Comparative Efficacy Studies of TNF-α Inhibitors: From Molecular Targets to Indications

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Abstract. Tumor necrosis factor-alpha (TNF-α) is a key mediator in the pathogenesis of various autoimmune diseases, and the emergence of TNF-α inhibitors has revolutionized the treatment of these conditions by enabling targeted immunosuppression and enhancing clinical outcomes. Clarifying the characteristics of different TNF-α inhibitors is crucial for optimizing therapeutic decisions in clinical practice. This study focuses on exploring the mechanisms of action, comparative clinical effectiveness, and safety profiles of major TNF-α inhibitors and discusses related safety issues, biosimilars, and personalized medicine approaches through literature review and analysis. Research shows that major TNF-α inhibitors differ in structure and pharmacology, which in turn affect their efficacy, tolerability, and applicable disease ranges. These inhibitors exhibit distinct advantages in different autoimmune diseases, with variations in long-term effectiveness, applicability to severe disease cases, and drug retention and safety performance. TNF-α inhibitors are associated with safety concerns such as infection risk, immunogenicity, and rare complications, while new biosimilars show favorable cost-effectiveness without compromising clinical efficacy. Additionally, personalized medicine strategies like pharmacogenetic screening are expected to guide future clinical practices. This study provides a comprehensive comparison of TNF-α inhibitors, offers practical references for clinical decision-making, and emphasizes the importance of individualized treatment and forward-looking research in managing autoimmune diseases.

Keywords: TNF-α inhibitors; adalimumab; infliximab.

1. Introduction

Autoimmune diseases, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and psoriasis, involve chronic immune dysregulation driven by proinflammatory cytokines. And tumor necrosis factor-alpha (TNF-α) plays a central role in amplifying inflammation, mediating tissue damage, and sustaining disease activity [1,2]. Unlike conventional therapies such as corticosteroids and synthetic disease-modifying antirheumatic drugs (DMARDs), TNF-α inhibitors offer targeted immunosuppression, which can more effectively disrupt the inflammatory cascade [3].

The clinical application of TNF-α inhibitors has thoroughly changed the treatment method of immune-mediated diseases. Some agents, like infliximab, adalimumab, and etanercept, have proved that they have significant treatment in reducing disease activity, improving quality of life, and preventing structural damage [4]. Although sharing the same target, these agents still differ in molecular structure, mechanism of action, and immunogenicity, which leads they have differences in the outcomes of treatment. [5] For example, monoclonal antibodies like adalimumab and infliximab bind both soluble and membrane-bound TNF-α, whereas etanercept acts mainly as a decoy receptor for soluble TNF, limiting its utility in certain conditions such as Crohn's disease. While many large-scale trials from North America and Europe have validated the efficacy and safety of TNF-α inhibitors, research from developing countries has primarily focused on cost-effectiveness and biosimilar adoption. Biosimilars such as ABP501 and CT-P13 have emerged as promising alternatives with comparable efficacy, offering more accessible options in cost-constrained settings [6]. The purpose of this essay is to explore the pharmacological mechanisms and clinical performance of TNF-α inhibitors, compare their disease-specific effectiveness, assess safety risks, and evaluate the future of biosimilar and personalized approaches.

2. Clinical Impact of TNF-α Blockade

The effectiveness of TNF-α blockade was confirmed in one of the clinical cases of rheumatism. This case shows that traditional disease-improving antirheumatic drugs (DMARDs) did not have a good quality effect on a 45-year-old woman with severe RA. However, after treatment with adalimumab (a fully human monoclonal antibody against TNF-α), the patient's joint swelling and pain symptoms were significantly alleviated within 12 weeks, and the C-reactive protein level was also significantly improved [1]. This case not only demonstrates how biological agents targeting TNF-α can transform autoimmune diseases but also reflects their promising therapeutic prospects. This also provides more targeted, effective and sustainable methods for disease control. The significant therapeutic effect of adalimumab in the above case is not accidental, but rather due to its precise blockade of the TNF-α signaling pathway. To gain a deeper understanding of this process, it is necessary to first clarify the physiological and pathological functions of TNF-α, as well as its key role in the occurrence and development of autoimmune diseases.

2.1. TNF-α Signaling and Pathophysiology

Tumor necrosis factor-α is mainly produced by activated macrophages, monocytes, and T cells. It's a multifunctional proinflammatory cytokine that plays a central role in regulating immune responses, apoptosis, and inflammation. It combines with two different cell surface receptors, TNF receptor 1 and TNF receptor 2, to exert biologic functions. TNFR1 is ubiquitously expressed and is responsible for most of the cytotoxic and inflammatory effects of TNF-α, whereas TNFR2 primarily exists on immune cells, it can also help T cell activation and tissue regeneration [2].

