Scholastic Medical Sciences

Review Article

Volume 2 Issue 1 January 2025

A Comprehensive Review of TNF inhibitors in Autoimmune Diseases

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Received: December 07, 2025; **Published:** December 15, 2025

Abstract

Autoimmune diseases have undergone a remarkable transformation in treatment strategies over the past few decades, largely due to the introduction of tumor necrosis factor (TNF) inhibitors. This paper offers an in-depth examination of TNF's role in inflammatory processes, the working mechanisms of TNF inhibitors, and their real-world clinical applications. We conduct an analysis of the five TNF inhibitors that have been approved by the FDA. This analysis focuses on their structures, methods of administration, and the indications for which they have been approved. The study examines recent clinical trial data that compares TNF inhibitors with newer biologics and investigates the effectiveness of improved treatment regimens. Additionally, the study assesses the influence of biosimilars on the availability of treatment options. The review focuses on new areas of study, such as tissue-specific inhibitors and combination therapy, while also discussing persistent issues like non-response in certain patients and long-term safety concerns. This paper presents a comprehensive analysis of the latest research and clinical data on TNF inhibitor therapy in autoimmune illnesses. It aims to provide healthcare practitioners and researchers with important information and perspectives in this quickly changing field.

Key words: TNF inhibitors, TNF blockers, autoimmune diseases, inflammatory cytokines, monoclonal antibodies, fusion proteins, biosimilars, clinical trials, rheumatoid arthritis, psoriasis, crohn's disease.

Abbreviations: Tumor Necrosis Factor (TNF), Food and Drug Administration (FDA), Tumor Necrosis Factor Receptor (TNFR), Nuclear Factor Kappa B (NF-κB), Mitogen-Activated Protein Kinase (MAPK), Polyethylene Glycol (PEG), Fragment Antigen Binding (Fab), Disease-Modifying Anti-Rheumatic Drug (DMARD), Janus Kinase (JAK), Interleukin (IL), Receptor Interacting Protein Kinase 1 (RIPK1), TNF Receptor Associated Death Domain (TRADD)

Introduction

Autoimmune illnesses encompass a diverse range of ailments characterized by an abnormal immune response that targets the body's own antigens, resulting in persistent inflammation and tissue damage [1]. Among these conditions, rheumatoid arthritis, Crohn's disease, and psoriasis are some widely recognized diseases. Collectively, these disorders have a significant impact on millions of individuals worldwide. These disorders frequently result in substantial disability that has a significant impact on the health of patients [2].

Tumor necrosis factor (TNF) is a crucial pro-inflammatory cytokine that has a major impact on the progression of several autoimmune diseases [3]. Tumor necrosis factor (TNF), mostly secreted by macrophages and T-cells, acts by inducing the production of cytokines in other immune cells, hence promoting the clearance of apoptotic cells [4]. TNF has been a central target for therapeutic approaches in the treatment of autoimmune diseases [5] because of its pivotal function in controlling inflammatory responses. TNF inhibitors are a class of biologic medications specifically formulated to neutralize the impact of TNF, a protein that amplifies inflammation. These inhibitors aid in reducing inflammation and inhibiting the progression of diseases [6]. These inhibitors have significantly transformed the approach to treating several autoimmune illnesses and have improved therapeutic outcomes for individuals who previously had limited therapy options [7]. The significant influence of TNF inhibitors on the quality of life of patients highlights their essential role in managing autoimmune illnesses [8].

This research seeks to comprehend the function of TNF inhibitors in the treatment of autoimmune illnesses. The study will provide

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a comprehensive scientific review of TNF and its biological roles, elucidate the mechanism by which TNF inhibitor's function, and classify the many types of TNF inhibitors now in use. Moreover, the article will comprehensively assess the TNF inhibitors t have received approval from the FDA, analyze the latest data from clinical studies, and investigate potential future improvements in TNF inhibitors. The objective of this study is to assess the present state and prospective future uses of TNF inhibitors in order to enhance our awareness of their effectiveness in treating autoimmune diseases and pinpoint possibilities for future investigation.

