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EVALUATION OF DRUG SIDE EFFECT PROFILES IN PATIENTS WITH INFLAMMATORY RHEUMATIC DISEASE USING TUMOR NECROSIS FACTOR-ALPHA INHIBITORS

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Abstract

Aim: The use of tumor necrosis factor-alpha (TNF-α) inhibitors is associated with potential side effects such as infusion reactions, anaphylaxis, development of infection, and cutaneous and paradoxical side effects. We evaluated the side effects observed with the use of these agents in patients with rheumatic diseases followed by TNF-α inhibitors in our clinic.

Material and Methods: Patients admitted to our clinic in the last 5 years with a diagnosis of inflammatory rheumatic disease and treated with TNF-α inhibitors were included in the study. Demographic data, diagnoses, treatment, and side effects were recorded. Statistical analysis was performed using SPSS version 21.0.

Results: Forty-two patients with rheumatic disease receiving TNF-α inhibitors were analyzed. Infliximab had cutaneous side effects in 26 patients, including one infusion reaction and two cases of anaphylaxis. These side effects included allergic rash, psoriasis, bullous pemphigoid, dermatitis herpetiformis, erythema AB Igne, dermatitis, and small vessel vasculitis. Golimumab caused neutropenia in two patients. The other adverse events were cervical intraepithelial lesions and Kaposi's sarcoma in one patient with psoriatic arthritis. Infections were the most common adverse events and were reported in four patients.

Conclusion: TNF-α inhibitors are widely used in the treatment of inflammatory rheumatic diseases. These agents have side effects, and it is important to be aware of and cautious about potential side effects.

Keywords: TNF alpha inhibitors, rheumatic diseases, side effects, paradoxical effects

INTRODUCTION

Tumor necrosis factor-alpha (TNF-α) is produced by many immune system cells, such as activated macrophages and lymphocytes. It is involved in inflammation and cell necrosis, proliferation, apoptosis, and differentiation. TNF-α exists in two forms: transmembrane and soluble. Both forms bind to TNF receptors (TNFR1 and TNFR2) but have different effects. TNFR1 is involved in cytotoxic and proinflammatory responses, whereas TNFR2 mediates cell activation, migration, and proliferation (1-5).

TNF-α inhibitors such as etanercept, infliximab, adalimumab, golimumab, and certolizumab can be used in autoimmune diseases in which TNF-α is involved in the pathogenesis, such as inflammatory bowel disease, rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis, and non-infectious uveitis. While etanercept inhibits both TNF-α and TNF-beta,

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infliximab, adalimumab, and golimumab specifically bind to TNF-α, and certolizumab is a modified monoclonal antibody that does not contain the fragment crystallizable (Fc) portion (6).

The side effects associated with TNF-α are divided into groups such as alpha, beta, gamma, delta, and epsilon. In alpha-type reactions, clinical findings include flu-like symptoms, arthritis, arthritis, and myalgia and occur because of excessive cytokine secretion (7). Beta-type reactions are immune-mediated hypersensitivity reactions. Protein components can cause immune complex development, complement activation, or mast cell release. Beta-type reactions include IgE-mediated type 1 reactions, type 2-3 hypersensitivity reactions, and T cell-mediated late-type reactions. Gamma-type reactions describe a reduced immune response or immunodeficiency. Examples of this group of side effects include infections, the development of malignancies, and autoimmunity. The development of autoantibodies such as antinuclear antibodies and antiphospholipid antibodies and clinical conditions such as cutaneous vasculitis, uveitis, psoriasis, and demyelinating disease are mediated by these reactions. Clinical regression after discontinuation of treatment supports a cause-and-effect relationship. Delta-type reactions can be defined as the development of autoantibodies and antibody-mediated cross-reactivity against molecular targets or structurally similar proteins. Epsilon-type reactions include non-immunologic side effects of biological agents. The mechanism of these side effects is unknown; the development of heart failure, asthma exacerbation, and granulomatous disease are examples of these reactions (7).

In our study, we evaluated drug side effect profiles in patients with inflammatory rheumatic disease admitted to a rheumatology clinic and treated with TNF-α inhibitors.

