REVIEW
JOURNAL OF UNIVERSITY OF BABYLON
For Pure and Applied Sciences (JUBPAS)
Vol.33; No.4.| 2025

Biologic Therapies in Autoimmune Diseases: A Review of Clinical Efficacy and Safety Trends

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العلاجات البيولوجية لأمراض المناعة الذاتية: مراجعة لاتجاهات الفعالية السريرية والسلامة

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Accepted: 12/10/2025 **Published:** 31/12/2025

ABSTRACT

Biologic therapies for rheumatologic illnesses, aimed at targeting molecules implicated in immune system mechanisms, offer an alternative to conventional treatments such as disease-altering anti-rheumatic medicines with additional immunosuppressive medications. Nonetheless, the existing limitations of biologic treatments, including the challenges of intravenous administration, the substantial prices of these pharmaceuticals, and the associated side events hinder their widespread use as first-line treatments. This review is an update on the recent research regarding the novel biologic medicines accessible. The review focuses on eight pharmaceuticals: Tocilizumab, Rituximab, Adalimumab, Ustekinumab, Infliximab Belimumab, Vedolizumab, and Secukinumab, utilized in the treatment of rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, systemic sclerosis, or vasculitis.

Keywords: Biologic Therapies, rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, systemic sclerosis.

ISSN: 2312-8135 | Print ISSN: 1992-0652
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ISSN: 2312-8135 | Print ISSN: 1992-0652
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1. INTRODUCTION

Biological therapies represent a pivotal development in the treatment of autoimmune and rheumatic diseases. Their use has expanded significantly in recent years due to improved scientific understanding of the mechanisms of immune disease and the discovery of precise therapeutic targets within the immune system[1]. Advances in biotechnology have contributed to the development of targeted drugs that target specific components of the immune system, such as cytokines, B cells, and cell-mediated interaction molecules[2]. This has resulted in substantial enhancements in the effectiveness of treatment and encouraging clinical results among a diverse patient population. Although these treatments are often better tolerated than conventional therapies, their use is still limited due to their high cost, intravenous administration, and potential side effects include infection and long-term complications[3]. Current biologic therapies including anti-tumor necrosis factor (TNF-α) agents, anti-interleukin-1 and -6 agents, and B-cell-directed therapies such as anti-CD20 antibodies and B-cell lymphoma modulators. Certain medicines have demonstrated efficacy in multiple immune-mediated diseases, whilst some are restricted to a particular illness [4].

Cytokines are essential components for the physiological balance as well as the body's immune system, significantly contributing to defense against infections and tumors [5]. TNF was a complex cytokine that alters the remodeling of tissues, permeability for epithelial cell barrier, macrophage stimulation, recruitment of inflammatory infiltrates, and an increase of attachment molecules. It has a vital function in the development, ,and adaptive reactions of the immune system [6]. The TNF production process begins with the ligand binding to a cell surface Toll receptor, triggering a signal transduction cascade that activates NFkB transcription factors [7]. Activated NFkB translocates to the nucleus and induces the transcription of inflammation-related genes, especially the genes that encode TNF. Its synthesis facilitates the recruitment of more inflammatory cells, which subsequently produce cytokines and enhance the immune response[8]. Investigations into the pathogenesis of rheumatoid arthritis (RA), performed in both laboratory animals and clinical settings, reveal a significant role for interleukin-1 (IL-1) in synovial inflammation and joint tissue deterioration. Although IL-1 and TNF-α share multiple biological activities, research employing animal models suggests that IL-1 was the primary cytokine responsible for cartilage breakdown [9]. Experimental studies have demonstrated that over 95% of IL-1 receptors must be inhibited to provide adequate suppression of IL-1 signaling [9].

The research arena is witnessing ongoing efforts to explore new therapeutic targets that could expand therapeutic intervention options, especially in complex or treatment-resistant cases. In light of these developments, this review aims to highlight the latest biological therapies used over the past five years in the management of a number of autoimmune diseases, including rheumatoid arthritis, ankylosing spondylitis, systemic scleroderma, systemic lupus erythematosus, and types of vasculitis[10]. This review focuses on evaluating the clinical efficacy of these treatments and common safety patterns while reviewing current challenges in clinical application and future directions in this field. This provides a scientific basis to help

clinicians and researchers choose appropriate therapeutic options and direct future research efforts towards achieving the best possible outcomes for patients.

Table 1: Recent developments in biological therapy for autoimmune diseases

Drug (trade name)	Mechanism of action	Indications
Tocilizumab	Recombinant monoclonal IgG1 anti-human interleuki6-receptor antibody	Rheumatoid arthritis (RA) after failure of anti-TNF therapy
Rituximab	Chimeric human monoclonal antibody against the CD20 protein	Rheumatoid arthritis (RA)
Adalimumab,	Fully human monoclonal antibody of the IgG1 class that targets the inflammatory cytokine tumor necrosis factor alpha (TNF-α)	Rheumatoid arthritis
Ustekinumab	fully human monoclonal antibody belonging to the IgG1κ class	Crohn's disease.
Infliximab	Infliximab is a chimeric monoclonal antibody directed against tumor necrosis factor alpha (TNF-α).	Spondylarthropathies
Belimumab	fully human monoclonal antibody used as a targeted biologic therapy	Systemic Lupus Erythematosus – SLE
Vedolizumab	humanized monoclonal antibody directed against the α4β7 integrin receptor, a receptor found on the surface of T lymphocytes	Ulcerative Colitis
Secukinumab	Fully human monoclonal antibody (IgG1κ) that targets and inhibits interleukin 17A (IL-17A)	Chronic Plaque Psoriasis

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2. SCREENING FOR BIOLOGIC TREATMENT

Screening is often performed when there are clear indications for the use of biological therapy. The screening process involves assessing the patient's general health, with a focus on current or past tuberculosis (TB) infection. This is based on medical history, a tuberculin skin test (PPD), and a chest x-ray. Serological tests for hepatitis B and C viruses are also performed, as well as a history of tumors or chronic neurological disease[11]. Screening results are used to determine the appropriateness of initiating biological therapy or whether pre-treatment interventions—such as preventive treatment for latent TB—are necessary before starting immunotherapy. Based on these data, the most appropriate type of biological agent is decided upon, and treatment is selected based on disease characteristics, the patient's clinical condition, and lifestyle, taking into account factors such as the degree of immune activity, comorbidities, and previous response to conventional treatments. This step aims to ensure the safe and effective use of biological therapy and to reduce potential short- and long-term complications[12].

