority has not been achieved [6]. It should be noted that these conclusions are derived from phase I/II trials with limited sample

sizes and short follow-up durations. The precise clinical positioning of ABT-122—such as whether it can demonstrate advantages in specific subgroups or overcome TNFi resistance—still awaits validation from larger phase III randomized controlled trials.

Table 1: Mechanisms and Switching Strategies for Treatment Failure of Biologic Agents

Failure Type	Core Mechanism	ADA Status	Drug Concentration	Key Issue	Recommended Strategy
Primary Nonresponse	Pathway mismatch	Negative	Normal or elevated	Incorrect drug selection	Cross-pathway switching
Secondary Loss of Response, Pharmacokinetic Failure	ADA-mediated accelerated drug clearance	Positive	Significantly below therapeutic window	Drug loss due to immunogenicity	Switch to different molecular structure targeting same pathway or add MTX
Secondary Loss of Response, Pharmacodynamic Failure	Pathway shift	Negative or low titer	Normal	Loss of pathway dependence	Cross-pathway switching or investigate comorbidities/adherence

4.2 CAR-T Therapy: "Rebooting" the Immune System

Chimeric antigen receptor T cell (CAR-T) therapy has achieved revolutionary success in B-cell malignancies. In recent years, this strategy has been attempted in patients with severe refractory SLE. A phase I/II trial in Germany enrolled five patients with refractory SLE who had failed multiple lines of therapy. Following infusion of CD19 CAR-T cells, all patients achieved remission with a SLEDAI score of 0 within 3 months, without the need for maintenance immunosuppressants—representing a true "drug-free remission." With a median follow-up of 12 months, remission was sustained [11].

This breakthrough has sparked in-depth discussions on "functional cure." CAR-T does not eradicate all aberrant genes but rather creates an "immune window" through deep depletion of the B-cell repertoire, allowing the immune system to reset and re-establish homeostasis. However, this therapy should still be interpreted with caution: the sample size is extremely small, and long-term safety remains unclear.

This breakthrough represents a major shift in treatment goals—moving from the "continuous suppression" achieved by traditional biologic agents toward the "functional cure" offered by CAR-T therapy. The former requires lifelong medication to maintain drug concentrations, whereas the latter aims to induce spontaneous restoration of immune tolerance through a single deep depletion. This fundamental difference in treatment philosophy suggests that the management paradigm for autoimmune diseases may be on the verge of a true shift.

Whether CAR-T can move from being a "salvage therapy for salvage therapies" to more widespread application depends on the results of future larger-scale studies with longer follow-up.

4.3 Biosimilars: Optimizing Pharmacoeconomics

Biosimilars are biologic agents that are highly similar to the original reference biologic and have no clinically meaningful differences. With the expiration of patents for major drugs such as infliximab and adalimumab, the introduction of biosimilars has reduced prices by 20–40% [12], significantly improving patient accessibility. Real-world data have shown that biosimilars have no clinically meaningful differences from reference biologics in efficacy, safety, and immunogenicity [12]. In China's healthcare insurance system, the widespread availability of biosimilars has made the goal of "early, adequate, and continuous" biologic therapy a reality.

5. Conclusion

Reviewing the evolution of autoimmune disease treatment over the past two decades, a clear trajectory can be seen from "non-specific immunosuppression" toward "precision targeted intervention." The core characteristic of the current therapeutic landscape is not a "one-size-fits-all" solution, but rather the necessity of individualized, stratified treatment—different diseases have distinct immunopathological mechanisms, and

different molecular subtypes within the same disease exhibit significant variability in response to the same targeted agent. Clinicians need to select the most appropriate regimen based on an understanding of drug mechanisms, integrating patients' clinical phenotypes, serological characteristics, comorbidities, and treatment history.

It must be recognized, however, that while current biologic therapies have significantly reduced disability rates, they have not resolved the issue of relapse after treatment discontinuation. Studies have shown that the majority of patients experience disease relapse within 6–12 months after drug withdrawal, suggesting that although current targeted therapies can effectively control circulating inflammatory factors, they fail to eliminate local “lesion reservoirs” in tissues—such as tissue-resident memory T cells (Trm) and ectopic lymphoid-like structures, which serve as the “kindling” for relapse.

Looking ahead, the widespread adoption of bispecific antibodies, CAR-T cell therapies, and biosimilars is expected to further break through existing treatment bottlenecks. In particular, the “immune system reboot” paradigm pioneered by CAR-T therapy offers an unprecedented opportunity to move from “long-term control” toward “functional cure.” The evolution of targeted biologic agents is propelling the treatment of autoimmune diseases into an entirely new historical phase.

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