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TNFα Therapy – Is Personalization of Treatment Selection Possible?

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ABSTRACT

TNF-α is a important inflammatory protein, involved in the pathogenesis of many immune-mediated diseases. It activates various cellular processes, including inflammation, cell death, and the production of other inflammatory molecules. TNF-α Interacts with two Types of Receptors (TNFR1 and TNFR2), triggering different cellular responses. Activation of TNFR1 typically leads to inflammation, while TNFR2 may have anti-inflammatory effects. Elevated levels of TNF-α are associated with many autoimmune diseases, such as rheumatoid arthritis and psoriasis. TNF-α contributes to damage in joints, bones, and other tissues. To block the inflammatory activity of TNF-α, various antibodies targeting it are used. These drugs are effective in treating many immune-mediated diseases. However, the effectiveness of anti-TNFα therapies can vary depending on the patient's genetic characteristics. Some genetic variations can predict the response to treatment. Besides genetics, other factors like gut microbiota composition, pharmacokinetics, pharmacodynamics, binding affinity and avidity, as well as the development of antibodies against the drug, can also affect treatment effectiveness. Anti-TNFα therapies are effective in treating immune-mediated diseases, but their success may vary based on individual patient characteristics.

Keywords: Tumor Necrosis Factor Alpha; Immune-Mediated Inflammatory Diseases; Plasma Concentration

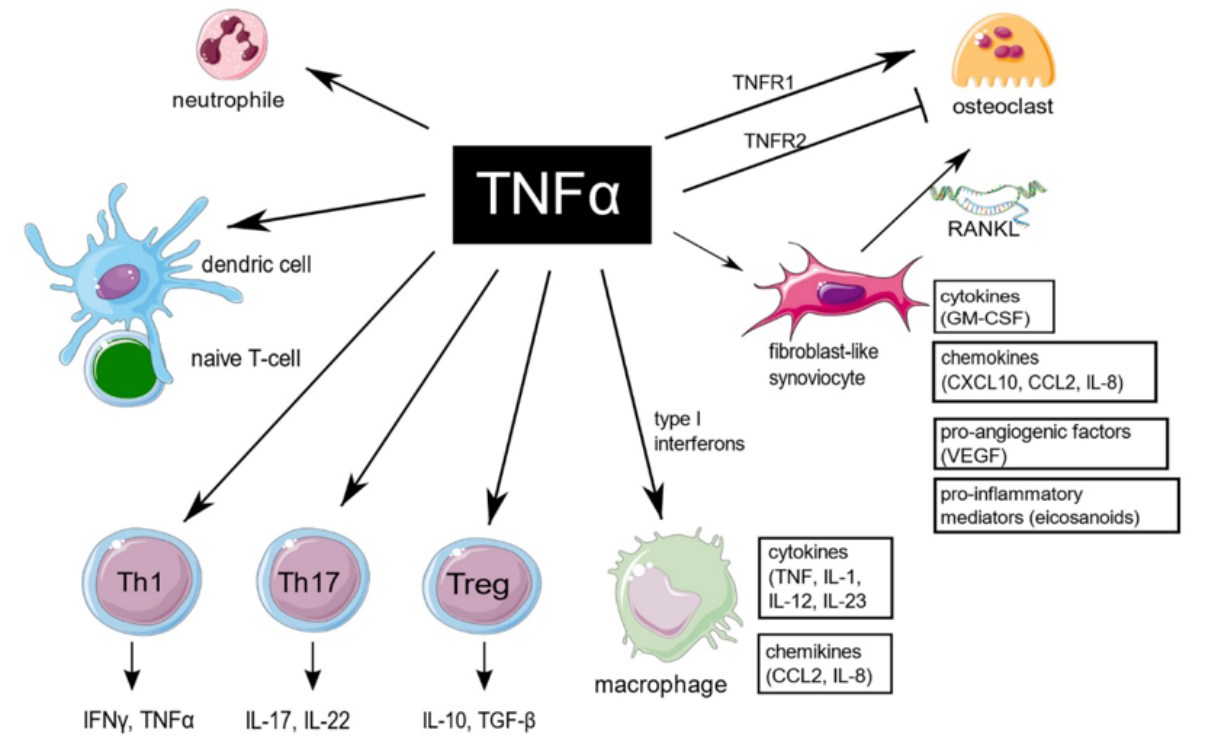
Abbreviations: MAB: Monoclonal Antibody; ADM: Mechanisms of Adalimumab; CDRs: Complementarity-Determining Regions; ETN: Etanercept; FC: Crystallizable Fragment; CZP: certolizumab pegol; GOL: golimumab; RF: rheumatoid factor; ABCG2: ATP-binding cassette G2; NAT2: N-acetyltransferase 2; PBMCs: peripheral blood mononuclear cells; ADAs: Anti-drug antibodies

