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Review Article

The current treatment strategies for autoimmune diseases, including immunosuppressive drugs, biologics and emerging immunotherapies like CAR-T cell therapy

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ABSTRACT

This review explores the evolving strategies in autoimmune disease (AID) management, focusing on the limitations of traditional therapies and the potential of emerging treatments. Traditional treatments, including corticosteroids, NSAIDs and DMARDs, are effective but often fail to restore immune tolerance and come with significant side effects. Emerging therapies, such as Janus kinase (JAK) inhibitors and sphingosine-1-phosphate (S1P) receptor modulators, offer targeted approaches by disrupting specific inflammatory pathways. Chimeric Antigen Receptor–T Cell (CAR-T) therapy, originally developed for cancer, is being investigated for AIDs, showing promise in targeting and eliminating autoreactive immune cells. Despite their benefits, these advanced therapies face challenges such as high costs and complex administration. This explored the role of biosimilars, like Exemptia, a biosimilar of Adalimumab, in addressing these challenges. By providing a cost-effective alternative without compromising efficacy or safety, biosimilars expand access to effective biologic therapies for AID management.

Keywords: Autoimmune diseases, Adalimumab (Exemptia), Biosimilars, CAR-T cell therapy, Emerging therapies

INTRODUCTION

Autoimmune diseases (AIDs) are a diverse group of disorders characterized by the immune system's aberrant response against the body's own tissues. These conditions affect millions of people worldwide, contributing significantly to morbidity and, in severe cases, mortality.[1] Autoimmune diseases encompass over 80 distinct illnesses, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS) and type 1 diabetes mellitus (T1DM).

They are categorized based on pathogenic mechanisms involving either self-reactive antibodies produced by B lymphocyte-derived plasma cells or self-reactive T lymphocytes. Globally, the incidence of autoimmune diseases stands at approximately 80 cases per 100,000 individuals, with a prevalence exceeding 3%.[2] The immune system is designed to protect the body against pathogens and other harmful entities. It distinguishes self from non-self through a complex network of cells, molecules and pathways. Central to this system are lymphocytes, which include T cells and B cells.

These cells recognize antigens through specific receptors and initiate appropriate immune responses.[3] In autoimmune diseases, this finely tuned system malfunctions. T cells and B cells mistakenly identify self-antigens as foreign, leading to an attack on the body's own tissues. This breakdown in self-tolerance can result from various factors, including genetic predisposition, environmental triggers and infections.[4] Environmental factors such as infections, smoking and dietary components can also modulate immune responses and

trigger disease onset in genetically susceptible individuals.[5] Self-reactive T lymphocyte-mediated AIDs involve autoreactive T cells recognizing target cells through their T cell receptors (TCRs) matching major histocompatibility complex I (MHCI) and autoantigen-derived peptides.[6]

These cytotoxic T cells then kill target cells by secreting cytotoxic granules (e.g., perforin and granzyme B) or activating the Fas-Fas ligand pathway, inducing apoptosis and releasing cytokines such as TNFα and IFN-γ, which cause further tissue injury.[7]

Traditional treatment strategies for autoimmune diseases aim to manage the disease symptoms rather than offering the cure. These approaches typically involve immunosuppressive and anti-inflammatory drugs.[8] These treatments can be categorized into several main groups: corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs), which include both conventional DMARDs and biologic DMARDs.[9] Corticosteroids, such as prednisone and methylprednisolone, are potent anti-inflammatory agents commonly used to control acute flare-ups of autoimmune diseases.

They work by inhibiting multiple inflammatory pathways, thereby reducing immune system activity and decreasing inflammation. Despite their effectiveness, long-term use of corticosteroids is associated with significant side effects, including osteoporosis, hypertension, diabetes, weight gain and increased susceptibility to infections.[10] NSAIDs such as ibuprofen and naproxen, are commonly used to manage pain and inflammation in autoimmune conditions like rheumatoid arthritis and ankylosing spondylitis.

They work by inhibiting cyclooxygenase (COX) enzymes, which play a key role in the inflammatory process. NSAIDs provide symptomatic relief and are often used in conjunction with other therapies. While NSAIDs are effective for pain relief, they do not alter the underlying disease process.[11]

DMARDs such as methotrexate, sulfasalazine, hydroxychloroquine and cyclosporine, can slow the progression of autoimmune diseases and preserve joint function by broadly suppressing the immune system.[12] However, these drugs take weeks to months to become fully effective and carry risks of toxicities, including liver damage, bone marrow suppression and increased infection risk.

