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Evaluation of long-term effect of tuberculosis chemoprophylaxis in patients using anti tumor necrosis factor alpha agents

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ABSTRACT

Aim: There is an increased risk of tuberculosis (TB) in patients with rheumatoid diseases (RD) treated with antitumor necrosis factor (TNF) alpha agents. Screening and, if necessary, chemoprophylaxis is recommended in patients undergoing anti TNF alpha treatment. This study aimed to determine the incidence of active TB due to long term anti TNF alpha usage in patients with RD and to evaluate the effectiveness of tuberculosis chemoprophylaxis regimen.

Material and Method: Patients treated with anti TNF alpha agents for more than 5 years with RDs were evaluated retrospectively. Demographic and clinical characteristics, use of chemoprophylaxis, laboratory tests before and after anti TNF alpha treatment and development of TB were examined.

Findings: A total of 150 patients (79 male [52.7%], 71 female [47.3%]) with a mean age of 45±13 years were evaluated. The tuberculosis rate over 5 years follow up was found as 1.3%. One male developed pulmonary TB 5 years and 1 female developed miliary TB 10 years after the beginning of anti-TNF alpha therapy despite chemoprophylaxis with isoniazid. The mean number of neutrophils, lymphocytes ($p<0.05$) and the N/L ratio was significantly decreased after anti TNF alpha treatment ($p<0.0001$).

Conclusion: In an RD patient treated with anti TNF alpha agents, the risk of TB should be kept in mind even after 10 years. Regular monitoring should be considered for long term TNF antagonist therapy.

Keywords: Anti TNF alpha, tuberculosis, isoniazid, chemoprophylaxis, long term effectiveness.

INTRODUCTION

The role of TNF alpha in the pathogenesis of rheumatic diseases (RD) is immunomodulation, particularly as a proinflammatory cytokine (1).

The biologic antagonists of TNF alpha (anti TNF alpha), represent a major advance in the management of RD. However, an increased risk of tuberculosis (TB) in patients with RD who treated with anti TNF alpha agents has been demonstrated by several researchers (2,3). 2-fold elevated risk of TB by anti TNF alpha agents was reported at a systematic meta-analysis of randomized clinical trials (4). Guidelines recommends implementation of screening and, if necessary, chemoprophylaxis in patients undergoing anti TNF alpha treatment (5). Several studies reported higher incidence of TB among RD patients who treated with anti TNF alpha than without anti TNF alpha, despite chemoprophylaxis (6,7). This study aimed to determine the incidence of active TB due to anti TNF alpha usage in patients with RD for a long time period and to evaluate the effectiveness of an antituberculosis chemoprophylaxis regimen.

MATERIAL AND METHOD

This retrospective study included patients with RDs (Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis and psoriatic arthritis) that treated with anti TNF-α agents, admitted to University of Health Sciences, Ümraniye Training and Research Hospital, Chest Diseases Outpatient Clinic between January 10, 2010 and January 10,2020. The study was approved by University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee (235/ June 11, 2020). The trial was conducted in accordance with the Helsinki Declaration principles. Clinical, radiological and laboratory information were collected from our hospital's medical database. Each patient's data

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were observed for at least 5 years from the beginning of assignment, and patient's data were analyzed to evaluate the risk of TB development.

Demographic characteristics including age and gender, and clinical characteristics including RD and development of TB were examined. In order to determine active and latent TB, all patients had undergone a tuberculin skin test (TST) and a postero-anterior chest radiograph (CXR). According to national tuberculosis guideline, patients with latent tuberculosis infection (LTBI) received isoniazid (INH, H, 5 mg/kg with maximum dose 300 mg/d) for 9 months. LTBI was diagnosed as having a positive PPD (≥5mm)result or a positive quantiferon TB test in presence of a negative PPD (8). Anti TNF alpha treatment was started 1 month later than TB chemoprophylaxis.

Statistical Analysis

Patient data collected in the study were analyzed with the IBM Statistical Package for the Social Sciences (SPSS) for Windows 21.0 package program (Statistical Package for the Social Sciences, Chicago, IL, USA).

Discrete data were given as frequency and percentage. The mean±Standard deviation for continuous data was given as a descriptive value. The repeated measures of ANOVA test was used for evaluation of pre and post-treatment data. The results were considered statistically significant when the p-value was less than 0.05.

RESULTS

Among the 150 patients included in this study, 79 were male (52.7%), 71 were female (47.3%), and the mean age was 45±13 years. 63 (42.0%) had Crohn's disease, 41 (27.3%) had rheumatoid arthritis, 33 (22.0%) had ankylosing spondylitis, 6 (4.0%) had ulcerative colitis and 7 (4.7%) psoriatic arthritis.

There were 18 patients with hypertension (12%), 8 patients with diabetes mellitus (5.3%), 3 patients with asthma (2%), 2 patients with chronic obstructive pulmonary disease and 3 patients with coronary arterial disease.

