Review Article

Risk of Tumor Necrosis Factor Alpha Inhibitors Usage and Related Adverse Effects

Abstract

Tumor necrosis factor (TNF) plays a role in host cell defense. TNF-alpha (TNF-α), secreted from macrophage has an important role in proinflammatory response mechanism. TNF-α levels increase in autoimmune, systemic inflammatory diseases, especially rheumatological diseases. Therefore, TNF-α inhibitors are alternant in the treatment of many inflammatory diseases. TNF-α inhibitors are not the first choice of clinicians due to their important adverse effects, despite the fact that successful results in diseases treatments. Treatment with TNF-α inhibitors causes different adverse effects including many bacterial, viral and fungal infectious diseases, lung diseases, demyelinating diseases, and malignancies. One of the most important adverse effect is tuberculosis (TB) by *Mycobacterium tuberculosis bacillus*. TB occurs through reactivation in Latent TB infection. Thus, TB screening tests appliedbefore TNF-α inhibitors treatment have an importance. In this review, TNF-α inhibitors and their important adverse effect TB flaming were discussed, and also genetic background features of these molecules have been explained.

Keywords: *Adverse effect, tuberculosis, tumor necrosis factor-alpha inhibitors, tumor necrosis factor-alpha*

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Introduction

Inflammatory and autoimmune diseases are very common. Substantial treatment options are sometimes being insufficient to cure diseases. Recent years new treatment options have been applied in patients that did not respond to substantial treatment. The technological advancement on DNA hybrid subject led to diverse biologicals which aims especially tumor necrosis factor (TNF)-alpha. The body produces TNF and it takes place on normal inflammatory and immune responses. Cytokines such as interleukin (IL)-1, IL-6, IL-8, platelet-derived growth factor-B, eicosanoids, platelet-activating factors, and granulocyte monocyte colony-stimulating factor that induce both autocrine and paracrine cell signaling systems. Anti TNF-alpha (TNF-α) therapy reduces the capacity of monocytes to generate proinflammatory cytokines and also stimulates an alteration to generate more anti-inflammatory TH2 cytokine. Transforming growth factor ß which is generated by diverse cell types such as T-cells and monocytes, soluble TNF receptor (TNFR)-1 that stimulates apoptosis by reverse TNF signaling and autocrine transforming growth, soluble IL-1 receptor, IL-4, IL-10, IL-11, IL-13, and IL-16 are anti-inflammatory cytokines. On the advancement on biologicals against TNF-α, therapeutic access to inflammatory diseases has significantly altered.[1] The most used TNF-α inhibitors in clinical medicine include infliximab, adalimumab, etanercept, golimumab, and certulizumab pegol. These inhibitors were thought as a new option for the cure of inflammatory and autoimmune diseases.[2] However, over time, it has been seen that, besides their therapeutic properties, they have unwanted side effects.

Tumor Necrosis Factor-alpha and Molecular Function

TNF- α is a polypeptide cytokine with autocrine and paracrine properties. It is generated mainly by monocytes and macrophages. It is believed that tumor necrotizing activity was caused by endotoxin and the concept of TNF-α was first defined in 1975. Two structurally

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different cytokines were found in 1985. These are macrophage derived TNF and lymphocyte-derived lymphotoxins. These cytokines were subsequently named TNF-α and TNF-beta, respectively, and associated with these cytokines, 17 more ligands were identified, together with the concept of the TNF superfamily. Pro-inflammatory activity, apoptosis, proliferation, morphogenetic changes, and differentiation are the important physiological features of the TNF superfamily, including TNF-α [Table 1].[3,4]

TNF-α's structure is different from other cytokines and provides lipopolysaccharide inactivation. TNF-α is mostly secreted by activated natural killer, activated macrophages, mast cells, and also antigen-stimulated T-lymphocytes. Besides that, it was seen that TNF-α is less secreted by glomerular mesangial cells, fibroblasts, endothelial cells, Kupffer cells, and astrocytes.[5,6]

There are two forms of TNF-α as membrane-embedded protein (transmembrane) and soluble cytokine. TNF-α interacts with two receptors, TNFR-I and TNFR-II. Although TNFR-I is widely found in the body, TNFR-II is predominantly found in immune system, nervous system, and endothelial cells. TNFR-I is activated by the soluble ligand (soluble TNF-α), while TNFR-II is mostly activated by the membrane-resident form (transmembrane TNF-α). TNF-α regulates the local inflammation through cell-to-cell contact with cell specific manner through binding target cells receptors.[7-9]