Biologic DMARDs, including TNF inhibitors (e.g., infliximab, etanercept), interleukin blockers (e.g., tocilizumab for IL-6, ustekinumab for IL-12/23) and B cell-depleting agents (e.g., rituximab), target specific components of the immune system, offering a more precise approach compared to conventional DMARDs.12

While effective, biologic DMARDs are expensive, require inconvenient parenteral administration and increase the risk of serious infections and malignancies. They do not restore immune tolerance and often necessitate continuous administration, with potential for patients to develop resistance over time.

Traditional treatments do not address the underlying issue of immune tolerance, often leading to relapses when therapy is discontinued.[13] These limitations highlight the need for more effective and safer treatments that restore immune tolerance and offer long-term disease control.

Emerging methods for treating autoimmune diseases focus on more precisely targeting the immune system to reduce side effects and improve efficacy. Advances in biologic agents, small molecule inhibitors and gene therapies have shown promise in achieving better disease control. These innovative approaches aim to modulate specific immune pathways and restore immune tolerance, potentially offering longer lasting and more effective treatments compared to traditional therapies.

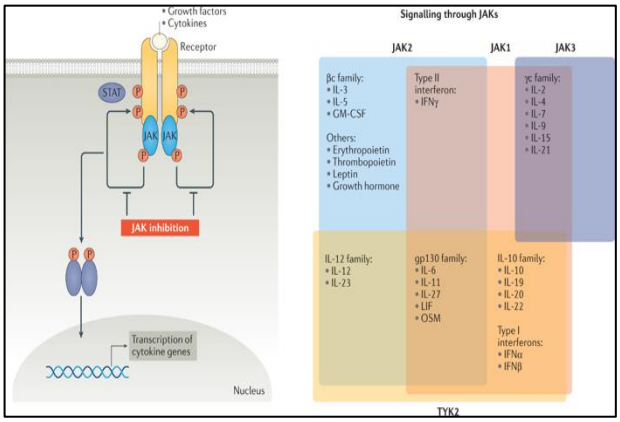

Figure 1: Mechanism of action of JAK inhibitors. Reproduced from reference no 15.

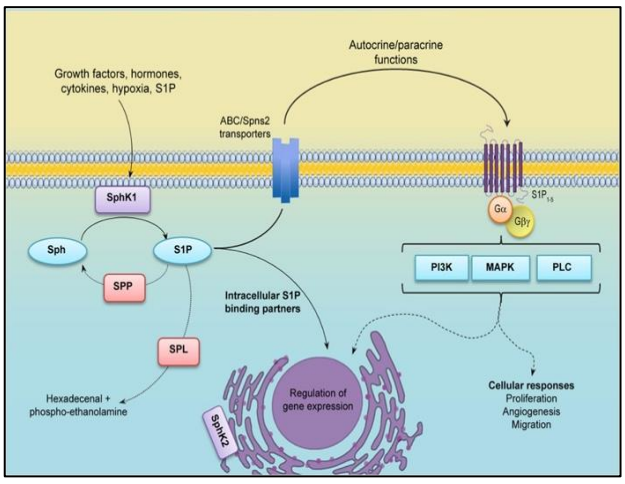

Figure 2: Mechanism of action of S1P receptors. Reproduced from reference no 25.