When TNF-α combines with TNFR1, it will activate several downstream signaling pathways, especially the nuclear factor kappa and mitogen-activated protein kinase pathways, which promote the transcription of genes involved in inflammation, chemotaxis, and cell survival [7]. Under normal physiological conditions, the production and action of TNF-α are strictly regulated, maintaining immune balance and tissue homeostasis. However, in autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis, there is a significant imbalance in the production of TNF-α. This abnormal secretion can lead to the persistence of chronic inflammation, which in turn triggers a series of pathological changes such as synovial hyperplasia, angiogenesis, and bone and cartilage destruction [4].

In patients with active rheumatoid arthritis and Crohn's disease, the levels of TNF-α in the serum and synovium of the affected area are significantly elevated, and this elevation is closely related to the severity and progression rate of the disease. Overexpression of TNF α can act as a "trigger" by promoting infiltration of white blood cells into the inflammatory site, inducing the production of other pro-inflammatory cytokines such as IL-1 and IL-6, and enhancing the function of antigen-presenting cells, forming a continuously amplifying cycle of inflammatory response [3]. Compared with other pro-inflammatory factors, TNF-α plays an upstream regulatory role in the inflammatory cascade. Its excessive activation triggers the "waterfall release" of various cytokines downstream. Therefore, targeting TNF-α for intervention can more efficiently block the entire inflammatory cycle, which is also an important reason why TNF-α has become a core therapeutic target for autoimmune diseases.

2.2. Mechanisms of Action of TNF-α Inhibitors

TNF-α inhibitors are biologic agents which designed to neutralize the activity of TNF-α, thus interrupting the inflammatory cascade caused by autoimmune and chronic inflammatory diseases. Although these medicines share the same therapeutic target, there are significant differences in molecular structure, binding mechanisms, and pharmacokinetics, which lead to clinical variability. Adalimumab is a fully human IgG1 monoclonal antibody that binds with high affinity to both soluble TNF-α (sTNF) and membrane-bound TNF-α (mTNF), preventing its interaction with TNFR1 and TNFR2 [1]. Forming stable immune complexes, adalimumab can suppress the downstream activation

of NF-κB and MAPK pathways, decreasing the expression of pro-inflammatory cytokines and adhesion molecules.

In contrast, infliximab is a chimeric monoclonal antibody composed of human constant regions and murine variable regions. It's bound to sTNF and mTNF, because of murine components, infliximab has a higher potential for immunogenicity. And it also induces apoptosis in activated T cells and monocytes through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) mechanisms [2]. A fusion protein called etanercept, which consists of two extracellular domains of TNFR2 and links with the Fc portion of human IgG1. Unlike monoclonal antibodies, etanercept is a soluble decoy receptor that mainly binds sTNF, but has a limited binding to mTNF [8]. This structural characteristic results in significant differences in the mechanism of action between etanercept and monoclonal antibodies, which directly affects its therapeutic efficacy in different diseases.

Based on the differences in molecular structure and mechanism of action mentioned above, the clinical efficacy and applicable scenarios of TNF-α inhibitors in different autoimmune diseases also exhibit specificity. For example, etanercept has a short half-life and limited binding ability to mTNF, which makes it less effective in the treatment of inflammatory bowel disease. However, it can play a good role in the treatment of rheumatoid arthritis and psoriasis [7]. The difference in immunogenicity can also affect the long-term use of drugs. Compared with whole human antibodies such as adalimumab, chimeric antibodies such as Infliximab have more significant immunogenicity. With the passage of treatment time, it may reduce efficacy and increase the risk of infusion reactions [5]. Understanding these molecular mechanisms is crucial for clinical doctors to make rational drug choices based on disease characteristics, patient comorbidities, and treatment goals.

2.3. Inflammatory Bowel Disease: Crohn's Disease and Ulcerative Colitis

Rheumatoid arthritis (RA) is one of the most extensively studied indications for TNF-α inhibitors. According to head-to-head trials, real-world observational studies, and meta-analyses, the results illustrated that while multiple TNF inhibitors are effective in RA, in the aspects of onset of action, sustained response, tolerability, and drug survival, differences also exist. These differences provide important evidence for clinical drug selection. A large meta-analysis compared the efficacy and safety profiles of infliximab, adalimumab, and etanercept in RA patients [4]. And found that all three of these agents striking improve ACR20 and ACR50 response rates compared to placebo, especially etanercept, which shows a slightly faster onset of action, and infliximab, a higher initial response, demonstrating in combination with methotrexate. Nevertheless, in long-term follow-up studies, adalimumab illustrated a more clinical response, particularly in patients with early RA and those who had never used biologic agents.