Transmembrane TNF-α has played essential act in host defense against various viral, parasitic, and bacterial infections such as Human Immunodeficiency Virus (HIV), *Listeria monocytogenes*, *leishmania* and *Mycobacterium tuberculosis*, as well as fine-tuning the immune response. It shows activity against acute infection of tuberculosis (TB) by initiating T-cell and macrophage migration and granuloma formation. Soluble TNF-α, which is proteolytically separated from the transmembrane form by TNF-α converting enzyme, also shows pro-inflammatory and apoptosis triggering effects after cleavage. The soluble form of TNF-α is delivered in reply to lipopolysaccharides, other bacterial products, and IL-1 and mediated pathological responses including autoimmune, neurological, cardiovascular, metabolic diseases, cancer, and lung diseases.[8,10-13] Many kinds of cells discharge TNF after that, it keeps going to induce other immune cells. Macrophages, dendritic cells, T-cells, fat cells, and fibroblasts release TNF and TNF influence various notable cells. Especially, it will make a difference to cells which line our blood vessels that give reason to vascular problems such as angiogenesis and hypervascularization. Shanmugam *et al*. also stated that TNF-α has a significant role in many diseases linked with oxidative stress, concluding cancer, diabetes, cardiac hypertrophy, and cardiomyopathy. In medicine, over 5 anti-TNF drugs are now being utilized and normally behave as deactivating antibodies or a soluble TNFR. It has been shown that chronical use of TNF-α blockers and anti-TNF-α therapies is destructive in diverse cells and organ systems and is united with threat of improving cancer, demyelinating irregularities, and cardiovascular complexities. TNF-α inhibition cause adverse effects are not clear. One probability is that extended TNF-α blockade may push Reactive oxygen species generation down the threshold which is wanted for physiological regulation of the Kelch like ECH associated protein 1 (Keap1)/Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. The expression of Nrf2 regulated proteins (NAD [P] H Dehydrogenase, Quinone 1 [NQO1], Heme oxygenase-1 [HO-1], Glucose-6-phosphate dehydrogenase [G6PD]) were considerably down regulated in hearts of the Double knock out (DKO). *In vivo* experiments with TNFR1/2-DKO show that the expression of Nrf2-regulated proteins (NQO1, HO-1, G6PD) were considerably down regulated in hearts of the DKO when crosschecked to wild type mice pointing out a weakened antioxidant system under basal conditions. Through, these effects point out that TNF-α display has a bimodal impact on the Keap1/Nrf2 system and when a condensed inflammatory activation pushes down the expression of antioxidant proteins at a low grade come in sight to be preventive. In this research, it is also demonstrated that the activity of Nrf2 and its nuclear translocation enhanced by exposure of TNF-α to cells at concentrations well below the threshold linked with sub-inflammation. Therefore, the transcriptional induction of Nrf2 and its next goals takes place in response to a low-dose of TNF-α, whereas concentrations higher than 10 ng/mL were significantly suppressive and linked with cell death. Other researchment has demonstrated that an exact neutralization gave reason to damaged immune function and enhanced threat of cancer more over to these, cardiovascular difficulties.[14] TNF also negatively influences intestinal cells, giving reason to cell death, leaky gut, Irritable bowel syndrome and Inflammatory bowel disease. TNF induces macrophages and effector T cells that cause more inflammatory cytokine production and apoptosis resistance that attends to cancer.[15]

TNFR1 and TNFR2 are the two main regulatory factors of TNF-α. TNFR1 activation initiates inflammatory and apoptotic mechanisms, whereas TNFR2 activation

Table 1: Physiological roles of tumor necrosis factor superfamily members (Aggarwal *et al*., 2012)

Morphogenesis	Proliferation	Apoptosis
TNF-alpha	TNF-alpha	TNF-alpha
EDA-A1	TNF-beta	TNF-beta
EDA-A2	LT-beta	CD40L
CD40L	CD27L	CD30L
TRAIL	RANKL	FasL
FasL	BAFF	VEGI