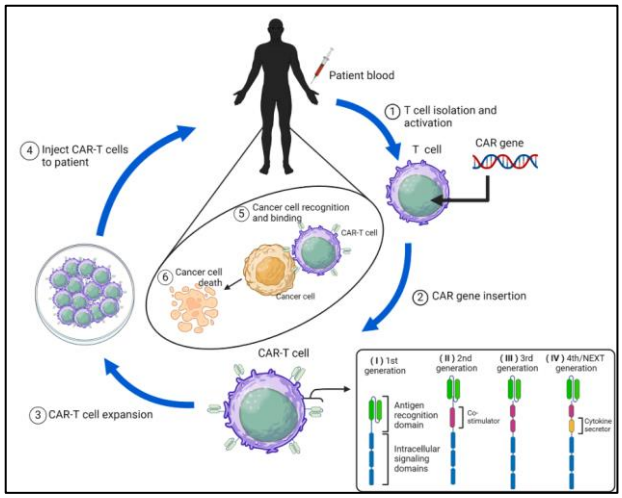

Figure 3: Schematic for manufacturing and administration workflow of chimeric antigen receptor (CAR) T-Cell Therapy. (1) T cells are isolated and activated from the patient's blood. (2) The CAR gene is inserted into T cells to form CAR-T cells. (3) CAR-T cells are expanded until a specific threshold. (4) Expanded CAR-T cells are injected back into the patient. (5) CAR-T cells recognize and bind to cancer cells. (6) Upon contact with tumour antigens, CAR-T cells proliferate and activate to induce the killing of cancer cells. (I) 1st generation CAR-T cells: An antigen recognition domain and intracellular signalling domains. (II) 2nd generation CAR-T cells: An antigen recognition domain, a single co-stimulator and intracellular signalling domains. (III) 3rd generation CAR-T cells: An antigen recognition domain, two co-stimulators and intracellular signalling domains. (IV) 4th/NEXT generation CAR-T cells: An antigen recognition domain, co-stimulator, cytokine secretor and intracellular signalling domains.

EMERGING THERAPIES

Janus kinase inhibitors

Janus kinase (JAK) inhibitors target the JAK-STAT signalling pathway, a crucial mediator of immune responses and inflammation. By inhibiting JAKs, these drugs disrupt the signalling cascade initiated by various cytokines, including interleukins, interferons and granulocyte-macrophage colony-stimulating factor. This inhibition reduces the production of pro-inflammatory cytokines, modulates immune responses and alleviates inflammation, making JAK inhibitors effective in treating autoimmune diseases.[14]

Mechanism of action

JAK inhibitors target the JAK-STAT signalling pathway, a critical mediator of immune responses. JAKs are a family of tyrosine kinases that include JAK1, JAK2, JAK3 and TYK2. These kinases associate with cytokine receptors on the cell surface. Upon cytokine binding to its receptor, JAKs are activated through trans-phosphorylation. Activated JAKs then phosphorylate specific tyrosine residues on the receptor, creating docking sites for STAT proteins. These STAT proteins are subsequently phosphorylated by JAKs, causing them to dimerize and translocate to the nucleus, where they regulate the transcription of genes involved in immune function and inflammation (Figure 1).[15]

The inhibition of JAKs by small molecule inhibitors prevents the phosphorylation and activation of STATs. This blockade disrupts the signalling cascade initiated by various cytokines, including interleukins (IL-2, IL-4, IL-6, IL-7, IL-9, IL-15, IL-21), interferons (IFN-α, IFN-β, IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF).[16] By inhibiting these signalling pathways, JAK inhibitors reduce the production of pro-inflammatory cytokines, modulate immune responses and alleviate inflammation, making them effective in treating autoimmune diseases.

Clinical evidence

Tofacitinib (Xeljanz) was the first JAK inhibitor approved for RA. It primarily targets JAK1 and JAK3, with additional effects on JAK2. Clinical trials, such as the ORAL Solo trial, demonstrated that tofacitinib significantly improved the signs and symptoms of RA compared to placebo. Beyond RA, tofacitinib has shown effectiveness in psoriatic arthritis (PsA), reducing joint pain and skin lesions and in ulcerative colitis (UC), where it has been shown to induce and maintain remission in patients with moderate to severe disease.[17,18]

Baricitinib (Olumiant) primarily inhibits JAK1 and JAK2 and has been approved for the treatment of RA, especially in patients who have had an inadequate response to one or more TNF inhibitors. In the RA-BEACON study, baricitinib demonstrated significant improvements in disease activity and physical function. It has also been associated with a rapid onset of action, with symptom relief observed as early as one week after treatment initiation. Additionally, baricitinib has shown promise in reducing the severity of atopic dermatitis in clinical trials.[19,20]