3. BIOLOGIC THERAPIES IN AUTOIMMUNE DISEASES

3.1 Rheumatoid Arthritis

3.1.1 Tocilizumab: Mechanism of Action

Tocilizumab (TCZ), known commercially as Actemra or Roactemra, is a humanized IgG1 monoclonal antibody directed against the human interleukin-6 receptor (IL-6R). This drug works by inhibiting the binding of IL-6 to its membrane-bound and soluble receptors, thereby preventing the interaction of this complex with the membrane signaling transporter gp130, which is essential for triggering a cascade of inflammatory signals. Inhibiting this process reduces the production of inflammatory factors, reduces angiogenesis, inhibits adhesion molecules, and prevents osteoclast activation[13].

IL-6 is known for its pivotal role in stimulating and regulating the immune response, activating both T and B cells and participating in the differentiation of B cells into antibody-producing plasma cells. Therefore, inhibiting this cytokine contributes to curbing the excessive inflammatory response, a therapeutic target in many autoimmune diseases[14].

In rheumatoid arthritis (RA), clinical and laboratory studies show elevated concentrations of IL-6 in the blood and synovial fluid within affected joints[15]. Animal experiments have demonstrated that the injection of TCZ into inflamed joints markedly decreased edema and activity of inflammation. These results support the clinical use of Tocilizumab as an effective option for controlling inflammation and relieving symptoms in RA patients, especially those resistant to conventional therapies or anti-TNF-α agents[16].

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3.1.1.1 Indications and Dosage of Tocilizumab

Tocilizumab (TCZ) is used to treat rheumatoid arthritis (RA) in patients who have not responded adequately to or failed treatment with disease-modifying anti-rheumatic drugs (DMARDs) or TNF-α antagonists. It has been approved for this purpose in the United States since January 2010. A starting dose of 4 mg/kg given by intravenous infusion every four weeks is typically recommended, with the dose gradually increased to 8 mg/kg based on the patient's clinical response[17].

The drug is given via intravenous injection (IV infusion), and the dose varies depending on the medical condition. In cases of rheumatoid arthritis, the recommended dose is between 4 and 8 mg/kg IV every four weeks, while in cases of systemic juvenile idiopathic arthritis (SJIA), the dose ranges between 8 and 12 mg/kg depending on body weight[18].

Long-term studies have shown that using TCZ monotherapy for five years resulted in a 55.3% rate of patients achieving disease remission according to the disease activity scale (DAS remission rate), confirming its high effectiveness as an independent treatment option in some cases[19].

3.1.1.2 Safety Profile and Adverse Effects of Tocilizumab

Both long- and short-term interventions for moderate to severe rheumatoid arthritis demonstrated favorable safety outcomes for TCZ. A meta-analysis indicated that TCZ was tolerated satisfactorily. extended for more than 2.4 years of therapy, and the adverse events were milder than those of other biologic treatments [8]. 66.1% of the 286 RA patients in a 24-week study had mild to moderate, short-lived adverse drug events (AEs) linked to the medication. Serious adverse events (AEs), which were primarily infections, occurred in a limited percentage of individuals [20]. In the research examining all three stages of TCZ safety, the adverse events were similar to those observed in both of the treatment groups (DMARDs or anti-TNF-alpha). The most common adverse events were infections, especially impacting the upper respiratory tract (URTI) and gastrointestinal (GI) tract [21]. Significant adverse events include cardiac incidents, significant infections, solid organ malignancies, other types of cancer, skin cancers, as well as hematological illnesses [21]. Increased incidences of severe infections were associated with prior anti-TNF-alpha therapy [21].

Multiple patients were identified with tuberculosis despite having completed screening prior to treatment in accordance with the stated guidelines. Increased dosages of TCZ (8 mg/kg) were associated with heightened infection risks; nevertheless, the rates were similar to those seen with DMARDs or anti-TNF-alpha inhibitors [21].

Although TCZ is highly effective in managing chronic inflammatory conditions such as rheumatoid arthritis, its use may be associated with a number of side effects that require close

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monitoring during treatment. Infections are prevalent adverse effects, especially URTI . pharyngitis, and bronchitis. More serious conditions, such as reactivation of latent tuberculosis, have also been reported; therefore, pre-screening for tuberculosis is recommended before initiating treatment[22].

In addition, TCZ may cause changes in liver parameters, such as elevated ALT and AST levels, requiring periodic monitoring of liver enzymes. It may also cause changes in blood counts, such as leukopenia or neutropenia, and elevated triglycerides and cholesterol, requiring regular monitoring of blood lipid levels. In additional investigations of TCZ monotherapy, the adverse events described were nasopharyngitis, gastrointestinal problems, and infections. The incidence of adverse events (AEs) was comparable between TCZ and anti-TNF-alpha blockers [23].

There was an association between TCZ and higher lever for cholesterol, an increase in the ratio of LDL to HDL cholesterol, and a total to HDL cholesterol that was also associated with an increase in these ratios [11]. To conclude, when anti-TNF-alpha medication fails to alleviate RA symptoms or is otherwise not appropriate, TCZ constitutes a safe and effective alternative.

3.1.1.3 Efficacy

TCZ exhibited non-inferiority compared to alternative biologic therapies according to the American College of Rheumatology (ACR) criteria for 20% (ACR20) and 50% (ACR50) improvement, while demonstrating superiority for a 70% improvement (ACR70) [24]. Furthermore, the reaction to TCZ occurred swiftly, just after the initial injection [25].
The results of numerous clinical studies have demonstrated the drug's clear efficacy in improving clinical symptoms and reducing inflammatory activity in patients who have not responded adequately to conventional treatments or anti-TNF. In the study [26], a randomized, double-blind trial comparing Tocilizumab with methotrexate, Tocilizumab was found to be significantly superior in reducing disease activity according to the ACR20 and ACR50 scales. The study [22] also showed that adding Tocilizumab to methotrexate resulted in significant improvements in inflammatory markers, such as CRP and erythrocyte sedimentation rate (ESR), along with reduced joint swelling and pain[27]. Monotherapy with TCZ for 52 weeks led to a significant reduction in radiographic changes (total Sharp score) compared to DMARDs [28]. Additional trials demonstrated a response to TCZ in patients with RA unresponsive to anti-TNF alpha antagonists [29]. In patients who previously failed to respond to anti-TNFs, the study by [30] demonstrated the efficacy of tocilizumab at a dose of 8 mg/kg every 4 weeks in achieving a statistically significant therapeutic response, confirming its role as an alternative and effective treatment option in this category. Tocilizumab's effectiveness is not limited to rheumatoid arthritis. Its effectiveness has also been documented in other conditions, such as giant cell arteritis (GCA). The study demonstrated that use of the drug in conjunction with corticosteroid dose reduction resulted in a sustained response and reduced long-term steroid dependence [31]. It has also been used with relative success in some cases of cytokine storm associated with

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COVID-19 infection, and studies such as the RECOVERY trial have shown improved survival rates for critically ill patients, although results vary depending on the timing of administration and severity of the condition[32].

