

Risk of Infections in patients using Anti-TNF Medications: A Literature Review

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Abstract

The paradigm for treating chronic Autoimmune Rheumatic Disorders (ARDs) has changed thanks to biologic disease-modifying anti-rheumatic medicines (bDMARDs), however one of its most significant adverse effects is an elevated risk of infections. The current research assessed the incidence, severity, and type of infections in ARD patients on bDMARDs. Disease activity is interwoven with both infectious and chronic inflammatory diseases. Infections are more likely to occur in people with Rheumatoid Arthritis as high disease activity actually reflects persistent inflammation, which may weaken immunity and encourage the spread of various types of infections. Those with RA had an adjusted risk of being hospitalized with an infection that was two times greater when age, sex, concomitant conditions, and prescription medication use were taken into consideration. The risk of mycobacterial infection appears to be lowest with Etanercept (ETN) and highest with Adalimumab (ADA) and Infliximab (INF). Centers of Disease Control and Prevention (CDC) recommends administration of shingles vaccine to all individuals who are on Tumor Necrosis Factor (TNF) inhibitors to prevent Skin and Soft Tissue Infections (SSTI).

Introduction & Background

The phrase "rheumatic disease" refers to a broad range of conditions that primarily impact the joints, tendons, ligaments, muscles, and bones but also manifest in a wide variety of extra-skeletal symptoms. Pain, stiffness, and swelling in the affected areas are the distinctive signs [1]. RA is more of a focus of this article since it affects a large portion of the population.

A variety of intracellular molecular processes, including, nuclear factor (NF- κ B) mediated inflammation and proliferation, apoptosis (via caspase-8 or fas-associated death domain [FADD]) are triggered by the interaction between TNF- α and its receptors. The flowchart in Figure 1 is a conceptual model developed to demonstrate the signaling pathways of TNF- α [14].

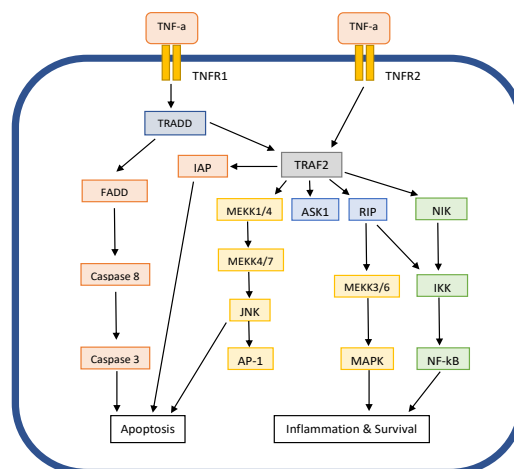


Figure 1: TNF- α Signalling Pathway

TNF- α – Tumor Necrosis Factor alpha

TNFR1 – Tumor Necrosis Factor alpha Receptor 1

TNFR2 – Tumor Necrosis Factor alpha Receptor 2

TRADD – TNF-R1-associated Death Domain Protein

FADD – Fas-associated Death Domain

IAP – Inhibitors of Apoptosis

TRAF2 – TNF Receptor-associated Factor

MEKK – MAPK/ERK

MAPK – Mitogen-activated Protein Kinase

ERK – Extracellular-signal-regulated kinase

JNK – c-Jun NH₂-terminal kinases

AP-1 – Activator Protein-1

ASK-1 – Apoptosis Signal-regulating Kinase-1

RIP – Receptor-interacting Protein

NF- κ B – Nuclear Factor-kappaB

NIK – NF- κ B inducing kinase

IKK – Inhibitory κ B Kinase

Rheumatoid arthritis (RA) affects more than 2.5 million people in the United States, and 1% of people worldwide are likely to be affected by the condition [2]. RA is an autoimmune symmetrical chronic inflammatory polyarthritis usually affecting the fingers, wrists, feet, and ankles that, if left untreated, may lead to joint erosions, deformities, and severe disability. Joint stiffness that is typically worse in the morning and after inactivity, fever, and painful, warm, swollen joints are some of the signs and symptoms of RA. RA also affects other parts of the body apart from the joints, and it may be especially difficult to treat these extra-articular manifestations, such as subcutaneous nodules, lung signs, vasculitis, and inflammatory eye disease.