Upadacitinib (Rinvoq) is a selective JAK1 inhibitor approved for the treatment of RA. Clinical trials such as SELECT-NEXT and SELECT-MONOTHERAPY have demonstrated that upadacitinib significantly improves disease activity and physical function compared to placebo. Upadacitinib has also been investigated in other autoimmune conditions, including ankylosing spondylitis and atopic dermatitis, with positive outcomes. Its selective inhibition of JAK1 is associated with a favorable safety profile, making it a valuable addition to the therapeutic options for autoimmune diseases.[21]

Extensive clinical trials have highlighted the effectiveness of these JAK inhibitors across various autoimmune

diseases. In RA, both tofacitinib and baricitinib have shown significant reductions in disease activity and improvements in physical function. The ORAL Strategy trial found that tofacitinib, in combination with methotrexate, was non-inferior to adalimumab in terms of efficacy.[22] Upadacitinib has provided similar benefits with an improved safety profile, as demonstrated in the SELECT trials.[23]

Safety and tolerability

While generally well-tolerated, JAK inhibitors are associated with some risks that necessitate careful monitoring. Increased susceptibility to serious infections, including opportunistic infections like tuberculosis and herpes zoster, has been reported due to immunosuppression. There is also a higher incidence of blood clots, particularly with higher doses.[22] Laboratory abnormalities, such as changes in blood counts, liver enzymes and lipid levels, are common and require regular monitoring. Despite these risks, the relatively short half-life of JAK inhibitors allows for rapid cessation of the drug if adverse effects occur, offering a safety advantage over some biologics.[23]

Sphingosine-1-phosphate receptor modulators

Sphingosine-1-phosphate (S1P) receptor modulators represent a promising class of therapies for autoimmune diseases. These modulators target the S1P signalling pathways, which play a critical role in immune cell trafficking, vascular integrity and central nervous system function.[24]

Mechanism of action

S1P receptors (S1PRs) are G protein-coupled receptors with five subtypes (S1PR1-S1PR5), each mediating distinct biological functions. S1P signalling is crucial for regulating lymphocyte trafficking from lymphoid organs to peripheral tissues. When S1P binds to S1PR1 on lymphocytes, it promotes their egress from lymph nodes into the circulation. S1P receptor modulators function primarily by binding to S1PR1 on lymphocytes, leading to receptor internalization and subsequent sequestration of these cells in lymph nodes, thereby reducing their circulation and migration to sites of inflammation (Figure 2).[25]

Clinical evidence and applications

Fingolimod (Gilenya) was the first S1P receptor modulator approved for relapsing-remitting multiple sclerosis (RRMS). Its efficacy was demonstrated in pivotal trials such as FREEDOMS I and II, which showed significant reductions in the annualized relapse rate (ARR) and MRI markers of disease activity compared to placebo.[26] The TRANSFORMS study further established fingolimod's superiority over intramuscular interferon beta-1a in reducing relapse rates. Beyond MS, fingolimod has been explored in conditions like acute renal transplant rejection and ischemic stroke, although with varying success.[27]

Siponimod (Mayzent) is a selective modulator of S1PR1 and S1PR5, developed to reduce the cardiovascular side effects associated with fingolimod. The EXPAND trial demonstrated siponimod's efficacy in secondary progressive multiple sclerosis (SPMS), showing significant benefits in reducing disability progression and MRI measures of disease activity.[28]

Ozanimod (Zeposia) selectively targets S1PR1 and S1PR5 and has shown effectiveness in both RRMS and ulcerative colitis (UC). The SUNBEAM and RADIANCE trials confirmed its efficacy in RRMS by significantly reducing ARR and MRI markers compared to interferon beta-1a.[29,30] In the TRUE NORTH trial, ozanimod demonstrated substantial clinical and histological improvements in patients with moderate-to-severe UC.[31]

Ponesimod (Ponvory) is another selective S1PR1 modulator, approved for RRMS. The OPTIMUM trial highlighted its superiority over teriflunomide in reducing ARR and MRI markers of inflammatory activity, with a favorable safety profile.[32]

Safety and tolerability

S1P receptor modulators are generally well-tolerated but require careful monitoring due to potential side effects. Cardiovascular effects, such as transient bradycardia and atrioventricular conduction delays, are significant concerns, especially with fingolimod, necessitating first-dose monitoring.[31] Siponimod and ozanimod have fewer cardiovascular side effects due to their selective receptor profiles and dose titration. Increased risk of infections, including opportunistic infections like herpes zoster and rare cases of progressive multifocal leukoencephalopathy (PML), is another concern, requiring vigilant infection monitoring.