TNF inhibitors mechanism of action

Tumor necrosis factor (TNF) is a significant proinflammatory cytokine that plays a crucial role in immune response and inflammation processes. While T-cells, natural killer cells, and fibroblasts have the ability to release Tumor Necrosis Factor (TNF), macrophages are primarily responsible for its production [9]. TNF regulates immune cell function, systemic inflammation, and mortality by binding to two receptors, TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2) [10]. Activation of these receptors initiates signaling cascades that lead to the expression of genes linked with inflammation and the induction of immune responses [9]. Figure 1a depicts a living cell where the activation of Complex I occurs through the interaction of TNF-TNFR1. This interaction leads to the activation of NF-κB and MAPK signaling pathways. When certain genes are activated, they contribute to the worsening of inflammation by producing signaling molecules known as cytokines and chemokines. Figure 1b depicts cellular apoptosis, in which the production of Complex II occurs through the interaction of TNF and TNFR1. Subsequently, this intricate process initiates lytic cell death and disintegration of the cell barrier. Microorganisms contribute to the generation of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) by infiltrating the body. These molecules then stimulate Pattern Recognition Receptors (PRRs) on adjacent cells, so propagating the inflammatory reaction. The shown diagram is labeled as Figure. (Fig 1[21]).

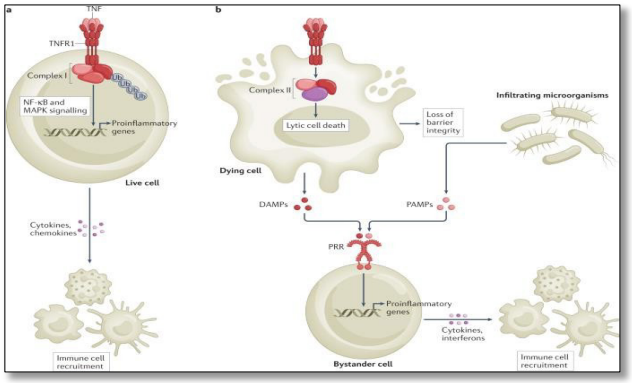

Figure 1: The image illustrates two scenarios of inflammatory signaling triggered by TNF and its receptor TNFR1[21].

TNF inhibitors restrict the activation of downstream signaling cascades, including as the nuclear factor-κB (NF-κB) pathway and the mitogen-activated protein kinase (MAPK) system, by decreasing the link between TNF and its receptors[11]. Figure 2 illustrates the TNF signaling pathways, including the activation and cascade events that occur when TNF-α interacts with TNFR1 and TNFR2. Complex I initiates a cascade of reactions when it binds soluble TNF-α (sTNF-α) to TNFR1, leading to the activation of IKKα and IKKβ. This pathway induces phosphorylation, leading to the degradation of IκBα. The NF-κB (p50/p65) signaling pathway is activated during this event, causing the translocation of NF-κB into the nucleus. This facilitates the transcription of genes associated with inflammation, cell survival, and catabolic processes. TNF-α, which is attached to the cell membrane, frequently initiates the activation of TNFR2. TNFR2 subsequently interacts with TRAF2 and TRAF3 to initiate MAPK pathways, which enhance the cellular survival responses. In addition, the activation of TNFR1 may lead to death by producing Complex II, which consists of TRADD, FADD, and caspase-8. This system ultimately results in mortality. The intricate network of signaling cascades regulates the balance between cell survival and apoptosis [22].

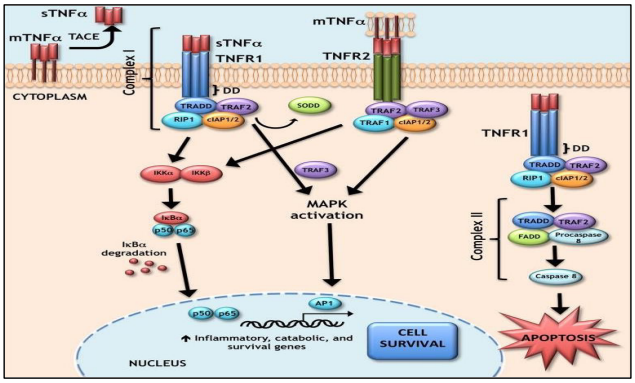

Figure 2: This figure denotes TNF Signaling Pathways focusing on activation and Cascading Mechanisms [22].

Initially, it was believed that TNF inhibitors hindered the binding of TNFR1, hence reducing inflammation through these pathways. However, TNFR1 signaling induces cell death through apoptosis, necroptosis, or pyroptosis, hence indirectly exacerbating inflammation. The released cellular components of this process elicit inflammatory responses and subsequently compromise tissue integrity. This exacerbates the duration of inflammation [12] and facilitates the infiltration of pathogens into the body.