3.1.2 Rituximab; Mechanistic Insights and Immunomodulatory Effects

Rituximab is a genetically engineered chimeric monoclonal antibody that specifically targets the CD20 antigen, a surface protein expressed on a range of B-cell subsets, including naive, mature, and memory B lymphocytes, but notably absent from plasma cells and hematopoietic stem cells. By binding to CD20, rituximab initiates a cascade of immunological events that lead to selective B-cell depletion, primarily through mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and induction of apoptosis[33].

Several studies have demonstrated that rituximab induces a sustained reduction in the peripheral B-cell pool, including markers of immature and memory B cells, along with modulation of pre-B-cell colony-enhancing factor (PBEF or visfatin) levels, which play roles in immune metabolism and inflammation[34]. Interestingly, beyond its direct depleting effect, rituximab also appears to influence interferon-mediated immune pathways. A study conducted by [35] in rheumatoid arthritis (RA) patients exhibiting clinical improvement following rituximab therapy, a marked upregulation in the expression of Type I interferon-stimulated genes (ISGs) such as *RSAD2*, *IFIT1*, *HERC5*, *LY6E*, and *Mx1* has been observed. Conversely, non-responders often fail to exhibit this gene expression signature, suggesting a potential link between the IFN-I response and treatment efficacy[36].

These findings not only highlight the multi-dimensional immunomodulatory role of rituximab, but also open avenues for exploring biomarkers of response, particularly those linked to interferon signaling, as predictors of therapeutic outcomes. Further investigation into these pathways may provide greater clarity on resistance mechanisms and guide personalized treatment approaches for autoimmune and B-cell–mediated diseases[37].

3.1.2.1 Doses and indications

The Food and Drug Administration (FDA) has exclusively sanctioned rituximab for the management of active rheumatoid arthritis unresponsive to DMARDs or anti-TNF-alpha therapies.. Rituximab helps individuals with Castleman's illness and autoimmune diseases including SLE for additional off-label indications. When combined with MTX, the most common treatment for RA involves an intravenous infusion of 1000 mg/m^2 on days 1 and 15. Depending on the clinical evaluation, subsequent sessions may be given every 24 weeks or more frequently if needed, but no less often than every 16 weeks. For individuals with rheumatoid arthritis, it is advisable to administer IV methylprednisolone 100 mg (or its equivalent) as pre-medication 30 mins prior to every rituximab dose [38]

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The treatment for granulomatosis with polyangiitis (GP), previously termed Wegener's granulomatosis, consists of an intravenous infusion of 375 mg/m2 administered weekly for four doses, alongside intravenous methylprednisolone for 1 to 3 days, succeeded by daily prednisone. The management of microscopic polyangiitis (MPA) was analogous to that of granulomatosis with polyangiitis (GPA).)[39]. A multicenter phase II experiment evaluated rituximab for chronic immunological thrombocytopenic purpura (ITP). Forty patients participated in the trial, and forty of them achieved stable platelet counts after four doses of intravenous infusion of 375 mg/m² [40]. Numerous studies suggest that a low-dose therapy of 100 mg/m2, whether delivered independently or alongside steroids, may be sufficient and result in fewer adverse effects; however, additional data regarding this dosage were lacking [41]. For patients with refractory pemphigus vulgaris (PV), the recommended treatment consists of ten doses spread out over six months, completed with weekly intravenous infusions of 375 mg/m2 rituximab for the first three weeks of each four-week cycle, followed by monthly doses for the next four months. Starting at 50 mg/hour, the rate should be increased by 50 mg every 30 minutes until reaching 100 mg/hour if no reaction is observed [42, 43].

3.1.2.2Effectiveness

It has been shown in several studies that rituximab could be useful in the treatment of SyS [44]. Eight patients were involved in the study. By reducing B-cell infiltration in the skin, rituximab infusion showed promise as a therapy for skin fibrosis in the context of SyS [45]. Histological improvement in skin after rituximab treatment was shown in a different trial with 15 people with SyS [45]. Rituximab plus prednisone did not significantly reduce disease activity in a study of 257 people with systemic lupus erythematosus when compared to a placebo. Rituximab treatment was found to be significantly more beneficial in a subgroup analysis of individuals who identified as African American or Hispanic. Furthermore, rituximab showed better results in open studies for extended treatment [46]. The overall trial's ineffectiveness may be linked to the clinical design, the inclusion of excessive subgroups, or the failure to stratify patients based on the presence or absence of anti-double-stranded DNA antibodies [47].

A case series suggested that rituximab may be advantageous in hemolytic anemia, thrombocytopenia, and arthritis-related systemic lupus erythematosus (SLE) [20]. A study involving 646 patients with rheumatoid arthritis who experienced treatment failure with anti-TNF-alpha blockers showed a favorable clinical response and disease remission at the 6-month follow-up after rituximab therapy [48]. There were 559 RA patients who had not responded adequately to at least one TNF-alpha inhibitor who participated in the SUNRISE study (Study of Retreatment with Rituximab in Patients with Rheumatoid Arthritis Receiving Background Methotrexate). In order to assess the effectiveness and safety of rituximab, these individuals underwent two treatment cycles of the medicine. As measured by the ACR20, 475 of the 559 patients who participated in the study showed a significant improvement compared to the placebo group after completing the second cycle of medication [13]. Rituximab, when administered alone, caused remission in 36 of 42 patients with severe PV for 8–64 months,

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according to the study. The safety profile was still favorable in those who needed an extra dose [49].

3.1.2.3 Negative consequences and safety

Infusion reactions are a potential side effect of rituximab. These reactions might include symptoms like fever, chills, rash, swelling of the extremities (including the feet, hands, and face), breathing difficulties and hypotension. The reaction usually happens quickly, between half an hour and two hours, usually after the first infusion, but it gets milder with each subsequent infusion [50]. It is advisable to premedicate with acetaminophen and an antihistamine to avert this infusion reaction. In the event of an infusion reaction, the infusion rate must be reduced or halted. Supplementary steroid treatment may also be necessary. Rituximab therapy necessitates the surveillance of many adverse events, which includes infections, TB, and malignancies [51]. You shouldn't take it if you're pregnant or nursing, have a current infection, have recently been live-injected with a vaccine, have severe congestive heart failure, have demyelinating disease in your family history, or have had non-lympoproliferative malignancy in your body for at least five years [52]. Out of 2,578 individuals with RA who were evaluated for safety with rituximab, 123 stopped taking the medication because of cancer, infection, a serious infusion reaction, or a heart event. This meta-analysis included patients treated for an extended period of time [53]. The majority of adverse events transpired during the initial treatment regimen. The incidence of malignancies wasn't increased in patients having rheumatoid arthritis receiving rituximab treatment [53]. Rituximab reduces gammaglobulin levels in relation to the total dosage; yet, this does not appear to increase the risk of severe infections [23]. Multiple cases of progressive multifocal leukoencephalopathy (PML) were recorded in patients subsequent to rituximab therapy [54].