Additionally, macular edema is a potential side effect, particularly with fingolimod, warranting regular ophthalmologic exams, especially in diabetic patients. Mild reductions in pulmonary function also necessitate caution in patients with pre-existing pulmonary conditions.[26] Despite these risks, the relatively short half-life of S1P receptor modulators allows for rapid cessation if adverse effects occur, providing a safety advantage. Careful management is essential to balance the benefits and potential risks of these therapies.

CAR-T THERAPY

Chimeric Antigen Receptor T-cell (CAR-T) therapy has shown significant promise in the treatment of autoimmune diseases by leveraging its ability to specifically target and eliminate autoreactive immune cells. This novel approach, originally developed for cancer treatment, is now being

explored for its potential to induce long-term remission in autoimmune diseases.

Mechanism of action

CAR-T cell therapy involves the extraction and genetic modification of a patient's T cells to express chimeric antigen receptors (CARs) designed to target specific antigens on diseased cells. The process starts with leukapheresis, where T cells are collected from the patient's blood. These T cells are then genetically engineered in a laboratory to express CARs, which are synthetic receptors combining an antigen recognition domain, usually derived from an antibody, with intracellular signalling domains that activate the T cell upon binding to its target.

Once the CAR-T cells are multiplied, they are administered back to the patient. After infusion, these engineered T cells move through the body, identifying and attaching to cells with the specific target antigen, triggering their activation and destruction of those target cells. This process involves the release of cytotoxic granules and cytokines that induce apoptosis in the target cells and recruit other immune cells to enhance the anti-disease response.[33]

In the treatment of autoimmune diseases, CAR-T cell therapy is designed to target autoreactive immune cells that mistakenly attack the body's own tissues. For example, CAR-T cells can be engineered to target CD19, a surface protein found on B cells, which are often implicated in the pathology of various autoimmune diseases. By targeting and depleting B cells, CAR-T cell therapy reduces the production of pathogenic autoantibodies, thereby alleviating the autoimmune attack on healthy tissues.[34]

Additionally, CAR-T cells can be tailored to target other specific markers relevant to different autoimmune conditions, such as B cell maturation antigen (BCMA) on long-lived plasma cells or other autoantigen-specific receptors.[35] This targeted approach helps in resetting the immune system by eliminating the autoreactive cells responsible for the disease, thus providing a potential long-term remission and reducing the need for chronic immunosuppression. The versatility of CAR-T cell therapy in addressing various autoimmune pathologies highlights its potential as a revolutionary treatment for refractory autoimmune diseases (Figure 3).

APPLICATION OF CAR-T CELLS IN AUTOIMMUNE DISEASES

Systemic lupus erythematosus

Kansal et al, (2019) investigated CD19-targeted CAR-T cells in lupus-prone mouse models. The study showed that CD8+T cells expressing CD19-targeted CARs achieved complete and sustained depletion of CD19+B cells, eliminating autoantibody production and reversing disease manifestations.[36] A 2021 case reported in The New England Journal of Medicine detailed the use of autologous CD19 CAR-T cells in a patient with severe, refractory SLE. The treatment led to complete remission, significant reduction in autoantibody levels and normalization of complement levels.[37]

Rheumatoid arthritis

Zhang et al, (2020) developed a customized CAR-T cell strategy using universal anti-fluorescein isothiocyanate (FITC) CAR-T cells combined with FITC-labelled antigenic peptide epitopes. This approach specifically targeted and eliminated autoreactive B cell subsets from RA patients, demonstrating potential for precise and effective treatment of RA.[38] A 2021 study by Whittington et al, explored CAR-T cells targeting CD4+ T cells in a mouse model of RA. The study found that these CAR-T cells effectively inhibited the development of autoimmune arthritis, suggesting a promising approach for treating RA by depleting pathogenic T cell subsets.[39]