According to the RA therapy recommendations, commencing with a traditional DMARD (tDMARD), such as methotrexate (MTX), is the first line of management for individuals with active disease. In the absence of a sufficient response to one or more tDMARDs, and depending on prognostic considerations, the introduction of a biologic anti-TNF (Tumor Necrosis Factor) medication, or biologic disease-modifying anti-rheumatic medicines (bDMARDs), is usually the next therapy option advised [3].

TNF-alpha (TNF-a) is a cytokine that plays a key role in inflammation and it is a trimeric protein that monocytes, macrophages, B-cells, T-cells, and fibroblasts all manufacture. The synthesis of IL-1, IL-6, IL-8, granulocyte monocyte-colony stimulating factor (GM-CSF), and intracellular adhesion molecule-1 (ICAM-1) expression in fibroblasts are all induced by this molecule. TNF-a plays a crucial and major role in RA, and the synthesis of the cytokines indicated above is decreased when this protein is blocked [4]. A total of five anti-TNF medications that all bind TNF-a are available on the market today: Adalimumab (ADA), Certolizumab Pegol, Etanercept (ETN), Golimumab, and Infliximab (INF). The use of biologics is linked to significant improvements in illness symptoms and manifestations, with the slowing of radiographic deterioration in inflammatory arthritis serving as an additional advantage [5].

When weighing the risks and advantages of using biologics for a patient with systemic autoimmune diseases, it is obvious that the benefits must outweigh the risks [6]. The influence of medication-induced imbalance on the immune system, cofactors, and intermediate factors is what leads to adverse drug reactions [7].

TNF-a can exist in both soluble and trans-membranous forms. The trans-membranous form of TNF-a (tm TNF-a), which may also function as a receptor and trigger an intracellular cascade in carrying cells, is crucial in managing granulomatous inflammatory conditions. ADA and INF seem to have the highest risk of infection and the development of Latent Tuberculosis Infection (LTBI), while ETN appears to carry the lowest risk [15, 16]. Despite the fact that all anti-TNF medications neutralise TNF, which disrupts the granuloma that typically confines Mycobacterium, ETN may have an alternative effect on immunity that would enable the granuloma to regenerate, therefore reducing bacillary dispersion [17]. According to one research, there were more incidences of Non-Tuberculous Mycobacterial (NTM) infection than TB in those who used anti-TNFs, although the risk was greater for TB than for NTM disease overall. Surprisingly, the risk of NTM connected to Leflunomide and other highly immunosuppressive medications than the risk associated with anti-TNF medications [18, 8].

The anti-TNF medication used and the country undergoing analysis both influenced the annual incidence rate. Therefore, before starting anti-TNF medication in patients with Rheumatic Diseases, it is crucial to create an accurate latent TB infection screening technique. Implementing guidelines for screening and (prophylactic) treatment of latent TB infections prior to starting anti-TNF medication may lower the infection rate.

Other infections

Patients on anti-TNF treatment were believed to acquire Skin and Soft Tissue Infections (SSTI), perhaps as a result of TNF's function in cutaneous immunity. The stimulation of cutaneous endothelial cells, which results in the migration of inflammatory cells to the skin, is indeed mediated by the important cytokine TNF [12]. Anti-TNF therapy increases the incidence of Shingles, which is significant since Shingles has a high morbidity rate. In British Society for Rheumatology Biologics Register, the anti-TNF group saw roughly 2% annual Shingles incidence. Early on after starting anti-TNF medication, the risk of SSTI and Shingles was highest [19]. Regardless of prior exposure status, the Centers of Disease Control and Prevention (CDC) in the USA has advised that all persons over the age of sixty be administered the shingles vaccine (Zostavax).

Biological drugs raise the risk of contracting infections, from minor respiratory and urinary tract infections to serious infections like pneumonia, activation of latent tuberculosis, and hepatitis B and C infection [8,1].

The illness itself (via altered immunologic function), as well as comorbidities and medication, are likely to be contributing factors in this. Although it is thought that RA alone raises the risk of infection, it is presently uncertain how much RA alone could do so without taking into account other relevant variables like DMARD medication [3]. The objective of the review is to summarize the relationship between the overall risk of infections and the usage of anti-TNF drugs in people with rheumatic disease.

Review

Search Methods

We collected and reviewed articles from 2012 to 2022. The database used was PubMed and PubMed Central. Keywords used: Rheumatoid Arthritis, Rheumatic Disease, Anti-TNF medications, TNF inhibitors, Infections, Hospitalized infections, Tuberculosis, opportunistic infections.

