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Infliximab: Pharmacological Properties, Mechanism of Action, and Clinical Applications in the Treatment of Selected Inflammatory Diseases

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Abstract

Introduction: Infliximab is a chimeric monoclonal antibody used to treat chronic inflammatory diseases by inhibiting tumor necrosis factor-alpha (TNF-α), a key mediator in the pathogenesis of conditions like rheumatoid arthritis, Crohn's disease and psoriasis. Since its approval in 1998, infliximab has significantly improved patient outcomes, especially for those unresponsive to conventional therapies. This article reviews infliximab's pharmacological properties, mechanism of action, approved uses, and safety profile, while also addressing potential risks and practical considerations for its clinical application

Materials and methodology: A literature review focused on keywords related to the topic was performed using databases such as PubMed and Google Scholar

Results: Infliximab has demonstrated significant clinical efficacy in the treatment of various chronic inflammatory diseases, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, and psoriasis. The studies reviewed consistently show that infliximab improves symptoms by reducing inflammation, alleviating pain, swelling, and skin lesions, and enhancing overall quality of life for patients with moderate to severe forms of these conditions.

Conclusion: Infliximab has proven to be a highly effective treatment option for chronic inflammatory diseases, providing significant clinical improvements in disease activity and patient quality of life. However, its use must be carefully managed, with regular monitoring for adverse effects, including infections and allergic reactions, as well as long-term risks such as malignancies. The ongoing clinical experience and research will continue to refine its therapeutic use, expanding its indications and improving its overall safety and efficacy profile.

Keywords: Infliximab; TNF-alpha (TNF-α); Inflammatory diseases; Rheumatoid arthritis (RA); Crohn's disease; Psoriasis; Biologic therapy; Monoclonal antibodies

1. Introduction

Infliximab is a chimeric monoclonal antibody that plays a crucial role in the treatment of various chronic inflammatory diseases by targeting and neutralizing tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine implicated in the pathogenesis of conditions such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, and psoriasis. Since its approval in 1998, infliximab has revolutionized the management of these conditions, offering significant clinical benefits for patients who have not responded adequately to conventional therapies.

As an effective TNF-α inhibitor, infliximab works by blocking the actions of TNF-α, which is central to the inflammatory processes underlying many autoimmune diseases [1].
Through this mechanism, infliximab reduces inflammation, alleviates symptoms such as pain and swelling, and improves overall quality of life for patients. Its ability to induce and maintain remission has been well-documented in clinical trials, making it a critical component of treatment for patients with moderate to severe forms of these diseases.

However, like all biological therapies, infliximab comes with potential risks and challenges. Adverse effects, including infections, infusion reactions, and long-term safety concerns such as an increased risk of malignancies, require careful monitoring and management during treatment. These considerations underscore the importance of a thorough understanding of infliximab's pharmacological properties, mechanisms of action, and clinical applications in order to maximize its therapeutic benefits while minimizing risks [2].

This article aims to provide a comprehensive review of infliximab's pharmacology, its mechanism of action, approved indications, and its clinical applications in treating various inflammatory diseases. We will also discuss its safety profile, long-term risks, and practical considerations for its use in clinical practice.

Purpose of the study

The aim of the study is to review and synthesize current information on pharmacological properties, mechanisms of action, and clinical applications. The study seeks to provide a detailed understanding of therapeutic potential, clinical benefits, and associated risks.

Materials and methodology

The literature was gathered through searches on PubMed and Google Scholar, as well as through references from previously retrieved articles.

Infliximab- Dosage and administration

Dosing of infliximab for various conditions:

Before administering infliximab, it is necessary to premedicate with the following:
Loratadine or Cetirizine: 0.5 mg/kg (maximum 25 mg), Hydrocortisone: 4 mg/kg (maximum 200 mg), Paracetamol: 15 mg/kg (maximum 1 g).
This premedication should occur 30–60 minutes prior to the infusion to prevent potential infusion reactions [3].
Infliximab is prepared as an intravenous infusion, with typical doses ranging from 3 to 10 mg/kg, most commonly 5 mg/kg. It has a half-life of 7–12 days due to its low elimination rate, leading to a dosing schedule that repeats at weeks 2, 6, and every eight weeks.

The pharmaceutical product contains 100 mg of lyophilized powder in a 20 ml vial. Each vial is reconstituted with 10 ml of sterile distilled water using a 21-gauge needle and gently mixed to dissolve the powder. After setting the vial aside for 5 minutes, the solution is diluted in 250 ml of 0.9% sodium chloride intravenous solution.