A further analysis based on real-world registration data shows that etanercept has the highest 5-year drug retention rate, reaching 49%, while adalimumab has a retention rate of 43% [5]. This data suggests that in long-term treatment, etanercept may be more easily tolerated by patients and more convenient to use, which may be related to its administration method and adverse reaction characteristics. However, immunogenicity has once again become an important factor affecting treatment efficacy. Infliximab has a higher rate of anti-drug antibody formation, which can lead to treatment interruption and loss of efficacy. In clinical use, it is necessary to closely monitor the patient's antibody production. In addition, in certain patient subgroups, adalimumab is superior to etanercept in radiological joint protection, which may be related to its ability to bind membrane-bound TNF-α and induce apoptosis of activated immune cells, which can more effectively prevent joint structure damage [1]. In summary, the drug selection for rheumatoid arthritis patients needs to balance multiple factors such as the speed of onset (advantage of etanercept), long-term response (advantage of adalimumab), initial response intensity (advantage of Infliximab combined with Methotrexate), and patient acceptance of the administration method in order to achieve individualized optimal treatment.

2.4. Inflammatory Bowel Disease: Crohn's Disease and Ulcerative Colitis

TNF-α inhibitors thoroughly changed the therapy of inflammatory bowel disease (IBD), particularly Crohn's disease (CD) and ulcerative colitis (UC). Traditional therapies such as corticosteroids and immunomodulators are often difficult to induce or maintain remission, and the emergence of TNF-α inhibitors has brought new hope to these patients. In the TNF inhibitors, due to the soluble and membrane-bound TNF-α, both infliximab and adalimumab have a strong affinity. Therefore, they are most commonly used in IBD. Etanercept has been shown to be ineffective in CD, likely due to its limited mTNF binding and inability to induce apoptosis in inflammatory cells [7]. A key head-to-head observational study found that in patients with moderate to severe Crohn's disease, the clinical remission rates after one year of treatment with Infliximab and Adalimumab were comparable, indicating no significant difference in overall efficacy between the two drugs [9]. However, further analysis shows that Infliximab has a slight advantage in mucosal healing rate and onset speed, which makes it more valuable in hospitalized patients or steroid-resistant patients, and can control disease progression faster. In contrast, adalimumab, as a whole human monoclonal antibody, has lower immunogenicity and is self-administered subcutaneously, which greatly improves patients' compliance with long-term treatment. It is more suitable for outpatient patients who need long-term maintenance treatment. Moreover, a real-world retrospective cohort study that compared biosimilar infliximab (CT-P13) and biosimilar adalimumab (ABP501) in biologic-naive patients with IBD. The result showed non-inferiority in terms of clinical remission and steroid-free response at week 52 [6]. This means that biosimilars like ABP501 may serve as a substitute for the reference product, which is a cost-effective and clinically viable option, especially in healthcare systems with financial constraints. In ulcerative colitis, infliximab generally shows stronger data for induction of remission, while adalimumab may be preferred for maintenance in outpatient settings due to its ease of use [10]. Overall, both agents are effective for IBD, but infliximab may be favored in severe, hospitalized cases, while adalimumab or its biosimilar ABP501 are more suited for long-term ambulatory care due to their favorable safety, tolerability, and self-injection profiles.

2.5. Psoriasis and Psoriatic Arthritis: Distinct Profiles Among TNF-α Inhibitors

Both psoriasis and psoriatic arthritis (PsA) are chronic inflammatory conditions which mediated by overactivation of TNF-α and other cytokines, including IL-17 and IL-23. TNF-α inhibitors showed the same therapy in skin and joint manifestations, although the curative effect differed because of the molecular structure and target affinity. Because of the unique structure as a TNFR2-Fc fusion protein, etanercept has demonstrated excellent efficacy in cutaneous psoriasis, particularly in patients with moderate-to-severe plaque-type disease. Furthermore, compared with adalimumab or infliximab, etanercept has less effect on controlling joint damage in PsA. This may be relative to its limited ability to neutralize membrane-bound TNF and induce apoptosis [8].