Types of TNF inhibitors

The groups of TNF inhibitors are defined by their composition and mechanism of action. The primary categories include monoclonal antibodies, receptor fusion proteins, and PEGylated Fab' fragments. Golimumab, adalimumab, and infliximab are antibodies that have the ability to precisely target and neutralize TNF-α, hence preventing its attachment to its receptors [13]. Etanercept is a fusion protein formed by combining the Fc component of IgG1 with two extracellular domains of the TNF receptor. By acting as a receptor, it binds TNF-α and TNF-β with a strong attraction, allowing it to function as a decoy receptor and prevent their interaction with regular receptors [14]. PEGylated Fab' fragments, similar to certolizumab pegol, are antibody fragments that have been chemically linked with polyethylene glycol. Conjugation enhances the stability of these medicines and extends their circulation durations [15]. Figure 3 [23] displays the types of TNF inhibitors.

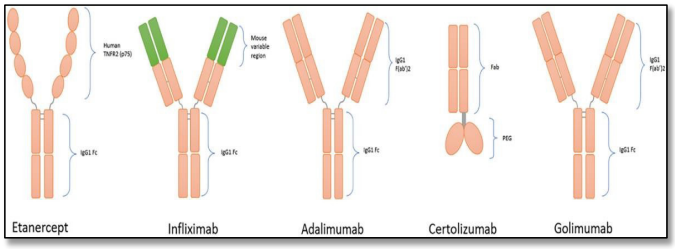

Figure 3: This figure represents different types of TNF inhibitors [23].

Benefits and Potential Side Effects

The effectiveness of TNF inhibitors in treating inflammatory illnesses is widely documented. Biologics have a significant effect in lowering inflammation, alleviating symptoms, and improving the quality of life in patients diagnosed with conditions such rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease [16]. By inhibiting the activity of TNF, these inhibitors reduce pain, inflammation, and tissue damage, improving physical function and slowing down the progression of the disease [17]. However, TNF inhibitors are linked to potential risks. Apotential outcome is an increased susceptibility to infections due to a compromised immune system. Patients who get TNF inhibitors are at a higher risk of developing severe infections, such as tuberculosis and fungal infections [18]. Frequently noted are local reactions at the injection site, which are marked by pain, swelling, and inflammation. Furthermore, there is a possibility of autoimmune responses, including the generation of autoantibodies and the emergence of a lupus-like condition [13].

The molecular mechanisms underlying the effects of TNF inhibitors are intricate. When tumor necrosis factor (TNF) attaches to tumor necrosis factor receptor 1 (TNFR1), it initiates the formation of a signaling complex including receptor-interacting protein kinase 1 (RIPK1) and TNFR-associated death domain protein (TRADD) [19]. This complex process entails the enlistment of TNFR-associated factor 2 (TRAF2) and the cellular inhibitors of apoptosis proteins (cIAP1 and cIAP2). This recruiting process enables the activation of MAPK and NF-κB pathways by building ubiquitin chains [19]. TNF inhibitors prevent the formation of this complex structure, hindering the following transmission of signals that lead to inflammation. Additionally, the formation of a secondary complex, known as complex II, is essential for initiating cellular death. This process entails the enlistment of FAS-associated death domain-containing protein (FADD) and caspase-8, which facilitate programmed cell death and inflammation-induced cell death [20].

TNF inhibitors have greatly revolutionized the treatment of chronic inflammatory diseases by directly targeting a vital cytokine that has a fundamental function in the development of numerous disorders. Their ability to block TNF-mediated signaling pathways provides significant therapeutic benefits, but requires careful control to minimize potential side effects. Ongoing research aims to acquire a more profound comprehension of the molecular mechanisms implicated in TNF signaling and improve the efficacy and safety of these biologics. The objective is to enhance therapy results for persons afflicted with inflammatory diseases [9].

Fda Approved Tnf Inhibitors

Five TNF-alpha inhibitors have been granted FDA clearance in the United States, with each one providing distinct advantages in the treatment of autoimmune illnesses [24]. These FDA approved inhibitors include Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab pegol), and Simponi (golimumab). The biologics can be classified into two primary categories: monoclonal antibodies and fusion proteins [25].