3.1.3 Adalimumab; Mechanism of Action

Adalimumab is a fully human monoclonal antibody of the IgG1 class that targets the inflammatory cytokine tumor necrosis factor alpha (TNF-α), a key immune mediator implicated in autoimmune diseases, particularly **rheumatoid arthritis[55]**. Normally, TNF-α plays an important role in immune defense, but when overexpressed in autoimmune conditions, it leads to persistent activation of T and B cells and macrophages, causing chronic tissue destruction, particularly in the joints. Adalimumab works by specifically and directly binding to TNF-α, preventing its interaction with its cellular receptors (TNFR1 and TNFR2) on the surface of immune cells. This inhibits the inflammatory cascade associated with the secretion of proinflammatory cytokines such as IL-1, IL-6, and GM-CSF[56].

Furthermore, adalimumab exhibits cytoprotective effects by inducing apoptosis in activated T cells and reducing the infiltration of inflammatory cells into the synovium, the primary target in rheumatoid arthritis. In this way, adalimumab inhibits the uncontrolled immune response in the joints, reducing swelling, pain, and joint deterioration over time[57]. This drug is one of the first

antibodies designed entirely using recombinant DNA technology, reducing the likelihood of an immune response compared to chimeric therapies such as infliximab[57].

This mechanism of action makes adalimumab effective not only in RA but also in other diseases such as psoriasis, ulcerative colitis, and Crohn's disease, demonstrating the central role of TNF-α in various immune disorders, this treatment does not suppress immunity in general, but rather selectively disrupts a portion of the inflammatory response, which explains its high efficacy with an acceptable degree of safety when preventive measures are adhered to[58-60].

3.1.3. 1 Dosage and Indications

Adalimumab has been approved by the US Food and Drug Administration (FDA) and several global regulatory agencies to treat a wide range of inflammatory and autoimmune diseases. It is a versatile biologic therapy with applications in rheumatology, dermatology, and gastrointestinal medicine[61]. Rheumatoid arthritis is a primary indication for adult patients with moderate to severe disease activity, particularly when conventional disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate fail to control symptoms. Other indications include: Ankylosing spondylitis, Psoriatic arthritis, severe plaque psoriasis, Crohn's disease and ulcerative colitis, Non-infectious uveitis, Juvenile idiopathic arthritis[62].

The dosage varies depending on the target disease, the patient's age, and their clinical condition. For RA in adults, adalimumab is usually administered at a dose of 40 mg subcutaneously every two weeks[63]. The dose can be adjusted to weekly in cases requiring a stronger therapeutic response. It is commonly used in conjunction with methotrexate, as the combination improves efficacy and reduces the production of anti-drug antibodies.

In Crohn's disease, treatment is initiated with a loading dose of 160 mg on day 1, followed by 80 mg on day 15, followed by a maintenance dose of 40 mg every two weeks starting on day 29[64]. In psoriasis, an initial dose of 80 mg is used, followed by a 40 mg dose a week later, followed by a repeat dose of 40 mg every two weeks. In uveitis and ankylosing spondylitis, the dosage pattern is similar to that for RA[63]. When prescribing adalimumab, consideration should be given to the patient's chronic or latent infections (such as tuberculosis or hepatitis B), so comprehensive testing is required before initiating treatment. It is not recommended for use in patients with active infections or severely impaired immune systems.

3.1.3.2 Efficacy

Large-scale clinical studies as well as long-term real-world trials have shown that adalimumab is one of the most effective biologic therapies in controlling rheumatoid arthritis (RA) symptoms and improving quality of life in patients, especially in moderate to severe cases that do not respond to conventional treatments such as methotrexate[65].

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In a study involving patients with RA, adalimumab proved highly effective when used in combination with methotrexate, with patients demonstrating significant clinical improvement in disease activity indicators such as joint swelling and pain, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)[66]. By week 24, approximately 65% of patients achieved an ACR20 response (20% or greater improvement in combined criteria), while 40% achieved an ACR50 response and 20% achieved an ACR70 response, rates that reflect improved efficacy compared to conventional treatments alone.

In the long term, extended follow-up data have shown that adalimumab slows the progression of joint damage, as documented using radiological measures such as the Sharp/van der Heijde score. This ability to limit structural joint deterioration makes it an important treatment not only for palliative care but also for limiting disease progression[65].

3.1.3.3 Risks to health and safety

Despite the high efficacy of adalimumab in the treatment of rheumatoid arthritis and other immune-mediated diseases, its use is associated with a number of side effects that must be considered within the benefit-risk balance. The drug's safety profile is acceptable in the short and long term, provided strict clinical recommendations regarding pre-treatment screening and continuous monitoring during treatment are adhered to[67]. Common side effects of adalimumab include: Upper respiratory tract infections such as rhinitis or pharyngitis. Injection site reactions, including pain, itching, redness, or swelling at the injection site, occur in approximately 20% of patients, but are usually mild and subside with continued treatment. Headache, nausea, and mild to moderate skin rashes may also occur. In terms of more serious side effects, infection is a major challenge with adalimumab treatment, given its role in inhibiting tumor necrosis factor alpha (TNF-α), which is part of the innate immune response[68]. Therefore, patients receiving this treatment are at increased risk of developing bacterial, viral, and fungal infections, particularly latent pulmonary tuberculosis (TB), which can reactivate after initiating treatment. This makes TB testing (TST or IGRA) an essential step before initiating treatment. In addition to opportunistic infections such as listeriosis, nocardiosis, and herpes viruses (such as herpes simplex or shingles)[69].

3.2 Crohn's disease.

3.2.1 Ustekinumab Tratments Mechanism of Action

Ustekinumab (trade name: Stelara) is a novel, highly targeted biologic. It is a fully human monoclonal antibody belonging to the IgG1κ class[70]. It works by co-targeting the p40 subunits of both interleukin-12 (IL-12) and interleukin-23 (IL-23), two key cytokines that play a pivotal role in triggering the inflammatory response in Crohn's disease and many other immune-mediated diseases[71].

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Physiologically, IL-12 induces differentiation into type 1 helper T cells (Th1), which secrete interferon gamma (IFN-γ) and contribute to the cellular immune response. IL-23 promotes the survival of Th17 T cells, which secrete IL-17 and IL-22, cytokines that play a key role in triggering chronic inflammation in the gastrointestinal tract. Ustekinumab binds to the p40 subunit common to both cytokines, preventing their interaction with cell receptors and suppressing inflammatory pathways associated with Th1 and Th17 cells[72].