Sjögren's syndrome

A 2023 case report described the use of CAR-T cell therapy in a patient with diffuse large B-cell lymphoma (DLBCL) and Sjögren's Syndrome. Following CAR-T cell infusion, the patient achieved complete remission for DLBCL and significant improvement in SjD symptoms, with undetectable autoimmune markers for the first time in a decade.[40] Systemic Sclerosis (SSc): In a 2023 study, Bergmann et al, reported the use of CD19-targeted CAR-T cell therapy in a patient with severe, refractory systemic sclerosis. The treatment resulted in complete B-cell depletion and marked clinical improvements, including reduced cardiac fibrosis and improved joint function. This case provides evidence for the efficacy of CAR-T cell therapy in severe SSc.[41]

Type 1 diabetes mellitus

A study by Zhang et al, (2018) investigated CD8+ CAR-T cells targeting the insulin B:9-23 peptide-MHC complex in a NOD mouse model of T1DM. The CAR-T cells delayed the onset of hyperglycemia and reduced diabetes incidence in treated mice.[42] Fishman et al, (2017) evaluated chimeric MHC molecules fused with TCR signalling motifs to reprogram CD8+T cells against diabetogenic CD8 T cells. The modified T cells reduced insulitis and diabetes incidence in NOD mice, offering a novel immunotherapeutic strategy for T1DM.[43]

Safety and tolerability

CAR-T cell therapy shows promise in treating autoimmune diseases, with early preclinical and clinical studies demonstrating potential benefits. However, its application faces challenges, including the complexity of targeting autoreactive cells without impairing normal immunity, stringent safety requirements and risks like

cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Though CRS and ICANS are typically mild to moderate and manageable, vigilant monitoring is necessary. Prolonged B cell depletion, particularly with CD19 or BCMA-targeted therapies, raises concerns about infections, often requiring prophylactic treatments like IVIG. Additionally, risks of off-target effects, secondary malignancies and prolonged immune suppression highlight the need for robust safety protocols.[43] Despite these concerns, CAR-T therapy holds significant potential for refractory autoimmune diseases with appropriate monitoring and management.

Biosimilars in autoimmune disease management

Advanced therapies like JAK inhibitors, S1P receptor modulators and CAR-T cell therapies have transformed autoimmune disease treatment, offering remarkable efficacy and potential for long-term remission. However, challenges such as high costs, complex manufacturing, severe side effects and limited accessibility hinder their widespread use. Biosimilars, cost-effective alternatives to biologics, address these gaps by maintaining comparable efficacy and safety while reducing financial burdens and enhancing access.[44] Their introduction broadens treatment options, making advanced therapies more accessible to a larger patient population. Table 1 outlines the role of selected biosimilars in autoimmune disease management.

Adalimumab (Exemptia) - a closer look

Adalimumab, a fully human monoclonal antibody targeting tumor necrosis factor-alpha (TNF-α), is a pivotal therapeutic agent for various autoimmune diseases. Initially approved by the FDA in 2002 for the treatment of rheumatoid arthritis, Adalimumab's scope has broadened to include other inflammatory conditions such as psoriatic arthritis, ankylosing spondylitis, Crohn’s disease and ulcerative colitis. This biologic agent works by neutralizing TNF-α, thereby mitigating inflammation and halting disease progression.

To enhance accessibility and affordability of this effective therapy, biosimilars such as Exemptia have been developed. Exemptia, a biosimilar of Adalimumab, was created by Cadila Healthcare Ltd. (Zydus Cadila) and is known as ZRC-3197.[50] The development of Exemptia involved a rigorous process to ensure that it matches the reference product in terms of purity, potency and safety. Comprehensive studies comparing Exemptia to the originator product, Humira, have been conducted to confirm its biosimilarity. Exemptia was produced in genetically engineered Chinese hamster ovary (CHO) cells. Functional assays confirmed that Exemptia exhibits comparable binding affinity to TNF-α and similar TNF-α neutralizing activity as Humira.[51]

Table 1: Overview of biosimilars in autoimmune disease management.