TNF: Tumor necrosis factor, EDA: Ectodysplasin A, TRAIL: TNF-related apoptosis-inducing ligand, FasL: Fas Ligand, RANKL: Receptor activator of NF-κB ligand, BAFF: B-cell activating factor receptor, VEGI: Vascular endothelial growth inhibitor

initiates anti-inflammatory and cytoprotective and repair mechanisms of cellular processes. Soluble TNF-α interacts with TNFR1 receptor and induces apoptosis mechanism via mitogen activated protein kinase, Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), Phosphoinositide 3-kinase signaling and caspases cascade. In turn, these cascades initiate cellular oxidative stress, necrosis and/or apoptosis.[16]

When TNF binds to a receptor, varied dissimilar facts can occur, depending on the cell type and receptor type. Transcription factor NF-κB, which controls cell survival and inflammatory response, gets activated. Primarily, TNF alpha has been aforethought as a pro-inflammatory molecule. On the other hand, preclinical and clinical instructions have demonstrated that it also remotes a paradoxical anti-inflammatory and immunomodulatory effect [Figure 1].[17-19]

Tumor necrosis factor-alpha inhibitors

TNF increases in various autoimmune diseases. In 1990, it turned into a famous therapeutic target for the treatment of diseases like rheumatoid arthritis (RA). An engineered monoclonal antibody, fusion proteins are the biological agents that target TNF. There are 5 types of TNF-α inhibitor drugs as etanercept, sertolizumab, adalimumab, golimumab and infliximab.[20] Etanercept is a fusion protein that contains two p75-soluble TNFR and binds to the Fc portion of human Immunoglobulin (Ig) G1. It inactivates by binding directly to TNF-6alpha. As a result of this binding, interaction with cell surface TNFR blocked and target cell activation via TNF is inhibited.[21] Etanercept show less affinity for TNFR1 than TNFR2. Etanercept's binds to TNF-α with lower affinity and reversible. Etanercept's elimination half-life is 68 h and it is excreted in bile or urine after metabolism with preteolytic enzymes. Widely distributed in tissues and reaching steady-state concentration before 12 weeks.[22]

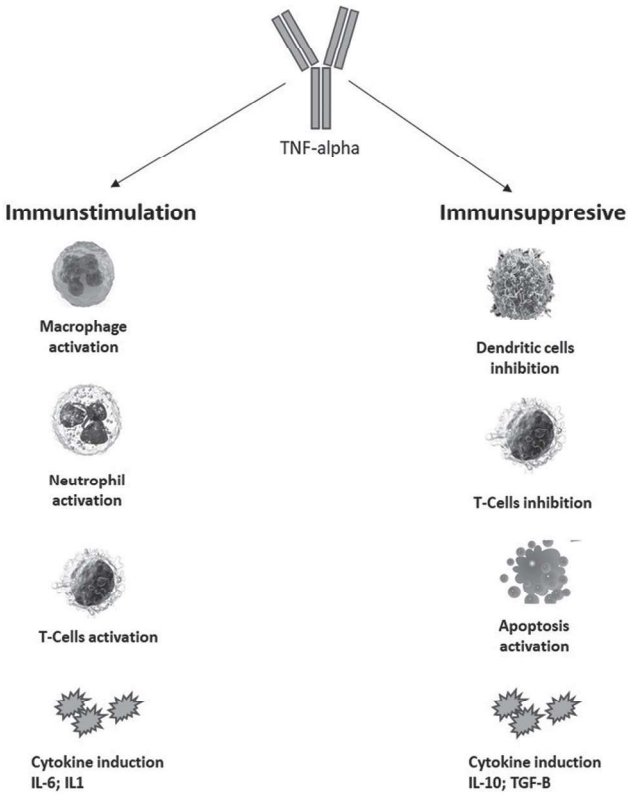

Figure 1: Suppressive and stimulatory effects of tumor necrosis factor-alpha on immune cells. IL: Interleukin, TGF: Transforming Growth Factor-β

Certolizumab pegol is a precise for TNF-α that it is a humanized monoclonal antibody. There is a Fab fragment conjugated with a 40-kDa polyethylene glycol chain that binds to TNF-α[23] and neutralizes transmembrane and soluble TNF-α. Due to certolizumab lacks a fixed Fc region, it does not cause antibody-dependent cell-mediated cytotoxicity.[24,25] Infliximab is a chimeric anti-TNF antibody combined with the human constant region. It prevents inflammatory cells' TNF's interaction with TNFR by binding them. It shows high affinity for transmembrane and soluble TNF. Therefore, it may show a cytotoxic response in macrophages and monocytes expressing the antibody on the surface. It has a half-life of about 8.5–9 days. Although it depends on the dose of the drug and the duration of treatment, it can be seen in serum up to the 28th week.[25,26]