This dual inhibition distinguishes ustekinumab from other therapies, such as anti-TNF-α drugs, and provides a promising treatment option for patients with Crohn's disease who are resistant to conventional therapy or have even failed previous anti-TNF drugs. Because its effect is limited to certain inflammatory pathways without complete immunosuppression, ustekinumab exhibits a relatively good safety profile and reduces the risk of systemic infection compared to some other immunosuppressants[73].

Inhibition of IL-12/23 has been shown to reduce the activity of intestinal mucosal effector lymphocytes, leading to improved ulcer healing and reduced secretion of harmful cytokines. This is reflected in improved gastrointestinal symptoms and intestinal inflammation in patients with Crohn's disease.

3.2.1.1 Indications and Dosage

Ustekinumab has been approved by the US Food and Drug Administration (FDA) for use in a range of chronic inflammatory immune diseases. It is considered one of the most prominent biologic therapies proven effective in moderate to severe Crohn's disease, particularly in patients who have not responded adequately to conventional or previous biologic therapies. Approved indications include: Crohn's disease — for adults and adolescents ≥ 6 years of age with moderate to severe active disease. Ulcerative colitis — when Ustekinumab has demonstrated clear and convincing efficacy in the treatment of moderate to severe Crohn's disease, particularly in patients who have failed to respond to conventional therapies or have failed to benefit from TNF-α inhibitors such as infliximab or adalimumab. Its efficacy has been evaluated in a large-scale series.

The loading dose is administered as a single intravenous infusion and is calculated based on body weight: ptients weighing less than 55 kg: 260 mg, patients between 55 and 85 kg: 390 mg, and ptients over 85 kg: 520 mg. The infusion is given over one hour and is necessary to stimulate a rapid immune response and inhibit IL-12/IL-23 cytokines associated with inflammatory activity in the intestinal wall. This initial dose has been shown to reduce symptoms within 3–6 weeks in the majority of patients[70].

3.2.1.2 Efficacy

In the study [74], which included Crohn's disease patients previously resistant to biologic therapy, 34% of patients who received a single loading dose of ustekinumab (6 mg/kg

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intravenously) achieved a clinical response by week 6, compared to only 21% in the placebo group. In the UNITI-2 study, which focused on patients who had failed to respond to conventional treatment (such as steroids or immunosuppressants), the response rate was higher, reaching 51% compared to 28% in the placebo group[75].

In these studies, a "clinical response" is defined as a reduction of ≥100 points in the Crohn's Disease Activity Index (CDAI) or clinical remission (CDAI < 150). The results of these trials have shown that efficacy is achieved relatively quickly and is maintained over long-term follow-up, particularly when transitioning to a maintenance phase with subcutaneous doses every 8 weeks.

In the study[76], which focused on the long term (up to week 44), approximately 53% of patients who responded to the loading dose maintained sustained clinical remission when using the 90 mg subcutaneous maintenance dose every 8 weeks, compared to only 36% in the placebo group. The study also showed a significant decrease in the proportion of patients requiring steroids in the treatment group, a strong indicator of real improvement in immune control of the disease

In addition to these clinical results, Ustekinumab has been documented to be effective in reducing objective markers of inflammation, such as CRP and fecal calprotectin levels, as well as evidence of improved intestinal mucosal healing, an important therapeutic target in modern Crohn's disease[77].

Other treatments have failed or are intolerable. Plaque psoriasis — for moderate to severe disease in adults, especially when topical treatments are insufficient. Psoriatic arthritis — alone or in combination with conventional immunomodulatory drugs[78].

3.2.1.3 Adverse Effects and Safety

Ustekinumab is a biologic with a relatively safe profile. Clinical studies and real-world trials have shown that the incidence of serious adverse events is low compared to some other biologics. Most reported adverse events were mild to moderate and included local reactions at the injection site (such as redness or itching), headache, fatigue, and flu-like symptoms[79].

One notable aspect of the safety profile of Ustekinumab is its lower risk of serious infections, including tuberculosis and viral infections, compared to TNF-α inhibitors. However, screening for latent tuberculosis and hepatitis B is recommended before initiating treatment. In the [76] and UNITI-2 [75] studies, no elevated rates of systemic infections, thrombosis, or tumors were observed.

Although it does not suppress the immune system comprehensively, its use may increase the risk of infection in some patients, particularly the elderly or those with comorbid conditions. Patients should be monitored clinically during treatment, with the dose deferred if an active infection is present[80].

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There are no confirmed reports of effects on fertility or pregnancy, but it is best to avoid its use during pregnancy unless the expected benefits outweigh the risks[81]. Overall, Ustekinumab is considered a safe and effective long-term biologic therapy for the management of Crohn's disease, making it a promising option for patients who require careful immunological control without extensive immunosuppression.

3.3 Spondylarthropathies

3.3.1. Infliximab, Mechanism of Action

Spondylarthropathies constitute a category of chronic autoimmune joint diseases. Arthritis related with acute anterior uveitis (82) and inflammatory bowel disease (IBD) are among the phenomena linked to this notion, as are psoriatic arthritis (PsA), reactive arthritis (ReA), and ankylosing spondylitis (AS) [82]. It was only natural to move on to investigating infliximab's effectiveness in ankylosing spondylitis patients after the first successful trials in rheumatoid arthritis, notwithstanding the distinct pathogeneses conditions [83].

Infliximab is a chimeric monoclonal antibody directed against tumor necrosis factor alpha (TNF-α), a key cytokine in the hyperinflammatory response that characterizes inflammatory bowel diseases, such as Spondylarthropathies. Infliximab works by directly binding to free and membrane-bound TNF-α, preventing its activation of its receptors and inhibiting the resulting inflammatory cascade [84]. It also inhibits the interaction between immune cells (such as T cells) and injured tissue elements, limiting damage to the intestinal mucosa. Studies indicate that infliximab leads to inhibition of the expression of endothelins (adhesion molecules) and NF-κB inhibitors, reducing the infiltration of inflammatory cells into the intestinal wall[85].

3.3.1.1 Loading Dose and Indications

Infliximab is used to treat moderate to severe Crohn's disease and is also used to treat ulcerative colitis, psoriatic arthritis, and ankylosing spondylitis, particularly in patients who have failed to respond to conventional treatments (such as corticosteroids or immunosuppressants). Clinical guidelines (such as AGA and ECCO) recommend initiating treatment with a loading dose of 5 mg/kg administered intravenously at weeks 0, 2, and 6, followed by a maintenance dose every 8 weeks to maintain response. In some cases, the dose may be adjusted to 10 mg/kg based on clinical response indicators or serum infliximab levels (TDM – Therapeutic Drug Monitoring).

3.3.1.2 Efficacy

A chronic inflammatory rheumatic illness with an incidence of 0.5-1.9%, similar to rheumatoid arthritis, ankylosing spondylitis (AS) is the archetype of spondylarthritis. The most common symptoms include inflammation of the spine, entheses, and sacroiliac joints. Immunohistochemical examinations of biopsies and magnetic resonance imaging (MRI) have provided strong evidence of inflammation at the cartilage-bone interface [83]. Limited research

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has been conducted on the treatment of patients with ankylosing spondylitis using disease-modifying antirheumatic medications, none of which have demonstrated unequivocal efficacy in axial illness.