Name of Biosimilar	Disease	Mechanism of Action	Side effects	Reference
Sarilumab	Rheumatoid arthritis	Human monoclonal antibody against IL-6 receptor	Infections, neutropenia, elevated liver enzymes	45
Anakinra	Rheumatoid arthritis	IL-1 receptor antagonist, blocking the inflammatory effects of IL-1	Injection site reactions, infections, neutropenia	46
Infliximab	Crohn's disease	Chimeric monoclonal antibody against TNF-α	Infusion reactions, infections, increased risk of lymphoma	47
Certolizumab	Rheumatoid arthritis, Psoriatic arthritis, Crohn's disease	PEGylated Fab fragment of a humanized anti-TNF-α antibody	Upper respiratory tract infections, bacterial infections, tuberculosis	48
Rituximab	Rheumatoid arthritis	Monoclonal antibody against CD20 on B-cells	Infusion reactions, infections, cytopenias	49

Mechanism of action

Adalimumab is a fully human recombinant monoclonal antibody that specifically targets and neutralizes TNF-α, a key pro-inflammatory cytokine involved in the pathogenesis of various autoimmune and inflammatory diseases. Adalimumab binds to both the soluble and transmembrane forms of TNF-α with high affinity and specificity, preventing it from interacting with the p55 and p75 cell surface TNF receptors. The inhibition of TNF-α signalling by adalimumab leads to a reduction in inflammatory processes and immune cell activation, thereby ameliorating the symptoms of diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel diseases.[52] Mechanistically, adalimumab has been shown to induce apoptosis of activated T cells and reduce the

production of other inflammatory mediators like interleukin-6 (IL-6) and matrix metalloproteinases.[53]

Furthermore, adalimumab modulates endothelial cell function and adhesion molecule expression, which contributes to its anti-inflammatory effects.[54] By blocking the interaction of TNF-α with its receptors, adalimumab disrupts the downstream signalling cascades that promote the production of inflammatory cytokines, chemokines and proteolytic enzymes.[55]

Analytical studies have demonstrated that adalimumab has highly similar physicochemical properties, purity and functional characteristics to the reference adalimumab (Humira), indicating a high degree of structural and functional similarity. This ensures that adalimumab can effectively recapitulate the mechanism of action of the reference product.

A real-world study involving 50 patients with plaque psoriasis evaluated the biosimilar Exemptia, revealing its effectiveness to be on par with the reference drug adalimumab. Patients were administered an initial subcutaneous dose of 80 mg, followed by 40 mg biweekly for a duration of 16 weeks. Key outcomes measured included the Psoriasis Area and Severity Index (PASI), the Dermatology Life Quality Index (DLQI) and the Physician's Global Assessment (PGA).

After 16 weeks of treatment, 93% of patients achieved at least a 75% reduction in PASI scores, with 24% reaching PASI75, 14% achieving PASI90 and 55% achieving complete remission (PASI100). The mean PASI score improved from 35.03 to 5.24. Furthermore, 52% of the participants achieved DLQI scores of 0 or 1, reflecting notable improvements in quality of life. Additionally, 93% of patients were assessed as 'clear' or 'minimal' on the PGA scale. The therapy was well tolerated, with reported adverse events being mild and self-limiting, including generalized itching, injection-site pain, headaches and common cold symptoms.[56]

Chandra A et al conducted a randomized, double-blind study to evaluate and compare the efficacy and safety of the biosimilar adalimumab (Exemptia) with the reference product adalimumab (Humira) in patients with rheumatoid arthritis. The results showed that after 12 weeks of treatment, 82% of patients in the Exemptia group achieved an ACR20 response, compared to 79.2% in the Humira group. For ACR50, the response rates were 46% and 43.4% respectively and for ACR70 the rates were 14% and 15.1%. There were no statistically significant differences between the two treatment groups for any of the efficacy endpoints.[57]

Midha et al conducted a retrospective study to assess the efficacy and safety of Exemptia, an adalimumab biosimilar, as induction therapy for moderate-to-severe steroid-refractory ulcerative colitis (UC). The analysis included 29 patients who followed an induction dosing regimen of 160 mg at week 0, 80 mg at week 2 and 40 mg biweekly from weeks 4 to 8. Clinical response and remission were evaluated at week 8 using the Mayo score. The results indicated that 24.1% of patients showed a clinical response, while only 3.5% achieved clinical remission. Adverse events included the development of extrapulmonary tuberculosis in 13.8% of patients and four required colectomy.[58]

In a study by Kapoor et al the real-life tolerability and effectiveness of the adalimumab biosimilar, Exemptia (ZRC-3197), were assessed in patients with ankylosing spondylitis (AS) as part of the Adalimumab Biosimilar Patient Registry (ASPIRE). Data from 308 patients were analyzed over a 24-week period. The study reported significant improvement in disease outcome, with the mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score decreasing from 6.2 to 2.1 and the median visual analogue scale (VAS) score improving from 8 to 2.