Adalimumab is a fully recombinant human IgG1 monoclonal antibody precise for human TNF-a. It prevents TNF activity by binding to TNF-a.[27] Similar to infliximab, the two have the same mechanism of action.[25] However, it is less antigenic than infliximab. It has a half-life of 10–20 days.[28] Golimumab; It is a fully humanized monoclonal antibody. It has a similar treatment of action to adalimumab and infliximab.[26] Its half-life is 14 days.[24,29]

In graft-versus-host disease (GVHD) in aiming TNF-α expectation and disillusion. Anti-TNF therapies can block the effect of TNF at varied steps of acute GVHD pathophysiology which includes initial host antigen–presenting cell activation, effector T cell support and activation in target tissues and direct cell necrosis. Anti TNF therapies also may have a harmful impact on suppressive cells by restraining TNF ligation to TNFR2 which are stated by regulatory T cells. TNF alpha inhibitors are broadly used for therapy of inflammatory illness. One third of patients who are in pain from inflammatory diseases like RA and Crohn's disease are nonresponder to TNF alpha inhibitors. In pharmacogenomics studies related to anti-TNF drug response, single nucleotide polymorphisms (SNPs) in TNF linked genes, HLA, IL related genes, signal network related genes have been examined.[30] Advanced genotyping technology can detect a great number of SNPs which play role anti-TNF drug response.[31] TNF-α G-308A polymorphism is the most common studied polymorphism related to TNF-inhibitor therapy.[32] TNF-α-308A locates in the promoter region of

gene and upregulates transcriptional activity and increases TNF alpha protein level.

TNF-α-308A is located in the gene promoter region, upregulating transcriptional activity, and increasing TNF alpha protein level. Additionally, Netz *et al*. described Fas ligand (rs763110) and the TNF gene-308 (rs1800629), as functional SNPs, for prediction of anti-TNF drug response in Crohn's disease.[33] Meta-analysis study of Salimi *et al*. underlined the powerful relationship between TNF-α-308A genotype and chronic obstructive pulmonary disease risk.[34] As non-TNF-α related genes, Bek *et al*. reported that genetic variants in CTCN5, CHUK, FCGR2A EYA4, IRAQ NFKBIB, NUBPL, PD2D2, and TEC and PTPRC, TRAF1/C5, and may influence the response to anti-TNF drugs in RA.[35]

In an 2014 report demonstrates anterior proof for an unification among the SNP +489, which is placed at the TNF locus and both sensitivity to the progress of PsA and to therapy answers to TNF-a blockers.[36] Although a considerable amount of targeted or genome wide genotyping studies, a biomarker has not been validated yet in clinical use. Mechanisms that cause differences in drug response may be highlighted by holistic approaches such as transcriptomics, proteomics, and metabolomics studies.[31] Applying anti TNF therapy to responders only may prevent adverse effects of inefficient drugs in nonresponder patients. Clinicians expect biomarker panels for optimal therapy management.[35]

Adverse effects of tumor necrosis factor-alpha inhibitors

In the treatment of various illnesses like RA, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, TNF-α inhibitors have become the standard.[37] However, TNF-α inhibitors cause side effects because of TNF-α's normal functions as normal immune response, granuloma formation and its maintenance, macrophage activation and differentiation, as well as viral immune responses.[38,39] The reported lateral impacts are injection site reactions, Infusion reactions, Neutropenia, Infections, Lung diseases, Demyelinating diseases, Heart failure, Cutaneous reactions, Malignancy, induction of autoimmunity.[1]

The most common side effects of TNF-α inhibitors on the lungs are diffuse interstitial lung disease and pulmonary fibrosis that can be seen in 0.5% to 0.6% of risky cases.[40] Autoimmune and inflammatory demyelinating diseases associated with anti-TNF-a therapy aremultiple sclerosis and neuropathy. In most of the studies, it was observed that neuropathies improved after the discontinuation of the TNF-a agents.[41]

It has been reported in studies that, TNF-α inhibitors may cause an increase of bacterial, fungal and opportunistic infections during the treatment.[42] With the utilization of TNF-α inhibitors, the most common respiratory tract infections are seen as bacterial and fungal infections. TB is caused by *M. tuberculosis* as bacterial infections and legionellosis (leyyoner's disease) is caused by Legionella pneumophila. Fungal infections are TB and histoplasmosis, which are caused by Pneumocystis jiroveci and Histoplasma capsulatum, respectively. Other bacterial and fungal infections are rare.[25] Also, apart from these infections, the most common toxicities on the lung of TNF-α inhibitors are diffuse interstitial lung disease and pulmonary fibrosis.[43]