Introduction

TNFα is part of the TNF superfamily, which includes at least 19 cytokines that regulate various biological processes such as inflammation, apoptosis, chemokine production, and metabolism. Soluble monomeric TNFα (sTNF) is a 17 kDa polypeptide, derived from the proteolytic cleavage of a 26 kDa membrane-integrated precursor (tmTNF) by the metalloproteinase TNFα-converting enzyme (TACE). TNFα is secreted by both immune and non-immune cells, such as macrophages, lymphocytes, endothelial cells, fibroblasts, neurons, adipocytes, and muscle cells, in response to exogenous (primarily infectious) and endogenous stimuli. Both sTNFα and tmTNFα are biologically active through interactions with two subtypes of trimeric glycoprotein receptors: TNF receptor 1 (TNFR1, p55, CD120a) and TNF receptor 2 (TNFR2, p75, CD120b). TNFR1 is ubiquitously expressed in all nucleated cells and preferentially binds to sTNFα, whereas TNFR2 is an inducible subtype typically expressed on immune cells, with its biological effects mainly mediated through binding to tmTNFα. Stimulation of TNFR1 and TNFR2 generates different cellular responses. TNFα signaling through TNFR1 and TNFR2 leads to the activation of the nuclear factor kappa-B1 (NF-κB1) signaling pathway, which is associated with cell survival. Activation of TNFR1 generally induces pro-inflammatory responses, while TNFR2 activation primarily mediates local homeostatic signals. TNFR1 activation can also trigger cell death processes such as apoptosis, necroptosis, and pyroptosis [1-13].

The binding of TNFα trimers (51 kDa) to the receptor activates the NF-κB1 pathway, leading to the production of pro-inflammatory cytokines like IL-1β, IL-6, IL-8, and adhesion molecules. In this way, TNFα directly participates in the defense against infectious agents,

while also playing role in the initiation and zeiyasyashehye of chronic inflammation. (Figure 1) TNFα Influences Inflammatory Responses Both Directly and Indirectly. TNFα contributes to inflammation not only by directly inducing the expression of pro-inflammatory genes but also by indirectly promoting cell death. This cell death then further amplifies pro-inflammatory activation in TNFα-driven immune--mediated inflammatory diseases (IMID). TNFα plays a key role in joint damage by facilitating leukocyte migration to the synovial membrane, promoting bone resorption, and contributing to cartilage collagen degradation through metalloproteinases. Studies of synovial fluid have shown significantly higher concentrations of TNFα in patients with PsA and RA compared to healthy individuals. TNFα is also a potent stimulator of osteoclasts and inhibits the differentiation of osteoblasts, while TNFR2-dependent signaling counteracts this by inhibiting osteoclastogenesis. TNFα is essential for the proper development of T cells. In patients treated with anti-TNFα therapy, regardless of the treatment's success, the Th17/Treg ratio tends to return to levels observed in healthy individuals. The variability in IMID suggests that TNFα may play different roles in their development. Blocking TNFα or its receptors is the cornerstone of treatment for these diseases, typically through anti-TNFα monoclonal antibodies (mAbs). However, whether different TNFα inhibitors offer varying clinical benefits remains a matter of debate, as large-scale randomized clinical trials comparing different TNFα inhibitors and subsequent meta-analyses are lacking.



Note: The figure was created using the Servier Medical Art template acessed on 21 January 2022.

Figure 1: TNF is a pleiotropic cytokine involved in the function of various cells crucial to the pathogenesis of rheumatoid arthritis (RA). TNF promotes the expression of proinflammatory genes in fibroblast-like synoviocytes and macrophages. It significantly affects T cells by expanding the Th17 lymphocyte subset, facilitating the transition of Th17 cells into the non-classical Th1 subset at inflammatory sites, and reducing Treg levels. TNF also enhances leukocyte infiltration at inflammation sites. Additionally, TNF stimulates neutrophils by delaying apoptosis, triggering respiratory bursts, and increasing cytokine production. TNF plays a key role in osteoclastogenesis and RA-related bone loss.