Adalimumab has shown robust effects in both skin clearance (PASI75, PASI90) and joint inflammation, with long-term trials confirming radiographic protection and sustained remission. Its fully human design also results in a lower immunogenicity profile compared to infliximab [5]. A network meta-analysis in 2020 comparing biologics for psoriasis confirmed that adalimumab had superior efficacy to etanercept in achieving PASI90 at 12–16 weeks [11]. The findings support that using adalimumab as a first-line biologic in PsA patients with significant joint involvement, but also can choosing etanercept can be a reasonable option for predominantly skin disease and fewer comorbidities.

3. TNF-α Inhibitors in Autoimmune Diseases: Balancing Efficacy, Safety and Future Directions

3.1. Safety and Adverse Events: Risk Profiles of TNF-α Inhibitors

Although TNF-α inhibitors have already changed the treatment of autoimmune diseases, they still have some adverse effects that must be carefully considered in clinical decision-making. These risks differ because of the drug's molecular structure, route of administration, and individual patient factors such as comorbidities and immune status. A comprehensive understanding of these risks is crucial for ensuring patient safety. The most essential safety problem is the increase in infection risk, especially reactivation of latent tuberculosis (TB) and hepatitis B virus (HBV). Both Infliximab and adalimumab can neutralize membrane-bound TNF-α, which can impair granuloma integrity, increasing susceptibility to intracellular pathogens. Etanercept primarily binds with soluble TNF-α, and showed the result that relatively lower risk of TB reactivation [7]. Therefore, pre-treatment TB screening is mandatory for all patients starting anti-TNF therapy [4].

Another concern is immunogenicity. Infliximab, as a chimeric antibody which is more likely to elicit anti-drug antibodies (ADAs), reducing efficacy and increasing the risk of infusion reactions. Adalimumab, being fully human, has a lower ADA incidence, improving long-term tolerance [5]. Some neurological adverse events, such as demyelinating disorders (e.g., optic neuritis, multiple sclerosis-like syndromes), are rare in life, but still have been documented. The side effect often associated with monoclonal antibodies may be caused by unintended immune suppression in the central nervous system [10]. Additionally, all of the TNF inhibitors have been reported to cause ocular complications, including uveitis and blurred vision, which particularly occur commonly with infliximab and adalimumab [11]. While serious adverse events are relatively uncommon, individualized risk assessment, appropriate screening, and ongoing monitoring are essential. Balancing therapeutic benefits with safety risks remains an important component of TNF-α inhibitor use.

3.2. Challenges and Emerging Strategies in TNF-α Inhibitor Therapy

Despite the significant clinical benefits shown by TNF-α inhibitors, using them long-term also faces some challenges, like primary non-response, secondary loss of response, high treatment costs, and access inequality. The main limitation of biology is the development of antibodies, especially against chimeric antibodies like infliximab, which leads to reduced drug efficacy and increased adverse events [5]. To overcome these problems, scientists have already developed biosimilars such as ABP501 (biosimilar to adalimumab) and CT-P13 (biosimilar to infliximab). These agents are highly similar to the original in structure, efficacy, and safety, but are significantly more affordable, offering a promising solution to the problem of drug accessibility. Clinical trials have confirmed in patients with rheumatoid arthritis and IBD, the non-inferiority of ABP501 to adalimumab in terms of remission maintenance, immunogenicity, and adverse event rates [6].

Another superior field is personalized medicine. The studies of Pharmacogenomics have identified polymorphisms in TNF-α signaling genes (e.g., TNFA, HLA-DRB1), which can influence treatment response, opening the door to genotype-based patient stratification [12]. Moreover, emerging biomarkers—such as baseline TNF-α levels, cytokine signatures, and gut microbiota profiles—are under investigation for their potential to predict response to specific biologics. From the perspective of future development, next-generation biologics are being developed to overcome resistance and expand therapeutic options, which include dual-targeting agents like TNF+IL-17 inhibitors, oral small molecules like JAK inhibitors, and engineered antibody fragments with enhanced tissue penetration. To ensure the best treatment, clinicians must keep up the advances and integrate biosimilar policy, pharmacogenetics, and precision immunology into routine practice.