Discussion

This section will discuss the many types of infections caused by anti-TNF medication as well as the patient risk factors linked with infection. In addition, a summary of several clinical research confirming the recommendations to lower the risk of infection has been provided.

Patient Risk Factors

Patients with RA had a higher risk of infection than those with Spondyloarthropathies, with over fifty percent of RA patients having an infection. Gender was the second factor that seemed to enhance the risk of infection in individuals taking anti-TNF drugs. Over a third of the women had an infection. The female to male Incidence Rate Ratio (IRR) was 2.8% (12.3% and 4.4%, respectively, per 100 patient-years) probably due to genetic factors [1]. It was shown that individuals with co-morbidities had a greater incidence of infection (23.88%) than those without (10%). In 19.14% of the patients, co-morbidities such as hypertension, diabetes, and ischemic heart disease were detected.

Although low dosage CS or MTX is not contraindicated, the CDC advises against administering the vaccination to anyone who receives anti-TNF medication since it is a live vaccine and caution is required in people who are immunocompromised [20]. According to Skalkou et al., using biologic medicines to treat systemic inflammatory diseases, in particular anti-TNFs, may cause paradoxical effects that affect the balance of cytokines and alter immune-mediated pathways, which might result in surprising clinical syndromes like Pyoderma Gangrenosum [21]. However, one study stated that, although no association was found between anti-TNF and SSTI, they did discover hospitalized SSTI as a significant risk factor for mortality throughout the study period [2].

TNF- α prevents Hepatitis B virus (HBV) replication, however in those with chronic hepatitis, this cytokine causes liver damage. TNF- α inhibition makes it easier for HBV to replicate by enabling it to get past the host's immune system's antiviral defences [22]. Studies have shown that individuals who are Hepatitis B Surface Antigen (HBsAg) negative and Hepatitis B Core Antibody (anti-HBc) positive are at risk of HBV reactivation [23], hence it is advised that these patients be monitored closely while receiving anti-TNF medication.

The primary mechanism for eliminating yeast following a systemic infection is an innate immune response. In the published literature, the use of at least one immunosuppressive drug, primarily CS, in conjunction with anti-TNF treatment was recorded in 98% of invasive fungal diseases such as Histoplasmosis, Candidiasis and Aspergillosis [24].

Aseptic Meningitis is reported in 0.55% of individuals treated with TNF- α inhibitors, however there were no incidences in people using conventional DMARDs or other biological medications. Rheumatoid Meningitis's pathophysiology is yet unclear, however inflammatory cytokines may play a part. When patients received high doses of steroids, a quick and complete neurological recovery was seen [25].

In one case report, a patient with severe RA and concurrent Human Immunodeficiency Virus (HIV) infection was described. Despite having a positive HIV infection status, they claimed that their patient had a great response to ETN, leading to full clinical remission of RA status with reduced joint swelling and lowered acute-phase inflammatory markers [26].

Diabetes mellitus had the greatest infection incidence rate among these disorders. [7]. Various studies states that the existence of chronic pulmonary comorbidity, increasing age, a mean MTX dose of >8 mg/week, a higher mean C-Reactive Protein, and a mean oral Prednisolone dosage of >10 mg/day have been found as independent risk factors for infections [9].

Since the majority of research have revealed a correlation between gender and infection risk in anti-TNF-treated patients, it is possible that female-specific genetic characteristics are responsible for these elevated risks, independent of the kind of inflammatory rheumatic illness. Focus should be placed on determining if there is a difference in infection risk based on gender; if so, medication regimens might be altered and women receiving anti-TNF drugs should be handled with more care.

Hospitalized Infections

When taking into account factors including age, sex, comorbid diseases, and prescription drug usage, those with RA had a two-fold higher adjusted risk of being hospitalized with an infection than people without RA. In a population-based analysis, individuals with RA had a rate ratio of 1.88 (95% CI 1.71 to 2.07), which was substantially higher than that of patients without RA for infections that required hospitalisation [5]. According to a Sakai et al., long-term use of TNF antagonists for up to three years was a risk factor for hospitalized infections (Relative Risk 1.97, 95% Confidence Interval 1.25-3.19), although the risk varied depending on the length of time the drug was used [9]. One study claimed that, if young patients on 7.5 mg/day of Prednisone were able to stop taking Glucocorticoids after starting an anti-TNF treatment, the total incidence of hospitalized infections would decrease as a result [10]. According to Yun et al., using ETN, IFN in RA patients who had previously been exposed to a biologic drug is associated with a higher one-year risk of serious infection than using Abatacept [7]. Curtis et al. found that, only individuals who had been exposed to INF showed a substantial increase in severe infections within the first six months after starting anti-TNF medication compared to those who had just taken MTX [11]. The relationship between TNF antagonists and infections in RA patients was examined in research from European biologics registries. Some studies suggest that TNF antagonists did not raise the risk for hospitalized infections [9].