ANTI-TNFα Drugs Available for Clinical Use in Bulgaria

Currently, five anti-TNFα drugs are available for clinical use in Bulgaria:

1. Infliximab (IFX-149 kDa)

A chimeric monoclonal antibody composed of a mouse antigen--binding fragment (Fab) fused with a human IgG1 crystallizable fragment (Fc). This antibody binds to both the soluble and transmembrane forms of TNFα with high affinity. IFX can also interact with both the

trimeric and monomeric forms of sTNFα. Up to three IFX molecules can bind to a single tmTNFα trimer, demonstrating a binding affinity four times higher than that of ETN, resulting in very few unoccupied receptor sites. IFX forms stable high-molecular-weight immune complexes with TNFα, reaching sizes of up to 14,000 kDa. In patients with RA, when administered intravenously every eight weeks, its half-life (t1/2) ranges between 7.7 and 9.5 days.

2. Etanercept (ETN-130 kDa)

A fusion protein that combines the Fc fragment of human IgG1 with the extracellular domain of the p75 TNFα receptor. ETN is a dimeric, soluble form of TNFR2, which has a higher affinity for TNFα compared to the monomeric cellular receptor. This allows ETN to compete with membrane TNFα receptors, preventing TNFα from binding to them. The Fc portion of the human immunoglobulin prolongs the half-life of ETN, resulting in longer-lasting biological activity compared to the natural TNFα receptor. Unlike infliximab (IFX) and adalimumab (ADM), ETN primarily binds to sTNFα, with very low affinity for the monomeric form. Additionally, ETN rapidly dissociates from its ligand and does not form stable complexes with TNFα. ETN blocks approximately 50% of sTNFα and 90% of tmTNFα within just 10 minutes of administration. Unlike selective anti-TNFα monoclonal antibodies, ETN does not activate complement or induce cell lysis in cells expressing tmTNFα but instead exhibits antibody-dependent cytotoxicity. Despite its short half-life of about 4 days, which may lead to a weaker and more reversible TNFα blockade, ETN is the only TNFα inhibitor capable of binding lymphotoxin-α (LTα). Although the role of LTα in the inflammatory process is not fully understood, the fact that some PsA patients who do not respond to anti-TNFα monoclonal antibodies respond to ETN suggests that LTα plays a role in the pathogenesis of IMID.

3. Adalimumab (ADM-150 kDa)

The first fully human monoclonal antibody. Similar to infliximab (IFX), adalimumab can bind both soluble TNFα (sTNFα) and transmembrane TNFα (tmTNFα), depending on the administered dose, preventing TNFα from interacting with its receptors.

In patients with rheumatoid arthritis (RA), adalimumab has several pharmacological effects:

- Reduces acute-phase inflammatory markers (Humira PI 2005).
- Lowers the levels of granulocyte-macrophage colony-stimulating factor and IL-1, IL-6, IL-8 in the serum (Choy and Panayi 2001).
- Decrease the levels of IL-1 receptor antagonist and IL-6 (Barrera et al. 2001).
- Significantly reduces baseline levels of MMP-1, MMP-3, pro--MMP-1, and pro-MMP-3 (den Broeder et al. 2002; Weinblatt et al. 2003).
- Reduces the release of adhesion molecules that help the migration of leukocytesthe (den Broeder et al. 2002; Humira PI 2005).

In RA patients, adalimumab concentrations in synovial fluid range from 31% to 96% of those found in serum. After subcutaneous administration, the drug is absorbed and distributed slowly, with a time to maximum concentration (tmax) of around five days and an average bioavailability of 64%. The plasma half-life (t1/2) is approximately 14 days.

4. Golimumab (GOL-147 kDa)

A fully human IgG1 monoclonal antibody that forms high-affinity complexes with both soluble TNFα (sTNFα) and transmembrane TNFα (tmTNFα), blocking TNFα from binding to its receptors. Similar to adalimumab (ADM), golimumab neutralizes TNFα-induced expression of adhesion molecules such as E-selectin, vascular cell adhesion molecule (VCAM-1), and intercellular adhesion molecule (ICAM-1) on endothelial cells. In vitro, golimumab also inhibits the secretion of IL-6 and IL-8, and reduces TNFα-induced stimulation of granulocyte colony-stimulating factor (GM-CSF). After subcutaneous administration, the time to reach maximum concentration (tmax) ranges from two to six days, with an average absolute bioavailability of 51% and a half-life of approximately nine days.