About 94% of patients achieved a BASDAI score lower than 4 and 95% achieved a BASDAI50 response. Both physicians and patients rated the efficacy and tolerability as 'good' to 'excellent' in over 98% of cases. Common adverse events included headache, nausea and fatigue, with serious infections such as tuberculosis occurring in 2% of patients. No new unexpected adverse reactions were reported.[59]

Khandpur et al conducted an open-labeled, prospective pilot study to evaluate the adalimumab biosimilar Exemptia (ZRC 3197) in 16 patients with psoriatic arthritis (PsA) and concomitant moderate to severe chronic plaque psoriasis. Patients received an 80 mg loading dose followed by 40 mg at weeks 1, 3, 5, 7 and 9, with follow-up at weeks 12 and 20. The primary efficacy endpoints were PASI 50 and DAPSA 20 at week 12. At week 12, PASI 50 and DAPSA 20 were achieved by 93% of patients. PASI 75 and PASI 90 were achieved by 57% and 35.7% of patients, respectively.

There was a significant reduction in Disease Activity in Psoriatic Arthritis (DAPSA) scores and improvement in Investigator Global Assessment (IGA) and Patient Global Assessment (PGA) scores. The median Psoriasis Disability Index (PDI) decreased from 29.5 to 10 at week 9. Adverse events included infections, headaches and gastrointestinal issues, with a higher rate of adverse effects compared to original adalimumab.[60]

Kamat et al conducted a multicenter study to assess the effectiveness and safety of Exemptia, an adalimumab biosimilar, in Indian patients with inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC). The study involved 70 patients-49 with CD and 21 with UC—treated between October 2015 and February 2018.

At 8 weeks, clinical remission was observed in 46.9% of CD patients and 52.4% of UC patients. By 52 weeks, 32.7% of CD patients and 33.3% of UC patients continued to maintain remission. Adverse events were noted in 28.6% of participants, with serious events occurring in 10%, including three cases of tuberculosis. The findings suggest that the biosimilar is an effective and affordable option for inducing and sustaining remission in IBD, making it a practical treatment choice for Indian patients.[61]

Safety and tolerability

Exemptia (adalimumab biosimilar) has a well-characterized safety profile, with adverse events similar to those reported for the reference adalimumab. Common adverse reactions include injection site reactions, upper respiratory tract infections, headache, rash, nausea, fatigue and mild gastrointestinal issues.

Serious adverse events are relatively rare but include tuberculosis, with an incidence rate ranging from 2% to 13.8% across studies. In clinical studies, Exemptia has shown a generally acceptable safety and tolerability profile across various conditions. In ulcerative colitis, Midha et al, reported a significant risk of tuberculosis (13.8%) and one cardiac-related death, though these events were not necessarily linked to Exemptia treatment.

For ankylosing spondylitis, serious infections were less frequent and no new unexpected adverse reactions were noted. Studies on psoriatic arthritis and plaque psoriasis reported mostly mild adverse events, with no severe or serious infections requiring hospitalization. In inflammatory bowel disease, adverse events occurred in 28.6% of patients, with 10% experiencing serious events, including tuberculosis. Overall, Exemptia is well-tolerated with manageable safety concerns, making it a viable and affordable treatment option for inflammatory conditions in clinical practice.

CONCLUSION

This review highlights the advancements in autoimmune disease treatments, emphasizing the need for more effective and safer options. Traditional therapies, though effective in symptom management, often fail to restore immune tolerance and carry significant side effects. Emerging therapies like JAK inhibitors, S1P receptor modulators and CAR-T cell therapy show promise but face challenges such as high costs and complex administration. Recent advances in biosimilars for autoimmune diseases offer cost-effective and accessible alternatives to reference biologics. Biosimilars modeled after TNF inhibitors and other biologics have shown comparable efficacy and safety, expanding treatment options for autoimmune diseases. However, continued monitoring and research are needed to address concerns about immunogenicity, regulatory policies and long-term efficacy.

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