However, (TNF-α) inhibitors have different important adverse effects. One of the important adverse effect is TB. TNF-α is released from macrophages and one of the important mediator of body defense. TNF-α induce antimicrobial activity in macrophages, T-cell activation and T-cell migration with interferon gamma (IFN-gamma). And also, trigger granuloma formation against to mycobacteria. Thus, with the use of TNF-α inhibitors, TNF-α expression levels decreases and the threat of developing TB disease increases.

Tuberculosis

In the worldwide, TB disease is seen as among the most extensive infectious illnesses. It is estimated that TB infects a third of the world's population. And most of this has a latent stage, which we call latent period, which can later progress to active TB disease. There are risk factors for activation of TB after a long latent period. The most important of these risk factors are contact with active TB patients, HIV co-infection, silicosis, diabetes, and initiation of anti-TNF therapy.[44]

TNF is alpha is the key cytokine in the preventive host guard counter to *M. tuberculosis* and has a very signifficant role in the cellular immune response generated against this *bacillus*. Basic contamination begins when bacilli attain the pulmonary alveoli and invading of the alveolar macrophages to infection area. TNF-α stimulates immature dendritic cells to become mature, thus contributing to the presentation of *bacillus* epitopes to T helper 1 cells and the formation of cellular immune response, and by providing apoptosis of macrophages, enabling the destruction of TB *bacillus* without spreading. In addition, lymphocyte proliferation and cell migration of lymphocytes (B and T cells) in the inflammation zone are caused by increasing cytokine (IFN-gamma) and chemokine release. As a result of this event, granuloma is formed and the bacilli that cannot be destroyed are locked into the granuloma and prevented from multiplying and spreading. With the effect of TNF-α, the active macrophages in the granuloma turn into epiloid cells and these cells are fused to form giant cells. Providing granuloma continuity depends on TNF-α release. Thus, TNF-α is necessary for the control of TB infection by ensuring the formation and continuation of granulomas.[18,44,45] When TNF-α is overexpressed, the systemic inflammatory process is

triggered by increased mesenchymal cell proliferation. With the continuation of this chronic inflammatory response, autoimmune systemic inflammatory diseases are occurring. Therefore, TNF-α inhibitors are used in the therapy of these illnesses. By the utilization of these, TNF activity is prevented; thus granuloma formation is suppressed and they can lead to the occurrence of TB disease.[11,46]

TB is one of the most significant infections linked with anti TNF treatment. It has been reported in many studies that the risk of TB and Latent TB infection (LTBI) increases along therapy with TNF-α inhibitors. In addition, it was observed that fatal reactivation occurred in the TB-infected animal, which received a large number of TNF blockages agents.[47-49] With the reactivation of the latent *Mycobacterium tuberculosis bacillus*, pulmonary TB can develop and as a result of this reactivation, extrapulmonary TB can also occur.[50] It is accepted that TNF-α inhibitors facilitate the development of TB. However, studies have shown that infliximab, adalimumab and etanercept do not show the same risk of developing TB.[51] Due to the existing throughput, it is seen that the threat of etarsept to cause TB is lower than infliximab. This is thought to be due to the difference in mechanism of action between the two drugs. These differences can be listed as follows; Both infliximab and etanercept have a high affinity for TNF, but the binding of infliximab to TNF is irreversible, whereas binding of etanercept is reversible. Down-regulation of IFN production by T cells by infliximab may contribute to loss of resistance to infection with *M. tuberculosis*. Etanercept has less effect on suppression of IFN production. Infliximab has been demonstrated to cause apoptosis and can also induce cellular cytotoxicity by causing cell lysis.[3] In addition, while infliximab directly inhibits TNF-α, etanercept demonstrates its impact according to linking to receptors.[52] TNF-α inhibitors have different active TB generation incidences as well as different active TB generation times. In a study by Gómez-Reino *et al*., active TB generation times were determined after anti-TNF therapy was initiated. Infliximab was found to induce active TB in 1–8 months, adalimumab in 12 months, and etanercept in <2.5 months.[24] Studies on TB risk increase that related TNF-α inhibitors usage listed in Table 2.