5. Certolizumab Pegol (CZP-90.8 kDa)

A humanized IgG4 monoclonal antibody that consists of an anti-TNFα Fab fragment conjugated to a 40 kDa polyethylene glycol (PEG) component. PEGylation extends CZP's half-life, allowing dosing intervals of at least two weeks. In arthritic mice, CZP penetrates inflamed joint tissue more effectively than adalimumab (ADM) and infliximab (IFX), likely due to the smaller molecular weight of its Fab fragment. CZP binds both soluble TNFα (sTNF) and transmembrane TNFα (tmTNF) with high affinity. Unlike full monoclonal antibodies, CZP lacks the Fc fragment, preventing it from binding complement or causing antibody-dependent cellular cytotoxicity. The absence of the Fc region also minimizes CZP's transplacental passage during pregnancy. Meta-analyses have shown that CZP is more effective than ADM and IFX in RA patients with very high serum rheumatoid factor (RF) levels. CZP has a bioavailability of about 80% and a half-life (t1/2) of approximately 14 days.

Analysis

Analyzing data from studies on various anti-TNFα drugs reveals that each Monoclonal Antibody (mAb) has unique characteristics. While the primary mechanisms of TNFα inhibition are similar, differences in clinical efficacy remain uncertain. No data currently compares the binding epitopes of these drugs, even though affinity and epitope specificity are crucial for the effectiveness of anti-TNFα mAbs. To better understand the inhibitory mechanisms of adalimumab (ADM) and to explore the differences in binding epitopes between infliximab (IFX) and ADM, a crystallographic analysis of the TNFα-ADM-Fab and

TNFα-IFX-Fab complexes was performed. ADM-Fab exhibits a quaternary immunoglobulin fold, with its complementarity-determining regions (CDRs) forming a large, deep pocket that accommodates the entire TNFα epitope. In contrast, not all CDRs of IFX engage in such interactions. The antigen-antibody interaction in IFX involves only one TNFα molecule in the TNFα-IFX immune complex. Structural comparisons between ADM and IFX show that ADM epitopes directly overlap with the TNFα receptor binding region, offering a larger interaction surface, whereas the IFX epitope is distant from TNFα receptor binding sites and interacts with a smaller surface area. Etanercept (ETN) blocks TNFα-TNFR interaction by occupying the receptor-binding site on TNFα, with one ETN/TNFR2 molecule interacting with two TNFα molecules. ETN also exhibits a faster ligand-binding rate.

Understanding the structural relationships between TNFα and the antibodies targeting it forms the basis for further research into optimizing these interactions, and through molecular engineering, designing mAbs with higher inhibitory effectiveness. The structural differences among TNFα inhibitors also influence their pharmacokinetics and pharmacodynamics. IFX, administered intravenously, achieves a high initial peak plasma concentration (Cmax), whereas ETN, ADM, golimumab (GOL), and certolizumab pegol (CZP), administered subcutaneously, display flatter pharmacokinetic profiles. These pharmacodynamic differences are crucial as they can guide the choice of a specific drug depending on the patient's needs. For example, ETN may be preferred for patients at high risk of activating latent infections, and CZP might be the best option for pregnant or breastfeeding women or those with very high serum rheumatoid factor (RF) levels. When planning biological therapy for patients undergoing major surgery or for older patients, drugs with shorter plasma half-lives, like ETN, might be preferable. Meanwhile, biologics with longer half-lives and extended dosing intervals can improve patient adherence to treatment. Considering the pharmacodynamics of TNFα inhibitors is essential when selecting a biological treatment for each individual patient. Research and clinical practice have shown that the effectiveness of treatment with anti-TNFα mAbs also depends on the patient's genetic predisposition.