Many studies using anti-TNF-α drugs, especially the biological agent's infliximab and etanercept, have been justified by the in situ detection of TNF-α mRNA and protein in the sacroiliac joint of AS patients. For this indication, infliximab, a chimeric monoclonal antibody, has received the most extensive research. More than half of the patients in the infliximab group showed a 50% increase in the activity index, compared to less than 10% in the placebo group, according to the study by J. Braun et al. [52]. By week 2, most patients had shown signs of improvement. Patients with higher blood C-reactive protein levels benefited more from treatment, according to subgroup analysis, suggesting that these people should be given infliximab treatment priority [52]. Van den Bosch et al.'s study confirmed the quick and significant improvement of axial, peripheral, and global disease symptoms [82]. From 67 and 67.5 to 18 and 16.5 respectively, the medians for patient and physician global assessments of illness activity decreased, showing improvements of 74% and 77%, respectively. These results, along with those from previous open-label studies on infliximab and a placebo-controlled trial of etanercept in psoriatic arthritis (PsA), indicate that tumor necrosis factor alpha (TNFα) plays a significant role in the development and symptoms of spondyloarthritis (SpA), and that blocking this cytokine is particularly effective in reducing symptoms in this group of diseases altogether [82]. Reductions in lining layer thickness, vascularity, and neutrophil and macrophage infiltration were among the synovial histological effects noted [86].

The treatment of ankylosing spondylitis with the soluble TNF-α receptor, etanercept, has not been widely researched; however, existing results suggest a distinctly positive effect [83]. Marzo-Ortega and colleagues proposed that TNF-α inhibition. Etanercept is very successful in managing the clinical symptoms of ankylosing spondylitis, with substantial improvement in enthesitis and related osteitis pathology as assessed by MRI [87]. The authors indicate that bone oedema resulting from enthesitis and osteitis precedes significant destruction and new bone formation in ankylosing spondylitis (AS), and that inhibiting diffuse osseous disease through TNF-α inhibition may avert destructive arthritis. Gorman *et al.* reported a notable and enduring clinical response in patients administered etanercept compared to those receiving a placebo [88].

3.3.1.3 Adverse Effects and Safety

Despite its high efficacy, infliximab may be associated with a number of side effects that must be closely monitored. Common reactions include symptoms during or after intravenous infusion, such as fever, rash, and shortness of breath. It can also induce the formation of antidrug antibodies (ATI)[89], reducing its efficacy and increasing the likelihood of allergic reactions. Rare cases of opportunistic infections have been reported, most notably tuberculosis (TB) and deep fungal infections, necessitating TB screening before initiating treatment. Rare cases of lymphoma have also been reported, particularly when combined with other immunosuppressants. However, infliximab's safety is acceptable for long-term use, and a systematic review,

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documented a lower rate of treatment discontinuation due to adverse events when used within active monitoring protocols. Data also suggest that early use of the drug during active disease results in better long-term efficacy and safety outcomes[90].

3.4 Systemic Lupus Erythematosus – SLE

3.4.1 Belimumab, Treatment & Mechanism of Action

Belimumab is a fully human monoclonal antibody used as a targeted biologic therapy for patients with systemic lupus erythematosus (SLE), particularly those who have not responded adequately to conventional treatments such as corticosteroids and immunosuppressants[91]. The drug works by inhibiting the activity of B-cell activating factor (BAFF), also known as BLyS, a protein essential for the survival and activation of B cells. In lupus, overactivation of B cells leads to the production of disease-causing autoantibodies, and BAFF contributes to the perpetuation of this abnormal immune state[92].

By binding to BAFF, belimumab reduces the survival and activity of B cells, reducing autoantibody production and helping to control excessive immune activity. It is the first biologic therapy approved specifically for SLE in over 50 years and is currently used to treat inactive systemic lupus erythematosus affecting the kidneys and brain. It has also recently been approved for the treatment of lupus nephritis (lupus nephritis)[93].

3.4.1.1 Indications and Dosage

Belimumab is approved for the treatment of patients with active SLE who have moderate to severe symptoms despite standard treatment, including steroids, hydroxychloroquine, and immunosuppressants. Belimumab is administered as an intravenous infusion at a dose of 10 mg/kg on days 0, 14, and 28, then every four weeks, or as a subcutaneous injection at a fixed dose of 200 mg once weekly. In 2020, the Food and Drug Administration (FDA) expanded the use of belimumab to include patients with lupus nephritis, based on its efficacy in preventing progressive renal decline [94].

3.4.1.2 Efficacy

Pivotal clinical studies have demonstrated the effectiveness of belimumab in reducing lupus disease activity and improving clinical and laboratory parameters. In the studies [37, 95], patients receiving belimumab at 10 mg/kg achieved a greater SLE Responder Index (SRI) response rate compared to placebo. The BLISS-LN study showed that adding belimumab to conventional lupus nephropathy therapy reduced the risk of kidney function decline by 49% compared to standard therapy alone[94]. Long-term follow-up by have shown that belimumab maintains disease stability, reduces exacerbations, and decreases the need for steroids over time[96].

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3.4.1.3 Adverse Effects and Safety

Belimumab is generally considered a safe and well-tolerated treatment. However, some side effects may occur, and they vary in severity[97]. The most common adverse reactions include nausea, diarrhea, fever, and symptoms of upper respiratory infection. Hypersensitivity reactions have also been documented during intravenous infusion, necessitating close monitoring during intravenous administration[98]. Rare reports of depression and suicidality have occurred, necessitating caution in patients with a history of psychiatric disorders. According to a meta-analysis[96], the use of belimumab was not associated with an increased rate of serious infections or mortality compared to conventional treatment, especially when used within controlled protocols. Although it is not used during pregnancy due to insufficient evidence, the safety data available to date indicate no confirmed teratogenic effects[99].

3.5 Ulcerative Colitis

3.5.1 Vedolizumab, Mechanism of Action

Vedolizumab (trade name: Entyvio) is a humanized monoclonal antibody directed against the α4β7 integrin receptor, a receptor found on the surface of T lymphocytes that contributes to their migration to the intestinal lymphoid tissue by interacting with the molecule MAdCAM-1 on the vascular endothelium of the gastrointestinal tract[100]. By disrupting this interaction, vedolizumab prevents immune cells from reaching the site of inflammation in the intestine, reducing the chronic inflammation characteristic of ulcerative colitis without significantly affecting systemic immunity. This selectivity toward the gastrointestinal tract distinguishes vedolizumab from other biologic therapies with a broader systemic effect[101].