MATERIAL AND METHODS

Patients admitted to our clinic in the last 5 years with a diagnosis of inflammatory rheumatic disease and treated with TNF-α inhibitors were included in the study. Demographic data, rheumatologic disease diagnoses, treatment information, and side effects were retrospectively recorded. The observed side effects were classified as infusion reactions, anaphylaxis, hematologic side effects, malignant/premalignant lesions, infectious side effects, cutaneous side effects, and other side effects. The study was approved by the Aydın Adnan Menderes University Non-interventional Clinical Research Ethics Committee (approval no: 2023/17, date: 03.08.2023).

Statistical Analysis

The data of the study were evaluated using SPSS 21.0. Descriptive statistics are given as mean ± standard deviation, median (25-75p), frequency (n), and percentage (%). Univariate and multivariate statistical methods were planned to be used according to the distribution structure of the data. The chi-square test was used to investigate whether two or more variables were independent of each other. Data were calculated at 95% confidence interval, and p-value<0.05 was considered statistically significant.

RESULTS

In this study, 42 patients on TNF-α inhibitors were analyzed. The patients were equally male and female with a mean age of 49.4 years. Twelve patients had RA, 28 had spondyloarthropathy, one had Behçet's disease, and one had juvenile idiopathic arthritis.

Of these patients, 8 were on adalimumab (19%), 7 on etanercept (16.6%), 5 on golimumab (11.9%), 14 on infliximab (33.3%), and 8 on certolizumab. Infliximab treatment resulted in one infusion reaction and two cases of anaphylaxis. In addition, 26 patients experienced cutaneous side effects. Among the side effects observed were allergic rash in 9 patients, psoriasis in 12 patients, bullous pemphigoid in 1 patient, dermatitis herpetiformis in 1 patient, erythema aligned in 1 patient, dermatitis in 1 patient, and small vessel vasculitis in 1 patient. Specifically, 6 of the patients with allergic rash were diagnosed with AS, 1 with enteropathic arthritis, and 2 with RA and are being treated with various biological agents. In the case of psoriasis, 6 patients had palmoplantar pustulosis and 6 had generalized psoriasis.

Golimumab treatment caused neutropenia in two patients. Cervical intraepithelial lesions occurred in one patient treated with infliximab and Kaposi's sarcoma in a male patient with psoriatic arthritis. Infections were the most common side effect of TNF-α inhibitor use. We reported serious infections in four patients. These infections included bacterial pneumonia, aspergillus pneumonia, and tuberculosis. The first patient was a 66-year-old woman who received adalimumab treatment for RA and was hospitalized for bacterial pneumonia. The other patient was a 52-year-old male patient who was diagnosed with enteropathic arthritis, received certolizumab treatment, and had aspergillus pneumonia. Tuberculosis infection was detected in two of our patients. One of these patients was a 59-year-old woman with pulmonary tuberculosis who received infliximab treatment and was diagnosed with psoriatic arthritis. The other patient diagnosed with tuberculosis was a 26-year-old woman who was diagnosed with AS and receiving certolizumab treatment. This patient presented to us because of widespread ascites in the abdomen and was diagnosed with tuberculous lymphadenitis. The side effects observed in patients with rheumatic diseases using TNF-α inhibitors are shown in Table 1.

Table 1. Side effects in patients with rheumatic diseases using tumor necrosis-alpha inhibitors

Side effects	Adalimumab	Etanercept	Golimumab	Infliximab	Certolizumab
Infusion reaction				n=1	
Anaphylaxis				n=2	
Hematological side effects			n=2		
Cervical intraepithelial neoplasia				n=1	
Kaposi's sarcoma				n=1	
Pneumonia	n=1				n=1
Tuberculosis				n=1	n=1
Allergic rash	n=4	n=2	n=1	n=2	
Palmoplantar pustulosis	n=1	n=1	n=1	n=2	n=1
Psoriasis		n=2	n=1	n=1	n=2
Bullous pemphigoid				n=1	
Dermatitis herpetiformis				n=1	
Erythema AB Igne		n=1			
Small-vessel vasculitis				n=1	
Dermatitis					n=1
Sarcoidosis	n=1				
Uveitis		n=1			
Erectile dysfunction					n=1
Asthma exacerbation	n=1				
Psoriasis flare-up					n=1

DISCUSSION

Some reactions may occur with the use of TNF-α inhibitors, which are effective and safe for treating inflammatory diseases. These reactions may be acute or delayed hypersensitivity reactions (8). Infusion reactions or anaphylaxis may occur with infliximab (9,10). Previous studies have reported anaphylaxis rates ranging from 8% to 23% for infliximab (11). Acute reactions can be minimized using steroids or antihistamines.