Comparison of effectiveness and method of administration

Infliximab, which received approval in August 1998, is a type of monoclonal antibody that is specifically engineered to attach to and deactivate TNF-alpha [26]. It is delivered through intravenously which enables the achievement of large levels of the medication throughout the body and a quick and powerful suppression of TNF [27]. Infliximab has demonstrated effectiveness in the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis [28]. Etanercept, which was authorized in November 1998, is a compound consisting of the TNF receptor and the Fc fragment of IgG [30]. It forms a bond with TNF-alpha, which stops it from interacting with receptors on the surface of cells [31]. Enbrel is administered through subcutaneous injection, which allows patients to administer it at home. This method of administration has the potential to enhance patient compliance [32]. It is prescribed for many autoimmune disorders, including as rheumatoid arthritis, juvenile idiopathic arthritis, and psoriasis [33]. Etanercept has sustained a robust market presence as a result of its extensive range of uses and easily controlled schedule for administration [34].

Adalimumab, approved by the FDA in December 2002, is a monoclonal antibody that specifically targets TNF-alpha, and it is derived from human sources. Similar to Etanercept, Humira is given through subcutaneous injection and provides versatility in dosing regimens [36]. It is utilized to treat several illnesses such as rheumatoid arthritis, psoriatic arthritis, and hidradenitis suppurativa [37]. The effectiveness and broad variety of uses of Humira have played a significant role in establishing its dominant position in the market.

However, the introduction of biosimilars has started to affect its market dominance [38]. Cimzia, which was approved in April 2008, contains a PEGylated formulation that increases its half-life and stability [39]. The medication is given through a subcutaneous route, starting with an initial loading dosage and then followed by regular maintenance doses [40]. Cimzia is highly effective in treating Crohn's disease and rheumatoid arthritis. Its PEGylation enables a less frequent dose schedule, which can improve patient adherence [41]. Simponi, which was authorized in April 2009, is a completely human monoclonal antibody that has unique pharmacokinetic characteristics when compared to other TNF inhibitors [42]. Simponi is administered subcutaneously and offers a less frequent dose schedule, which can be beneficial for people who want to inject less frequently [43]. It is employed to treat illnesses such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis [44].

Market Dynamics and Biosimilars

Historically, Humira and Enbrel have been the dominant players in the market due to their wide variety of applications and long-established track records [51]. However, Cimzia and Simponi are advantageous alternatives because of their distinct compositions and suggested dosages [52]. The emergence of biosimilars, particularly for Humira, has led to intensified price rivalry and is fundamentally reshaping market dynamics [53].

The TNF inhibitor market has expanded as a result of the introduction of biosimilars in recent years [54]. Biosimilars are highly similar versions of biologics that have received approval, offering the potential for more affordable alternatives [55]. For instance, biosimilars of infliximab, adalimumab, and etanercept have been granted approval and are gradually gaining market share [56]. Continued gathering of long-term real-world data is required to completely confirm the interchangeability of these products, despite their demonstrated comparable effectiveness and safety to their reference items [57].

Ongoing Clinical Trails

Current research in the field of TNF inhibitors focuses on the creation of new drugs, expanding the scope of diseases that can be treated with existing medicines, and enhancing treatment procedures [58]. Ongoing clinical trials are currently examining the efficacy and safety of TNF inhibitors in comparison to newer biologics and targeted synthetic DMARDs. The objective is to enhance treatment approaches for various autoimmune illnesses [59].

Currently, there is an ongoing phase 3b/4 research (NCT02629159) that aims to evaluate the effectiveness of upadacitinib, a JAK inhibitor, with placebo and adalimumab in persons with rheumatoid arthritis who have an inadequate response to methotrexate [60]. The aim of this study is to assess the feasibility of using JAK inhibitors as an alternative to TNF inhibitors for treating rheumatoid arthritis. This has the potential to expand the selection of tailored medications available to clinicians [61]. A distinct continuing clinical trial (NCT04909801) is presently examining the effectiveness of abatacept in comparison to adalimumab, both when used alongside methotrexate, for treating early-stage rheumatoid arthritis in individuals who are seropositive and have shared epitope-positive status [62]. This study has the potential to provide useful insights into the optimal selection of biologic therapy for specific patient groups, perhaps leading to the creation of more personalized treatment regimens [63].

Scientists in the field of pediatric rheumatology are studying new treatment methods for juvenile idiopathic arthritis (JIA) [64]. A clinical trial (NCT04527380) is evaluating the efficacy of ixekizumab, an IL-17A inhibitor, compared to adalimumab in the treatment of children diagnosed with enthesitis-related arthritis and juvenile psoriatic arthritis [65]. This investigation has that potential to expand the scope of therapeutic choices for pediatric patients with these disorders, therefore filling a notable void in medical care for this particular demographic [66].