Discussion

TNF-α has an effective role in body defense. It provides lymphocyte migration to the primary focus of the patient infected with *M. Tuberculosis* and lymphocytes etc. gets a significant role in the creation of granulomas surrounded by cells. In addition, TNF-α is wanted for the continuation of granulomas. By anti-TNF treatment, the continuity of the granuloma is suppressed and the threat of TB development increases. This risk has been determined in many researches.[53,54] WHO recommends that all patients who will begin Anti-TNF therapy be tested systematically and treated for LTBI if indicated. Tuberculin skin test (TST) or IFN gamma release assay (IGRA) tests can be used to diagnose LTBI. In patients who does not show any symptoms of TB, active and positive for TST or IGRA, chest radiography ought to be demanded to exclude active TB. If the radiography is negative, LTBI therapy is specified.[55]

TB is a bacterial infection gave rise to the *M. tuberculosis bacillus*. It is forecasted that one third of the world is contaminated with the *bacillus M. tuberculosis*.[56] There

Table 2: Studies list of tuberculosis risk increase that related tumor necrosis factor-alpha inhibitors

Drug	Study population disease	Tuberculosis occurred cases/total anti-TNF used patients	References
Infliximab	Rheumatoid arthiritis	525/100.000	[49]
Infliximab, etanercept and adalimumab	Rheumatoid arthiritis	230/62.321	[53]
Infliximab, etanercept	Rheumatoid arthiritis	2/90 - Infliximab 0/103 - Etanercept	[54]
Infliximab, etanercept and adalimumab	Rheumatoid arthiritis, ankylosing spondylitis, psoriatic arthritis	2/179	[44]
Infliximab, etanercept and adalimumab	Rheumatoid arthiritis, ankylosing spondylitis, psoriatic arthritis	3/192 (2 infliximab and 1 etanercept)	[55]
Infliximab, etanercept, adalimumab, anakinra, rituximab	Rheumatoid arthiritis, ankylosing spondylitis	14/53 (5 infliximab, 2 etanercept, 1 adalimumab, 6 others)	[45]
Infliximab, etanercept and adalimumab	Rheumatoid arthiritis	144/100.000 adalimumab 136/100.000 infliximab 39/100.000 etanercept	[49]
Infliximab, etanercept, and adalimumab	Rheumatoid arthiritis	51/100.000 infliximab 47/100.000 adalimumab 20/100.000 etanercept	[56]

TNF: Tumor necrosis factor

is an asymptomatic silent phase when the *bacillus* enters the body extend over diseases symptoms occur that called as LTBI. During LTBI phase, there is no active disease in the body. LTBI can in turn active TB with the impaired of general resistance of the body with diabetes, stress, etc. TNF-α inhibitors, suppresses the TNF-α release and this cause impairment of mycobacterium granuloma formation via TNF-α and results with TB flaming. Many studies have found that the rate of TB enhances by TNF-α inhibitors. For this reason, TB diagnostic tests are performed before anti-TNF treatment, and treatment is not initiated in active TB patients. Chemo-prophylactic treatment is started in patients with LTBI findings before anti-TNF therapy.[1,12] TB, which is one of the serious adverse effects of TNF-α inhibitors and the risk of its occurrence compared to TNF-α inhibitors, LTBI diagnosis and treatments were emphasized in this review.

As a result; the increased risk of TB with the use of TNF-α inhibitors in many diseases, especially rheumatological diseases, has been proven by studies. TB diagnostic tests should be performed before anti-TNF treatment, and anti-TNF therapy should not be started in patients with active TB. If TB improves along anti-TNF therapy, TNF-α therapy should be discontinued. Screening should be done routinely, especially in countries with high TB incidence. Chemoprophylactic treatment should be started 1 month before anti-TNF treatment in patients with LTBI. In this study, it was aimed to underline the subject that it is important to get attention to related side effects of anti-TNF therapies. Before to begin treatment of targeted diseases, necessary tests should be done cautiously.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

There is no need for ethics committee approval.

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Conflict of Interest

There is no conflict of interest to declare.

Author Contributions subject and rate

- Şükran Erik (21%): Study conception and design
- Esmanur Bülbül (24%): Data collection, Draft manuscript preparation, reviewing results, approving final version.
- Çiğdem Sevim (19%): Analysis and interpretation of results.
- Seda Eren Keskin (18%): Draft manuscript preparation.
- Mehtap Kara (18%): Data collection.

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