For instance, the study on "Genetic polymorphisms in tumor necrosis factor receptors (TNFRSF1A/1B)" highlights this aspect. Another gene expression analysis identified 59 distinct genes associated with the therapeutic response to TNFα inhibitors. In the future, analyzing specific genetic profiles could become a vital tool for personalizing biological treatment in clinical practice. Pharmacogenetic testing is already used in various medical specialties to predict therapeutic outcomes. In rheumatology, several studies indicate that common variants in genes encoding N-acetyltransferase 2 (NAT2) and ATP-binding cassette G2 (ABCG2) are linked to sulfasalazine toxicity. Carriers of the LARRC55 rs717117G allele exhibit reduced serum IL-6 levels following stimulation of peripheral blood mononuclear cells (PBMCs), indicating a potential link between a diminished IL-6-mediated pro-inflammatory response and a poor response to anti-TNFα drugs. Additionally, a connection has been found between the initial response to ETN and the MED15 gene (rs113878252), which is likely involved in polymerase II transcription. In the ETN cohort, the TNFα receptor signaling gene TRAF6 was also differentially expressed between responders and non-responders. Moreover, gene expression profiles in peripheral blood neutrophils may help predict the effectiveness of TNFα blockers. For instance, a study by Wright et al. identified type I interferon (IFN) signaling as a key indicator of response to anti-TNFα therapy. The study of synovial biomarkers can also help predict the therapeutic response to anti-TNFα treatment.

In RA, for instance, inflamed synovial tissue shows significant cellular and molecular diversity. This heterogeneity is reflected in different cellular and molecular signatures, or "pathotypes," of rheumatoid synovitis. Dennis et al. identified four distinct types: lymphoid, myeloid, pauci-immune (low-inflammatory), and fibroid. These four phenotypes correspond to specific gene expression patterns in synovial tissue, with all groups showing increased expression of the IL-6 receptor and the related STAT3 protein transcription of genes. Genetic polymorphisms can be predictors of response to anti-TNFα therapy, and genotyping these polymorphisms in IMID patients would significantly aid in personalizing treatment by predicting responses to specific anti-TNFα drugs. There is growing evidence that disturbances in the microbiome play a pathogenic role in the development of IMID. There are not a few studies proving the effectiveness of anti-TNFα therapy on the gut microbiota. For example, Kolho et al. showed that anti-TNFα therapy in children with Crohn's disease altered gut microbiota biodiversity, making it more similar to that of healthy controls. In psoriasis, the role of gut and skin microbiota in disease pathogenesis has been established. In untreated RA patients, gut dysbiosis is more common than in controls, with a significant increase in lactobacilli and a decrease in Faecalibacterium bacteria. Picchianti-Diamanti and colleagues observed a partial recovery of beneficial microbiota in RA patients receiving ETN therapy, which may play a role in the drug's clinical effectiveness.

Similarly, a study by Bazin et al. found that the composition of gut microbiota in ankylosing spondylitis patients could predict their response to anti-TNFα treatment. Anti-drug antibodies (ADAs) against therapeutic mAbs play a significant role in the effectiveness and tolerability of biological treatment. The protein structure of all biologic drugs can induce the production of ADAs, which may lead to reduced therapeutic response or increased risk of adverse drug events, including anaphylactic reactions. The immunogenicity of each drug is determined by its molecular structure, the patient's genetic factors, and the type of IMID. Concurrent administration of methotrexate can reduce the formation of ADAs in patients receiving anti-TNFα therapy, likely due to methotrexate's immunosuppressive effects.

Conclusion

The use of TNFα inhibitors has shown positive clinical responses in IMID, and the number of patients on this treatment continues to grow. However, not all patients achieve satisfactory outcomes. Both primary and secondary non-response to TNFα inhibitors is observed in practice. Approximately 20–40% of RA patients and 20–50% of those with psoriatic disease fail to respond to this biological therapy (primary non-response). A meta-analysis of 14 double-blind, randomized controlled trials involving patients with psoriasis (4 ustekinumab studies, 3 ADM, 3 IFX, and 4 ETN) reported that ADM, IFX, and ETN could be considered clinically equivalent for treating this condition. The authors concluded that the choice of TNFα inhibitor is primarily determined by safety profiles, patient contraindications, and cost rather than differing efficacy profiles. Additionally, studies show that about 25% of RA patients treated with anti-TNFα drugs fail to meet treatment goals initially, with roughly 55% of primary responders experiencing a loss of effect within 12 months of starting treatment. Currently, there are no dependable tools available to predict individual responses to TNFα inhibitors. The growing number of drugs drives the development of new diagnostic algorithms for selecting personalized disease-modifying therapies in IMID, aiming to adapt treatment to the individual patient's characteristics. Pharmacogenomics, as a crucial component of personalized medicine, could reveal the relationship between genetic variations and drug effectiveness.

Future research will focus on selecting the best anti-TNFα drug for each patient based on their genetic profile. Data collection from global biologic registries, combined with artificial intelligence, will support the personalization of therapy for patients with inflammatory joint diseases.

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