The research on optimizing therapy choices for TNF inhibitors remains a critical area of concentration [67]. Currently, a phase 4 clinical research (NCT01793519) is investigating the feasibility of quitting TNF-alpha drugs (etanercept, infliximab, adalimumab) in rheumatoid arthritis patients who have achieved sustained remission over a lengthy period of time [68]. This study has the potential to provide valuable insights into ways for diminishing the intensity or extent of therapy, which could result in a reduction in the quantity of medication used over an extended period and lead to cost savings [69]. A clinical trial (NCT04251741) is examining the use of adalimumab serum concentration in identifying the optimal subsequent biological DMARD for rheumatoid arthritis patients who have exhibited inadequate response to adalimumab therapy [70]. This approach represents a move towards personalized healthcare in the management of autoimmune illnesses, with the ability to improve treatment outcomes and optimize resource utilization [71].

Ongoing research in the field of biosimilars aims to broaden treatment options and potentially reduce costs [72]. A comparative study (NCT05842213) is evaluating the efficacy of AVT05, a prospective biosimilar of golimumab, in patients diagnosed with rheumatoid arthritis [73]. This experiment has the potential to lead to the approval of a new biosimilar, so expanding the variety of TNF inhibitor medications that are accessible [74].

Several emerging tendencies are impacting the progress of TNF inhibitor development [75]. Researchers are presently examining biomarkers that have the capacity to predict how individuals will react to TNF inhibitors. This knowledge can assist physicians in customizing treatment strategies for individual patients, leading to more accurate and efficient procedures. Current endeavors are being made to develop alternative methods for administering TNF inhibitors, including oral and topical formulations. These techniques have the potential to enhance patient convenience and potentially mitigate adverse effects on the entire body [77]. Furthermore, scientists are exploring nanotechnology-based approaches to enhance drug stability, better tissue targeting, and potentially reduce the frequency of dose [78].

Several emerging avenues for TNF inhibitor research and development are becoming evident. The objectives include optimizing TNF inhibitors to selectively target particular tissues and reduce general side effects, investigating the impact of TNF inhibition on autoimmune-related neurological disorders, and exploring the potential of TNF inhibitors in cancer immunotherapy, particularly when combined with checkpoint inhibitors [80, 81, 82]. Current research is investigating the advancement of "smart" TNF inhibitors that can be activated just in the presence of certain inflammatory signals. This field of study is aesthetically pleasing [83]. Table 1 presents a comprehensive overview of the trials that have been covered.

NCT Number	Study Title	Conditions	Interventions	Sponsor	Collaborators	Study Type
NCT03915964	A Study of Baricitinib (LY3009104) in Participants With Rheumatoid Arthritis	Rheumatoid Arthritis	DRUG: Baricitinib|DRUG: TNF Inhibitor	Eli Lilly and Company	Incyte Corporation	INTERVENTIONAL
NCT01793519	Stopping TNF Alpha Inhibitors in Rheumatoid Arthritis	Rheumatoid Arthritis	DRUG: Etanercept|DRU G: Infliximab|DRU G: Adalimumab|DRUG: Placebo	Georgetown University	National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)|University of Maryland, Baltimore|Washington D.C. Veterans Affairs Medical Center|-Medstar Health Research Institute|Patient- Centered Outcomes Research Institute|Arthritis and Pain Associates of PG County|Arthritis & Rheumatism Associates, P.C.|Rheumatology Associates of Baltimore, L.L.C.|The Arthritis Clinic of Northern Virginia, P.C.|Arthritis and Rheumatic Disease Associates, P.C.	INTERVENTIONAL