The infusion should begin within 3 hours of dilution and be administered over 2–3 hours. During this period, vital signs—such as temperature, pulse, blood pressure, and respiratory rate—should be monitored for up to 1 hour after the infusion [4].

TDM- therapeutic drug monitoring

Infliximab is increasingly used in the treatment of patients with moderate to severe inflammatory bowel disease (IBD) in individuals over 6 years of age who have had an insufficient response to corticosteroids or immunomodulators.

However, nearly 40% of IBD patients experience a loss of response (LOR) to anti-TNF therapy annually, which may require dose intensification or switching to another medication [5].

Studies show that higher serum concentrations of infliximab are associated with better therapeutic outcomes, including improved mucosal healing. In patients who experience LOR, the presence of anti-drug antibodies (ADA) has been observed, which may result from prolonged subtherapeutic drug levels.

It has been demonstrated that therapeutic drug monitoring (TDM) of anti-TNF agents reduces immunogenicity and improves long-term outcomes, including fewer hospitalizations and surgical interventions related to IBD. Given the high costs of biologic therapy in Europe—where the average direct annual cost per patient with Crohn's disease (CD), including diagnostic procedures, hospitalizations, and biologic treatment, is approximately 3500 EUR—TDM becomes an essential tool for optimizing therapy and reducing healthcare costs [6] [7] [8].

FDA-Approved Indications and Dosages

Crohn's disease and ulcerative colitis: 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks; doses can be increased to 10 mg/kg depending on the patient's response.

Psoriasis and psoriatic arthritis: 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks.

Rheumatoid arthritis: 3 mg/kg at weeks 0, 2, and 6, then every 8 weeks; the dose can be increased to 10 mg/kg every 4 weeks depending on the response.

Ankylosing spondylitis: 5 mg/kg at weeks 0, 2, and 6, then every 6–8 weeks [9].

History of Development and Approval of Infliximab:

Infliximab (IFX) is a biological agent that specifically targets the immune mediator, tumor necrosis factor-alpha (TNFα), which is involved in the pathological process. Since its introduction in 1998, anti-TNF agents have become popular therapeutic modalities, however, their first application in dermatology occurred in 2002 when they were used to treat psoriasis [1]. The first anti-TNF therapy was discovered by Knight et al. in the form of a chimeric monoclonal antibody, now known as infliximab. This antibody comprises 25-30% of a murine fusion or variable antigen-binding segment and 70-75% of a human IgG constant segment [2]. The initial study of infliximab was conducted in 1994 with patients suffering from rheumatoid arthritis, where it demonstrated significant clinical improvement compared to placebo [10].

3. Infliximab - mechanism of action in inflammatory diseases

Infliximab, a TNFα inhibitor, functions by blocking TNFα, a proinflammatory cytokine integral to immune defense mechanisms. The role of TNFα varies with its concentration: low levels provide protective effects, while elevated levels can be pathogenic [11]. TNFα exists in two forms—soluble and transmembrane—both of which are biologically active through TNF receptors (TNFR) Type 1 and Type 2 [12].

The most significant role of TNFα is its protective effect during infections. It contributes to resistance against infectious agents but can also have a pathogenic role in septic shock. TNFα induces anti-inflammatory effects via TNFR Type 2. This cytokine enhances resistance by activating polymorphonuclear leukocytes and platelets, boosting the cytotoxic activity of macrophages and natural killer cells, thereby stimulating the immune response [13]. For instance, elevated TNFα levels have been observed in patients with meningococcal disease, correlating with its cytotoxic effects [14] [15].

Additionally, TNFα plays a role in tumor resistance, mediating cytotoxic effects that lead to cell lysis or apoptosis. Research has shown that TNFα directly affects tumor cells, especially in conjunction with interferon [16]. It also exerts proinflammatory effects on vascular endothelium, resulting in hemorrhagic necrosis [12].

While the biological effects of TNFα are beneficial in various host responses, it can also exhibit pathogenic roles under certain circumstances. The involvement of TNFα in

inflammatory diseases was first identified in 1988 when increased TNFα expression was found in the synovial fluid of patients with rheumatoid arthritis, establishing it as a prototypical TNFα-related disease. This was further confirmed by increased TNFR expression in active diseases, with shed receptor levels correlating with disease activity. Evidence indicates that TNFα regulates proinflammatory cytokines, central to inflammatory processes [17].