3.5.1.1 Indications and Dosage

Vedolizumab is approved for the treatment of adult patients with moderate to severe active ulcerative colitis who have not responded adequately or have lost response to conventional or biologic therapy. The drug is administered intravenously at a dose of 300 mg at weeks 0, 2, and 6, and then every 8 weeks as a maintenance dose[102]. A subcutaneous dosage of 108 mg once every two weeks after completion of intravenous loading has also been approved. Studies show that continuing regular intravenous dosing helps maintain clinical remission and reduce exacerbations[103].

3.5.1.2 Efficacy

In the pivotal GEMINI 1 study, vedolizumab demonstrated a significant superiority over placebo in achieving clinical response after 6 weeks, with a response rate of 47.1% versus 25.5% in the control group[104]. A clinical remission rate of 41.8% was also achieved after 52 weeks. Longer-term follow-up in the VISIBLE 1 study, showed that subcutaneous vedolizumab after intravenous loading maintained its efficacy, with remission rates of 46.2% at week 52[105]. The

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proportion of patients requiring corticosteroids was significantly lower compared to conventional therapy alone. Real-world data indicate excellent efficacy even in patients who had previously failed TNFα inhibitors [106]. Recent real-world evidence further supports the long-term effectiveness and safety of vedolizumab in UC. Study [107] show over 80 % persistence at one year and nearly 50 % at five years, with better outcomes in biologic-naïve patients. Similarly, study [108], found that vedolizumab showed significantly longer persistence compared to infliximab when used as a first-line biological agent in moderate-to-severe ulcerative colitis

3.5.1.3 Adverse Effects and Safety

Vedolizumab is a biologic with a relatively excellent safety profile, due to its selective action on the gastrointestinal tract without extensive systemic immunosuppression[109]. The most common side effects include headache, pharyngitis, sinusitis, and occasional nausea or fatigue. Serious infections were not common, nor were rare cases of PML (leukoencephalopathy), which has been a concern with other similar treatments such as natalizumab, observed. A comprehensive safety analysis over 6 years in study [110] showed relatively low rates of severe infections and immune reactions. There is insufficient evidence regarding pregnancy, but its use is not contraindicated if the potential benefits outweigh the risks, particularly in active cases unresponsive to other treatments.

3.6 Chronic Plaque Psoriasis

3.6.1 Secukinumab, Mechanism of Action

Secukinumab (trade name: Cosentyx) is a fully human monoclonal antibody (IgG1κ) that targets and inhibits interleukin 17A (IL-17A), a key cytokine in the immune-inflammatory pathway of psoriasis[111]. IL-17A plays a pivotal role in stimulating keratinocyte activation, proliferation, and production of inflammatory factors that increase immune infiltration and intensify the inflammatory cycle in the skin. By selectively binding to IL-17A and preventing it from interacting with its receptor, secukinumab disrupts the inflammatory pathway responsible for the cutaneous symptoms of psoriasis, reducing redness, scaling, and skin thickening. Studies have shown that this inhibition leads to significant and rapid clinical improvement in patients with moderate to severe psoriasis [112].

3.6.1.1 Indications and Dosage

Secukinumab is licensed for the treatment of moderate to severe plaque psoriasis in adults who require systemic or photodynamic therapy. It is also used in psoriatic arthritis and ankylosing spondylitis[113]. The usual starting dose for skin psoriasis is 300 mg administered subcutaneously at weeks 0, 1, 2, 3, and 4, followed by a maintenance dose of 300 mg once monthly. In some patients with low weight or less severe disease, a 150 mg dose may be used based on clinical assessment. Studies have shown that strict adherence to the loading dose improves long-term treatment efficacy[114].

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3.6.1.2 Efficacy

Secukinumab's efficacy has been studied in a series of major clinical trials, such as ERASURE and FIXTURE. In the FIXTURE study [115], secukinumab demonstrated a 77.1% improvement rate with patients achieving PASI 75 (75% improvement in psoriasis severity index) at week 12, compared to 44% in the etanercept group and 4.9% in the placebo group. Studies also demonstrated continued excellent response through week 52 and beyond[116]. Subsequent studies have demonstrated similar efficacy in improving quality of life and reducing skin symptoms, as well as improving joint symptoms in the presence of concomitant psoriatic arthritis. Real-world data supported the clinical results, with excellent efficacy in patients who had not responded to other TNFα or IL-12/23 inhibitor treatments [117]. Results in Japanese patients aligned with prior trials, revealing that 70% of the entire population responded to Secukinumab'20 medication at week 16, with 68% of patients not on TNF inhibitors (n = 22) and 75% of those on TNF inhibitors (n = 8) responding [118]. The overall response rates to Secukinumab'20 therapy at weeks 1, 4, and 24 were 23%, 53%, and 70%, respectively. Enhancements in all secondary endpoints were noted at week 16, with these enhancements sustained or further augmented by week 24[118].

3.6.1.3 Adverse Effects and Safety

Secukinumab has a generally good safety profile. Common side effects include upper respiratory tract infections, diarrhea, and nasal and pharyngeal congestion. However, it may increase susceptibility to certain fungal infections, such as *Candida albicans*, due to its inhibition of the IL-17 pathway, which is important in mucosal defense. However, these infections are often superficial, mild, and easily treated[119]. In long-term trials, secukinumab did not show a significant increase in serious systemic infections, and no strong association with cancer or other autoimmune diseases was observed. The risk of injection-site reactions is also low compared to some TNF inhibitors. Regarding pregnancy, its use is only recommended after a risk-benefit assessment, as sufficient data are currently lacking. Recommendations suggest careful monitoring of patients with a history of inflammatory bowel disease, as there have been rare reports of flare-ups of Crohn's disease symptoms during treatment [120].

4. Other Diseases

Adult-onset Still’s disease (AOSD), initially documented by Eric By waters in the 1970s, is a rare condition of uncertain an etiology that impacts various systems and organs. Clinical Symptoms typically encompassed elevated fever, arthritis, transient salmon-pink rashes, lymphadenopathy, splenomegaly, and other signs. Laboratory results frequently indicate neutrophilic leukocytosis, heightened erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), hyperferritinemia, and high inflammatory markers[121, 122].