NCT05540743	Biologic Therapy in Pediatric JIA Uveitis	Juvenile Idiopathic Arthritis Associated Uveitis	DRUG: biologic DMARDs	Kasr El Aini Hospital		INTERVENTIONAL
NCT02629159	A Study Comparing Upadacitinib (ABT- 494) to Placebo and to Adalimumab in Adults With Rheumatoid Arthritis Who Are on a Stable Dose of Methotrexate and Who Have an Inadequate Response to Methotrexate	Rheumatoid Arthritis	DRUG: Placebo for Adalimumab|D RUG: Adalimumab|DRUG: Placebo for Upadacitinib|D RUG: Upadacitinib	AbbVie		INTERVENTIONAL
NCT04251741	Using Adalimumab Serum Concentration to Choose a Subsequent Biological DMARD in Rheumatoid Arthritis Patients Failing Adalimumab Treatment	Rheumatoid Arthritis	DIAGNOSTIC_TEST: Adalimumab trough concentration|OTHER: Usual care	Reade Rheumatology Research Institute	ZonMw: The Netherlands Organisation for Health Research and Development|Sint Maartenskliniek	INTERVENTIONAL
NCT05842213	Comparative, Multicenter Study in Subjects With Rheumatoid Arthritis, ALVOFLEX	Rheumatoid Arthritis	BIOLOGICAL: AVT05 (proposed biosimilar to golimumab)|BIOLOGICAL: Simponi (Golimumab)	Alvotech Swiss AG		INTERVENTIONAL
NCT04527380	A Study of Ixekizumab (LY2439821) in Children With Juvenile Idiopathic Arthritis Categories of Enthesitis-related Arthritis (Including Juvenile Onset Ankylosing Spondylitis) and Juvenile Psoriatic Arthritis	Juvenile Psoriatic Arthritis|Enthesitis Related Arthritis	DRUG: Ixekizumab|DRUG: Adalimumab	Eli Lilly and Company		INTERVENTIONAL

NCT02277444	A Study to Evaluate the Pharmacokinetics, Efficacy and Safety of Intravenous Golimumab in Pediatric Participants With Active Polyarticular Course Juvenile Idiopathic Arthritis Despite Methotrexate Therapy	Arthritis, Juvenile	DRUG: Golimumab|DRUG: Methotrexate	Janssen Research & Development, LLC	INTERVENTIONAL	NCT02277444
NCT04909801	A Study to Compare the Response to Treatment With Abatacept vs Adalimumab, on Background Methotrexate, in Adults With Early, Seropositive, and Shared Epitope- positive Rheumatoid Arthritis and an Inadequate Response to Methotrexate	Rheumatoid Arthritis	DRUG: Abatacept|DRUG: Adalimumab|DRUG: Methotrexate	Bristol- Myers Squibb		INTERVENTIONAL

Conclusion and Future Considerations

Tumor necrosis factor (TNF) inhibitors have significantly transformed the treatment options for several autoimmune diseases, leading to significant improvements in disease control and overall quality of life for a considerable number of patients [84]. The effectiveness of these biologics prompted additional research and progress in this field, leading to ongoing improvements in treatment methods and the development of new medications [85]. Significant advancements have been achieved in the field, namely through the development of biosimilars. These biosimilars can increase the accessibility of these highly efficacious medicines [86]. Moreover, ongoing research on novel TNF inhibitors and innovative delivery methods has the capacity to expand the array of treatment options, perhaps addressing specific limitations of current medications [87].

Exploring the utilization of combination medications and personalized medicine strategies is a vital progression in enhancing treatment outcomes [88]. By tailoring treatment to unique patient characteristics and combining TNF inhibitors with other immunomodulatory medications, clinicians may enhance disease control and overcome treatment resistance. However, there are still several challenges that must be resolved in the field of TNF inhibitor therapy [90]. Sustained surveillance and examination are imperative to guarantee the enduring safety of these medications, particularly when employed in conjunction with other treatments [91]. In addition, whereas TNF inhibitors show significant effectiveness in many patients, a considerable proportion still do not achieve adequate disease control. This highlights the need for alternative approaches and continuous progress in this field [92].

It is recommended that further research focuses on developing more accurate treatments with improved safety features, identifying reliable indicators for evaluating treatment effectiveness, and exploring the potential of TNF inhibition in a broader range of autoimmune and inflammatory disorders [93]. Integrating artificial intelligence and big data analytics into drug discovery and clinical decision-making can accelerate progress in these areas, potentially leading to more efficient medication development and improved patient outcomes [94]. In general, TNF inhibitors have had a notable impact on the treatment of autoimmune diseases. Nevertheless, ongoing research and development endeavors strive to increase and expand the utilization of these technologies, perhaps leading to enhanced patient outcomes in the future [95]. The field of TNF inhibitor therapy is continuously evolving as a result of clinical demand, scientific progress, and the necessity to discover more effective and personalized therapeutic approaches for autoimmune diseases [96].

Funding Sources

There is no funding to report for this study.

Conflict of Interest

Authors declare that there is no conflict of interest.

Acknowledgements

Gurleen Dhoat expresses appreciation to Professor Bill Tawil for overseeing the framework of this review, which contributed to the development of this paper.

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