Psoriasis is another condition linked to TNFα, with studies revealing heightened expression of TNFα in psoriatic skin lesions. Research has shown increased TNFα mRNA expression in the peripheral blood mononuclear cells of psoriatic patients compared to healthy controls [12][18].

Infliximab binds to both soluble and membrane-bound forms of TNFα, demonstrating stable, high-affinity interactions that neutralize its activity. This binding induces apoptosis in TNFα-releasing cells, alters cytokine secretion, and upregulates p38 MAP kinase, which is involved in downstream signaling of TNFα [19].

Intracellular signaling triggered by Infliximab initiates various responses, including the reduction of cytokines, [20] increased vascular permeability, decreased expression of adhesion molecules, and inactivation of specific cell lines [21].
Additionally, it delays the recruitment of immune cells to inflammation sites, although regulatory T-cells, which play a beneficial role in immune responses, may still be recruited, leading to their increased expression [22] [23] [24].

4. Pharmacological Properties Of Infliximab

Administration of single intravenous infusions of infliximab at doses of 5, 10, or 20 mg/kg to patients with rheumatoid arthritis resulted in dose-dependent increases in maximum plasma concentration (192.1, 426.7, and 907.4 mg/L, respectively) and in the area under the concentration-time curve (49,909, 78,178, and 173,043 mg·h/L, respectively). Most of these patients had detectable serum infliximab concentrations 10 weeks after treatment. In patients with rheumatoid arthritis, serum infliximab concentrations appeared to be sustained longer with concomitant administration of methotrexate. Patients with Crohn's disease who received

multiple infliximab infusions had stable serum concentrations 8 weeks after each infusion; most patients had detectable serum infliximab concentrations 12 weeks after the last dose.
The studies showed that the volume of distribution of infliximab is independent of dose, ranging from 3.1 to 4.3 L, suggesting mainly intravascular distribution. The clearance is approximately 0.011 L/h, and the terminal elimination half-life is between 215 and 295 hours [25].

6. Safety And Long-term risks of Infliximab

Infliximab, as a biological therapy, is associated with various risks and adverse effects that need to be carefully monitored. Clinical studies have shown that patients receiving infliximab are at increased risk of infections, including serious bacterial, viral, and fungal infections, which may be related to the immunosuppressive effects of the drug. Furthermore, there are reports of potential allergic reactions and infusion reactions that can lead to anaphylactic shock. Long-term use of infliximab also raises concerns about cancer risk, particularly in patients with inflammatory diseases, where this risk may be heightened due to chronic stimulation of the immune system. It is important for physicians, when evaluating therapeutic benefits, to consider these potential hazards, implementing appropriate monitoring and risk management strategies, which can contribute to improving patient safety in infliximab therapy.
The potential carcinogenic risk arises from reports of tumors in children, adolescents, and young adults who received infliximab for a median of 30 sessions. This hypothesis is based on the finding that TNF-α causes tumoral hemorrhagic necrosis, which is why it is used in the treatment of selected tumors [26]. The assessment of the treatment response can be measured using appropriate evaluation tools, such as the Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), PCDAI, and PUCAI, initially after three months and then every six months.
A complete blood count and hemogram should be repeated after three months and then every six months. Liver function tests, kidney function tests, serum electrolyte levels, and urine analysis should be evaluated after three months and then every six months [27].

7. Clinical particulars of Infliximab

Infliximab is widely used in clinical practice as a biological therapy for patients with inflammatory diseases, particularly in the treatment of rheumatoid arthritis, Crohn's disease and psoriasis.

Infliximab treatment for rheumatoid arthritis (RA) is an effective therapeutic option for patients who have not responded well to other treatment methods. Infliximab, a biological drug, works by inhibiting tumor necrosis factor-alpha (TNF-α), a key mediator in the inflammatory processes associated with RA. Clinical studies have shown that infliximab significantly reduces symptoms such as pain, swelling, and stiffness in the joints, while also improving patient functionality and quality of life.

Infliximab can be used both as a monotherapy and in combination with methotrexate, which results in even better clinical outcomes. The drug is administered intravenously, with the standard treatment regimen involving an initial series of infusions at a dose of 3 mg/kg every 2 weeks, followed by maintenance doses every 8 weeks. During treatment, patients should be monitored for potential side effects, such as allergic reactions, infections, or changes in laboratory test results. Infliximab therapy carries a risk of infections, particularly in patients with compromised immunity or pre-existing health conditions.

Infliximab can be especially beneficial for patients with severe RA who have not achieved sufficient improvement with other therapies (e.g., NSAIDs, methotrexate). Due to its immunosuppressive properties, infliximab helps control chronic inflammation, thereby reducing the risk of joint damage and improving long-term prognosis for RA patients [28].