Therefore, individuals with a stable HIV infection status and CD4 lymphocyte counts may benefit from anti-TNF medications, such as ETN, for the treatment of HIV-associated arthritis.

Limitations

This literature review has several limitations. First, No attempt was made to look for unpublished or original data; instead, our search was limited to published research. Second, the included research was restricted to the English language and two databases only from the previous ten years, meaning that excellent articles from preceding years may have been missed. Third, Heterogeneities were significant, particularly for severe infections and general infections, and this could not be explained by subgroup analysis of various kinds of mono-antibodies or concurrent CS medication, since infections are impacted by a range of variables including research designs and clinical characteristics. Moreover, these variations were seen in the research we considered.

Conclusion

Anti-TNF medication usage by rheumatologic patients has been steadily rising over the last several years, and data on their safety are still being gathered. We conducted a literature analysis on the subject since it was unclear how these agents might affect the risk of SSTI, general infections, TB, and hospital-acquired infections. The incidence of infection was shown to be higher in female RA participants with co-morbidities, with diabetes mellitus having the highest incidence rate. When TNF inhibitors were administered for a prolonged period of time, up to three years, the incidence of hospitalized infections was increased by a factor of two for those with RA. The risk of general infections more than triples when anti-TNF drugs are taken with CS. ADA and INF seem to carry the greatest risk of mycobacterial infection and the development of LTBI while, ETN seems to have the lowest risk, due to an alternative effect that would enable the granuloma to regenerate, therefore reducing bacillary dispersion. CDC recommends administration of shingles vaccine to all individuals who are on TNF inhibitors in order to prevent SSTI. For patients to provide their informed consent before to beginning biologic therapy, doctors must first educate them about the potential for infection.

We can understand that the risk of hospitalized infections differs across the various bDMARDs used to treat RA. The different immune system components that these medications target might explain the differential in vulnerability to adverse drug responses (such as hospitalized infection, cancer, and death) identified for these agents.

General Infections

Both infections and chronic inflammatory illnesses are intertwined with disease activity. In actuality, high disease activity is a reflection of chronic inflammation, which may compromise the immune system and facilitate the rise of infections. Pneumonia is the most frequent bacterial infection associated with TNF inhibitors, followed by skin or soft tissue infection, joint/bone and urinary tract infection [12]. The findings related to treatment type are the most intriguing. TNF inhibitors by itself raises the risk of infection. It more than triples when taken with Corticosteroids (CS) compared to DMARDs alone. DMARDs, particularly MTX, seem to pose less of an infection risk. The absence of pro-infective effects from MTX, may be partially attributed to its anti-methylenetetrahydrofolate reductase activity, which has the ability to limit bacterial and viral multiplication [13]. According to a Pap et al., RA subjects used considerably more DMARDs and CS ($p=0.016$ and 0.032 , respectively). However, they could not discover any statistical relevance between the emergence of infections and the usage of CS or DMARDs after adjusting for the presence of infection [1]. Patients on anti-TNF drugs were more likely to have had at least one flu shot, according to Schneeweiss et al. Additionally, the multivariate analysis revealed that receiving an influenza vaccination at least once was substantially protective against the overall risk of getting an infection [13]. One of the factors influencing the risk of infection could also be the age of the patients who are on anti TNF therapy and the duration of anti TNF therapy. However, in recent years, the risk has steadily reduced, perhaps as a result of improved treatment criteria and recommendations.

Mycobacterial Infections

TNF- α aids in protection against a variety of infectious pathogens, including Mycobacterium Tuberculosis (TB), by binding to its transmembrane receptors TNFR1 and TNFR2. Studies performed both in vitro and in vivo have shown that TNF- α is required for phagocytosis or granuloma development to be effective in treating mycobacterial infections [6].

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