TNF-α inhibitors may also have various dermatological side effects, including local reactions, serious infections, malignant lesions, and immune-mediated reactions (12,13). Bullous pemphigoid, dermatitis herpetiformis, and erythematous hyperpigmented lesions have been reported in some patients (14,15). A male patient on etanercept for AS developed erythematous hyperpigmented lesions on both ankles. Dermatological evaluation determined that the erythema was unrelated to treatment and was probably caused by heat exposure. Skin findings resolved spontaneously during follow-up (16). Another patient with AS on certolizumab treatment developed erythematous skin lesions on the extremities, which were treated locally and considered unrelated to the treatment. During our follow-up, urticarial skin eruptions were observed in 8 patients, 3 associated with adalimumab, 2 with infliximab, 2 with etanercept, and 1 with golimumab.

Paradoxical reactions may occur during treatment with some biological agents and may lead to psoriasis and inflammatory bowel disease (16). We reported paradoxical psoriasis in 12 (26.2%) of our patients followed by TNF-α inhibitors; six of the patients presented with disseminated disease. Palmoplantar pustulosis was observed in patients on infliximab, certolizumab, etanercept, adalimumab, and golimumab. The skin lesions of four patients with palmoplantar pustulosis resolved with steroid treatment and a change of biological agent. Different drugs have been associated with these reactions, but switching to a different anti-TNF-α agent may help relieve symptoms. Another case of infliximab-associated palmoplantar pustulosis treated with high-dose steroids and methotrexate. The patient is still being followed up at our clinic.

Hematologic side effects of TNF-α inhibitors are rare but may include thrombocytopenia, neutropenia, and aplastic anemia (17,18). The risk of malignancy is not increased with these drugs, but the risk of cervical intraepithelial neoplasia may be higher

in women with RA (17-19). Both of our patients who developed neutropenia were receiving golimumab treatment, and neutropenia regressed with treatment change. Infections are common with TNF-α inhibitors and the risk is highest in the first year of treatment (20). In our clinic, TNF-α inhibitor-associated serious infections were observed in four patients (9.6%): bacterial pneumonia in one patient (2.4%), fungal pneumonia in one (2.4%), and tuberculosis infection in the other two (4.8%).

Sarcoidosis-like reactions may occur with the use of TNF-α inhibitors (21). TNF-α inhibitors may also cause sexual dysfunction, but this may improve with treatment (22). In our study, sarcoidosis developed in only one patient treated with adalimumab. During our follow-up, erectile dysfunction due to certolizumab use was reported in only one patient. The patient's symptoms regressed with the treatment change. There are case reports in the literature regarding the development of mild asthma associated with adalimumab, etanercept, and infliximab (23). Asthma attacks were intensified in a patient who was being followed up in our clinic and was taking adalimumab for RA. The disease was controlled when the treatment was discontinued, but attacks recurred when the drug was restarted. Caution should be exercised in these patients with a family history, and routine asthma treatment recommendations should be applied (23).

CONCLUSION

In conclusion, TNF-α is critical in rheumatic diseases, and its inhibitors are widely used in inflammatory rheumatic diseases. However, these agents have side effects, and it is important to be aware of and cautious about the potential side effects that may result from their frequent use.

Ethics

Ethics Committee Approval: The study was approved by the Aydın Adnan Menderes University Non-interventional Clinical Research Ethics Committee (approval no: 2023/17, date: 03.08.2023).

Informed Consent: Informed consent was not obtained due to the nature of this study.

Authorship Contributions

Surgical and Medical Practices: C.D., G.S., S.Ç., T.Ş., Concept: C.D., G.S., S.Ç., T.Ş., Design: C.D., G.S., S.Ç., T.Ş., Data Collection or Processing: C.D., G.S., S.Ç., T.Ş., Analysis or Interpretation: C.D., G.S., S.Ç., T.Ş., Literature Search: C.D., G.S., S.Ç., T.Ş., Writing: C.D., G.S., S.Ç., T.Ş.

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