Infliximab, when used in combination with purine analogs (such as azathioprine or 6-mercaptopurine), is likely more effective than purine analogs alone in achieving remission in Crohn's disease. It may also be more effective in alleviating symptoms. Both treatment options may have similar safety profiles.

Infliximab alone may be more effective than purine analogs alone in achieving remission of Crohn's disease and improving symptoms. Both treatment options may have similar safety profiles.

Infliximab may be as effective as a biosimilar in treating Crohn's disease and relieving symptoms. Both treatment options may have similar safety profiles. A biosimilar to infliximab is a biological drug (containing substances produced using living cells or organisms) that is very similar to the original brand of infliximab [29].

Clinical studies have shown that infliximab is effective in improving the symptoms of psoriasis, such as reducing the number and size of skin lesions, as well as improving patients' quality of life. The drug is administered intravenously, usually at an initial dose of 5 mg/kg, and then repeated every 2-4 weeks, depending on the patient's response. Infliximab is particularly effective in patients with plaque psoriasis, where skin lesions can be extensive and resistant to topical treatments.

In psoriasis treatment, infliximab is often used in combination with other systemic therapies, such as methotrexate, especially in patients who do not respond to topical treatments or other biologic drugs. The therapy requires regular monitoring, including assessment of potential adverse effects such as infusion reactions, infections, and monitoring of liver and kidney function [2].

8. Conclusion

Infliximab, a TNF-alpha inhibitor, has proven to be an effective therapeutic agent for a range of inflammatory diseases, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, and psoriasis. Its mechanism of action involves neutralizing the proinflammatory cytokine TNF-alpha, which plays a pivotal role in the pathogenesis of these conditions. By inhibiting TNF-alpha, infliximab alleviates inflammation, reduces symptoms such as pain, swelling, and skin lesions, and improves patient quality of life.

Clinical studies have highlighted infliximab’s role in inducing and maintaining remission in conditions like Crohn's disease and psoriasis, where it has shown significant clinical benefits compared to traditional therapies. When used in combination with other treatments, such as methotrexate or purine analogs, it may offer enhanced efficacy, particularly in cases resistant to standard therapies.

However, like all biological therapies, infliximab carries potential risks, including infections, allergic reactions, and long-term concerns such as an increased risk of malignancies. Regular

monitoring of vital signs, laboratory parameters, and potential side effects is essential to ensure patient safety.

In summary, infliximab is a valuable option for managing chronic inflammatory diseases, particularly for patients who have not responded adequately to other therapies. Ongoing research and clinical experience will continue to refine its use and expand its indications, potentially enhancing its role in the treatment of inflammatory conditions.

Disclosure

Author's contribution

Julia Słowik: Conceptualization, writing rough preparation,

Daniel Zapasek: Writing rough preparation, formal analysis,

Mateusz Bajak: supervision,

Michał Szczepański: visualization, data curation,

Maciej Mamczur: Methodology, software,

Marcin Kuliga : check,

Julia Inglot: writing and editing,

Jadwiga Inglot : project administration

Dominik Maciej Feret : resources, investigation,

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References

[1] Cordoro KM, Feldman SR. TNF-alpha inhibitors in dermatology. Skin Therapy Lett. 2007;12(7):4-6.

[2] Wang J, Zhan Q, Zhang L. A systematic review on the efficacy and safety of Infliximab in patients with psoriasis. Hum Vaccin Immunother. 2016;12(2):431-437. doi:10.1080/21645515.2015.1081322

[3] Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol. 2004;31(10):1912-1917.

[4] Knight DM, Trinh H, Le J, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol. 1993;30(16):1443-1453. doi:10.1016/0161-5890(93)90106-l

[5] Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies [published correction appears in Lancet. 2020 Oct 3;396(10256):e56. doi: 10.1016/S0140-6736(20)32028-6]. Lancet. 2017;390(10114):2769-2778. doi:10.1016/S0140-6736(17)32448-0

[6] Zhao M, Gönczi L, Lakatos PL, Burisch J. The Burden of Inflammatory Bowel Disease in Europe in 2020. J Crohns Colitis. 2021;15(9):1573-1587. doi:10.1093/ecco-jcc/jjab029

[7] Qiu Y, Chen BL, Mao R, et al. Systematic review with meta-analysis: loss of response and requirement of anti-TNFα dose intensification in Crohn's disease. J Gastroenterol. 2017;52(5):535-554. doi:10.1007/s00535-017-1324-3