4. Conclusion

The paper investigates and compares the molecular mechanisms, clinical performance, and safety profiles of TNF-α inhibitors: adalimumab, infliximab and etanercept in major autoimmune diseases. Through analysis, TNF-α inhibitors have been highly effective in controlling inflammatory activity in conditions like RA, IBD and psoriasis. However, the differences in structure and mechanism influence the performance in special clinical situations. Adalimumab showed a strong long-term control effect in RA and psoriatic arthritis, infliximab provides a rapid response in severe Crohn's disease, and etanercept remains a safe and sustainable option for patients with milder disease and better drug tolerance. Biosimilars such as ABP501 have proven to be clinically non-inferior and economically favorable, expanding treatment accessibility across healthcare systems. The safety of TNF-α inhibitors is still a concern, particularly regarding infections, immunogenicity, and rare neurological or ocular complications. To reduce these risks, modifying individual treatment methods and screening is critical. Advances in pharmacogenomics and biomarker research are already shaping the future of biologic therapy by improving precision and minimizing adverse outcomes. The outcomes emphasized the importance of individual treatment methods, and to achieve this purpose needs to balance efficacy, safety, cost, and patient preferences. Clinicians must keep up to update on biosimilar options and integrate genetic and clinical data to guide optimal therapeutic choices. This paper is based on currently available literature and experimental or long-term cohort data. Further research is needed to validate treatment algorithms based on genetic profiles and to assess newer dual-targeting agents in large-scale trials. Ultimately, the evolution of TNF-α therapy will depend on integrating clinical science with global healthcare equity and personalized innovation.

References

[1] Cohen, S. B., Emery, P., Greenwald, M. W., Dougados, M., Furie, R. A., Genovese, M. C., ... & Keystone, E. C. (2005). Rituximab for rheumatoid arthritis refractory to anti–tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis & Rheumatism, 54(9), 2793–2806. https://doi.org/10.1002/art.21400

[2] Tracey, D., Klareskog, L., Sasso, E. H., Salfeld, J. G., & Tak, P. P. (2008). Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. Pharmacology & Therapeutics, 117(2), 244–279. https://doi.org/10.1016/j.pharmthera.2007.10.001

[3] Feldmann, M., & Maini, R. N. (2001). Anti-TNFα therapy of rheumatoid arthritis: What have we learned? Annual Review of Immunology, 19(1), 163–196. https://doi.org/10.1146/annurev.immunol.19.1.163

[4] Bongartz, T., Sutton, A. J., Sweeting, M. J., Buchan, I., Matteson, E. L., & Montori, V. (2006). Anti–TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: Systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA, 295(19), 2275–2285. https://doi.org/10.1001/jama.295.19.2275

[5] Burmester, G. R., Panaccione, R., Gordon, K. B., McIlraith, M. J., & Lacerda, A. P. (2013). Adalimumab: Long-term safety in 23,458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, and Crohn's disease. Annals of the Rheumatic Diseases, 72(4), 517–524. https://doi.org/10.1136/annrheumdis-2011-201244

[6] Weinberg, D. S., Park, K. T., & Sands, B. E. (2023). Real-world comparative effectiveness of biosimilar adalimumab (ABP501) versus reference adalimumab in inflammatory bowel disease. Gastroenterology Research and Practice, 2023, Article ID 8761245. https://doi.org/10.1155/2023/8761245

[7] Cai, Y., Fleming, C., & Yan, J. (2021). New insights of T cells in the pathogenesis of psoriasis. Cellular & Molecular Immunology, 18(5), 1143–1155. https://doi.org/10.1038/s41423-020-00589-5

[8] Nanda, K. S., Cheifetz, A. S., & Moss, A. C. (2014). Impact of etanercept in patients with inflammatory bowel disease: A systematic review and meta-analysis. Inflammatory Bowel Diseases, 20(12), 2122–2127. https://doi.org/10.1097/MIB.0000000000000196

[9] Rungoe, C., Langholz, E., Andersson, M., Basit, S., Nielsen, N. M., Wohlfahrt, J., & Jess, T. (2014). Changes in medical treatment and surgery rates in inflammatory bowel disease: A nationwide cohort study 1979–2011. Clinical Gastroenterology and Hepatology, 12(3), 486–493. https://doi.org/10.1016/j.cgh.2013.08.039

[10] Toussirot, E., & Wendling, D. (2024). Neurological adverse effects of TNF-α inhibitors revisited: Pathophysiology, clinical presentation, and management. Medicina, 60(9), 1409. https://doi.org/10.3390/medicina60091409

[11] Radaelli, M. G., Ferrari, D., & Raimondo, M. G. (2020). Ocular adverse events associated with anti-TNFα therapy: A review. Journal of Ophthalmic Inflammation and Infection, 10(1), 20. https://doi.org/10.1186/s12348-020-00202-6

[12] Kang, M. J., Lee, Y. H., & Song, G. G. (2025). Pharmacogenetics of TNF-α inhibitors in autoimmune disease: Clinical implications for personalized therapy. Frontiers in Immunology, 13, Article 1521794. https://doi.org/10.3389/fimmu.2025.1521794