The pathophysiology of Still's disease may involve TNF-α and lymphotoxin. Small groups of individuals with adult-onset Still's illness were treated with infliximab, which indicated the possible therapeutic efficacy of anti-TNF-α. Following the initial treatment rounds, the disease's

symptoms subsided and the serological variables stabilised [123]. According to research [124], etanercept may also be useful in the treatment of Still's disease in conjunction with active arthritis. It is possible that the pathogenetic mechanisms of systemic vasculitides, particularly those associated with antineutrophil cytoplasmic antibodies (ANCA), could be responsive to anti-TNF-α Ab. This is because TNF-α is involved in the cytokine cascade that leads to vascular injury and the formation of granulomas [125].The administration of infliximab, which is a TNF-α blocker, has been administered to select groups of individuals who have Wegener's granulomatosis (WG) that is resistant to treatment [126]. There were two different dosing regimens for the antibody, which were 3 mg/kg and 5 mg/kg, and the dosing regimen that was greater appeared to be more successful [127]. Patients who are experiencing active Behcet's disease have higher serum concentrations of TNF and soluble TNF receptors than those who do not have the condition. A single infusion of infliximab was administered to patients who were experiencing recurrent panuveitis while they were undergoing immunosuppressive medication. The results of this treatment were a rapid and efficient suppression of acute ocular inflammation as well as extraocular symptoms [128].

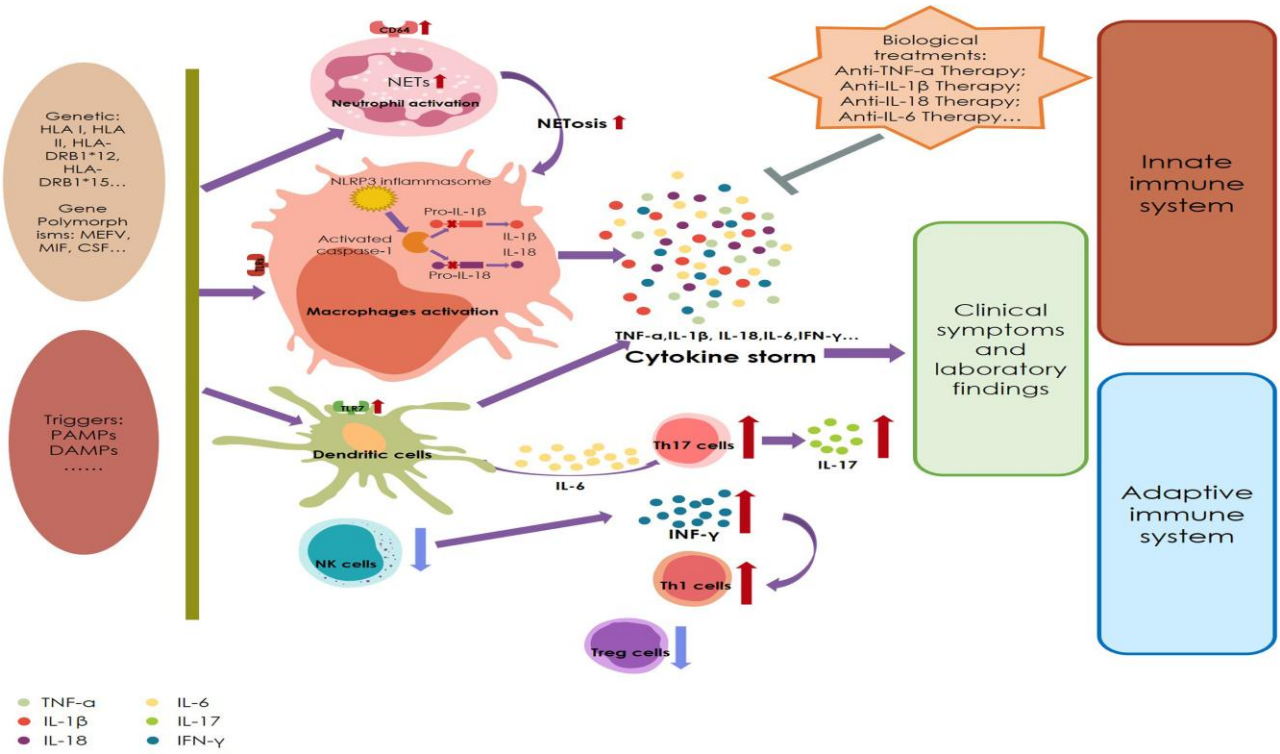

Figure 1. A summary of the pathogenesis of adult-onset Still's disease[129].

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CONCLUSION

The repertoire of biological therapy for autoimmune illnesses is rapidly increasing due to enhanced comprehension of molecular mechanisms and increased production capabilities. Their classification includes innovative anti-TNF alpha blockers (totally humanised or pegylated), anti-IL medicines (targeting IL-1 and IL-6), B-cell-directed treatments (targeting CD20 and CD22), co-activation signalling (CTLA4-Ig), and intravenous immunoglobulin (IVIG). While the majority of FDA-approved biologic medicines are designated for rheumatoid arthritis, Belimumab is the inaugural FDA-approved targeted medication for systemic lupus erythematosus. The efficacy and safety of biologics for off-label indications are promising for individuals with refractory autoimmune disorders.

Furthermore, the evidence reviewed demonstrates disease-specific efficacy of individual biologics. Adalimumab and infliximab are highly effective in rheumatoid arthritis and spondylarthropathies, respectively, while rituximab and tocilizumab offer alternatives even for refractory rheumatoid arthritis. Ustekinumab, vedolizumab have potent effects in Crohn's disease and ulcerative colitis. secukinumab is particularly effective in chronic plaque psoriasis. Belimumab remains the targeted therapy that has shown the most consistent benefit in SLE. Together, these results underline that biologic agents should be tailored to individual autoimmune diseases with a perspective of optimizing both the benefit-risk ratio.

Financial support and sponsorship
Nil.

Conflict of interest.

There are non-conflicts of interest.

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الخلاصة

تُقدم العلاجات البيولوجية للأمراض الروماتيزمية، التي تستهدف الجزيئات المؤثرة في آليات الجهاز المناعي، بديلاً عن العلاجات التقليدية، مثل الأدوية المضادة للروماتيزم التي تُغير مسار المرض، بالإضافة إلى أدوية مثبطة للمناعة. ومع ذلك، فإن القيود الحالية على العلاجات البيولوجية، بما في ذلك تحديات الإعطاء الوريدي، وارتفاع أسعار هذه الأدوية، والآثار الجانبية المصاحبة لها، تُعيق استخدامها على نطاق واسع كعلاجات من الدرجة الأولى. تُقدم هذه المراجعة تحديثًا للأبحاث الحديثة المتعلقة بالأدوية البيولوجية الجديدة المتاحة. تُركز المراجعة على ثمانية أدوية: Tocilizumab, Rituximab, Adalimumab, Ustekinumab, Infliximab Belimumab, Vedolizumab, and Secukinumab ، تُستخدم في علاج التهاب المفاصل الروماتويدي، والتهاب الفقار، والذئبة الحمامية الجهازية، والتصلب الجهازي، والتهاب الأوعية الدموية.

الكلمات المفتاحية: العلاجات البيولوجية، التهاب المفاصل الروماتويدي، التهاب الفقار، الذئبة الحمامية الجهازية، التهاب التصلب الجهازي