[8] Ungar B, Levy I, Yavne Y, et al. Optimizing Anti-TNF-α Therapy: Serum Levels of Infliximab and Adalimumab Are Associated With Mucosal Healing in Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2016;14(4):550-557.e2. doi:10.1016/j.cgh.2015.10.025

[9] Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. Int Immunol. 2015;27(1):55-62. doi:10.1093/intimm/dxu102

[10] Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;41(9):1552-1563. doi:10.1002/1529-0131(199809)41:9<1552::AID-ART5>3.0.CO;2-W

[11] Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther. 2008;117(2):244-279. doi:10.1016/j.pharmthera.2007.10.001

[12] Schottelius AJ, Moldawer LL, Dinarello CA, Asadullah K, Sterry W, Edwards CK 3rd. Biology of tumor necrosis factor-alpha- implications for psoriasis. Exp Dermatol. 2004;13(4):193-222. doi:10.1111/j.0906-6705.2004.00205.x

[13] Wong M, Ziring D, Korin Y, et al. TNFalpha blockade in human diseases: mechanisms and future directions. Clin Immunol. 2008;126(2):121-136. doi:10.1016/j.clim.2007.08.013

[14] Waage A, Halstensen A, Espevik T. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. Lancet. 1987;1(8529):355-357. doi:10.1016/s0140-6736(87)91728-4

[15] Esposito E, Cuzzocrea S. TNF-alpha as a therapeutic target in inflammatory diseases, ischemia-reperfusion injury and trauma. Curr Med Chem. 2009;16(24):3152-3167. doi:10.2174/092986709788803024

[16] Fiers W. Tumor necrosis factor. Characterization at the molecular, cellular and in vivo level. FEBS Lett. 1991;285(2):199-212. doi:10.1016/0014-5793(91)80803-b

[17] Feldmann M. Development of anti-TNF therapy for rheumatoid arthritis. Nat Rev Immunol. 2002;2(5):364-371. doi:10.1038/nri802

[18] Uyemura K, Yamamura M, Fivenson DF, Modlin RL, Nickoloff BJ. The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response. J Invest Dermatol. 1993;101(5):701-705. doi:10.1111/1523-1747.ep12371679

[19] Mitoma H, Horiuchi T, Tsukamoto H, Ueda N. Molecular mechanisms of action of anti-TNF-α agents - Comparison among therapeutic TNF-α antagonists. Cytokine. 2018;101:56-63. doi:10.1016/j.cyto.2016.08.014

[20] Charles P, Elliott MJ, Davis D, et al. Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. J Immunol. 1999;163(3):1521-1528.

[21] Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. J Clin Invest. 2003;111(6):821-831. doi:10.1172/JCI16069

[22] Souto-Carneiro MM, Mahadevan V, Takada K, et al. Alterations in peripheral blood memory B cells in patients with active rheumatoid arthritis are dependent on the action of tumour necrosis factor. Arthritis Res Ther. 2009;11(3):R84. doi:10.1186/ar2718

[23] Leipe J, Skapenko A, Lipsky PE, Schulze-Koops H. Regulatory T cells in rheumatoid arthritis. Arthritis Res Ther. 2005;7(3):93. doi:10.1186/ar1718

[24] Bayry J, Lacroix-Desmazes S, Dasgupta S, Kazatchkine MD, Kaveri SV. Efficacy of regulatory T-cell immunotherapy: are inflammatory cytokines key determinants?. Nat Rev Immunol. 2008;8(1):1p-86. doi:10.1038/nri2138-c1

[25] Keating GM, Perry CM. Infliximab: an updated review of its use in Crohn's disease and rheumatoid arthritis. *BioDrugs*. 2002;16(2):111-148.

[26] Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. *Drug Saf*. 2004;27(5):307-324. doi:10.2165/00002018-200427050-00003

Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. Drug Saf. 2004;27(5):307-324. doi:10.2165/00002018-200427050-00003

[27] Svenson M, Geborek P, Saxne T, Bendtzen K. Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. *Rheumatology (Oxford)*. 2007;46(12):1828-1834. doi:10.1093/rheumatology/kem261

[28] Blumenauer B, Judd M, Wells G, et al. Infliximab for the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev*. 2002;2002(3):CD003785. doi:10.1002/14651858.CD003785

[29] Gordon M, Sinopoulou V, Akobeng AK, et al. Infliximab for medical induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2023;11(11):CD012623. Published 2023 Nov 20. doi:10.1002/14651858.CD012623.pub2