Sixty six (44%) of the patients received adalimumab, 35 (23.3%) of the patients received infliximab, 17 (11.3%) of the patients received etanercept, 12 (8.0%) of the patients received golimumab, 10 (6.7%) of the patients received certolizumab. Ten patients (6.7%) received other anti TNF alpha agents such as tofacitinib, vedolizumab and abatacept. Additionally 61 (40.7%) of the patients received immunosuppressive drugs (**Table 1**). The mean number of peripheral blood cell counts and neutrophil/lymphocyte (N/L) ratio before and after anti TNF alpha treatment was shown in **Table 2**. The mean number of leukocytes were similar before and after treatment (p>0.05) while the mean number of neutrophils and lymphocytes were decreased significantly (p<0.05). The N/L ratio was significantly decreased after anti TNF alpha treatment (2.83±1.819 and 2.19±1.392 respectively, p<0.0001).

Table 1. Clinical, demographic and laboratory features of the patients

		n (%) or mean±SD*
Sex	Female	71 (47.3)
	Male	79 (52.7)
Age (years)		45±13
Follow up duration (years)		6±1
Rheumatoid disease	Crohn's disease	63 (42.0)
	Rheumatoid Arthritis	41 (27.3)
	Ankylosing Spondylitis	33 (22.0)
	Ulcerative colitis	6 (4.0)
	Pseuriatic arthritis	7 (4.7)
Anti-TNF alpha agent	Adalimumab	66 (44.0)
	Sertolizumab	10 (6.7)
	Etanercept	17 (11.3)
	Infliximab	35 (23.3)
	Golimumab	12 (8.0)
	Tofacitinib	4 (2.7)
	Vedolizumab	2 (1.3)
	Abatacept	4 (2.7)
INH chemoprophylaxis		124 (82.6)
TST	Negative (0-4 mm)	28 (18.7)
	Positive (≥5 mm)	122 (81.3)
Quantiferon TB	Not performed	136 (90.7)
	Negative	12 (8.0)
	Positive	2 (1.3)
Developed active TB		2 (1,3)
Additional immunosuppressive agent	None	89 (59.3)
	OCS**	6 (4.0)
	OCS+Leflunomide	5 (3.3)
	OCS+MTX***	7 (4.7)
	OCS+azathioprine	1 (0.7)
	Leflunomide	4 (2.7)
	Leflunomide+MTX	1 (0.7)
	MTX	6 (4.0)
	Azathioprine	27 (18.0)
	OCS+Leflunomide+MTX	4 (2.7)

*SD: Standard deviation, *OCS: Oral corticosteroid, **MTX: Methotrexate

Table 2. Laboratory values before and after anti TNF alpha treatment

	Pre-treatment (mean±SD)	Post-treatment (mean±SD)	p value
Number of leukocytes $\times 10^3$/ml	9758±17743	7604±2178	0.612
Number of neutrophils $\times 10^3$/ml	5367±2219	4440±1747	0.013
Number of lymphocytes $\times 10^3$/ml	2225±814	2415±950	0.003
N/L* ratio	2.83±1.819	2.19±1.392	0.0001

N/L: Neutrophil/lymphocyte.

Among the 150 patients, LTBI was diagnosed in 124 cases (122 had a positive PPD and 2 had a negative PPD but positive quantiferon test result) and were administered isoniazid. Two over 124 patients with LTBI developed active TB, one developed pulmonary TB 5 years after and one developed military TB 10 years after the beginning of anti TNF alpha therapy. Both of the patients had received chemoprophylaxis. Anti TNF alpha therapy was discontinued in patients immediately after the diagnosis of active TB. The characteristics of these patients are shown in the **Table 3**.

Table 3. Characteristics of patients with active TB

Characteristics	Patient 1	Patient 2
Age, years	38	49
Sex	Male	Female
Rheumatoid disease	Crohn's disease	Crohn's disease
Medication for RD	Adalimumab	Infliximab
TST (mm)	9	4
Quantiferon TB	Not perfomed	Positive
Chemoprophylaxis regimen	INH 9 months	INH 9 months
Site of active TB	Pulmonary	Miliary
Interval to active TB	5 years	10 years
Immunosuppressive drug	Yes (MTX)*	No
Number of lymphocytes, pre-treatment, $\times10^3$/ml	3410	780
Number of neutrophils, pre-treatment, $\times10^3$/ml	8690	4770
N/L ratio, pre-treatment	2.54	6.11
Number of lymphocytes, post-treatment, $\times10^3$/ml	3110	1150
Number of neutrophils, post-treatment, $\times10^3$/ml	4220	3820
N/L ratio, post-treatment	1.35	3.32

MTX: Methotrexate

DISCUSSION

To our knowledge this study is unique for the long duration of follow up the RD patients with anti TNF alpha therapy.

Adalimumab, infliximab and etanercept has been licensed and widely used in the treatment of rheumatoid diseases in our country. A nationwide study showed 6-fold increase in relative TB risk due to 2 years anti TNF alpha use in rheumatologic diseases and 4. 7-fold during 1 year anti TNF alpha therapy (9). In our study the patients who received anti TNF alpha therapy were followed at routine quarterly intervals for long term (5-10 years). Tuberculosis was diagnosed in two (1.3%) of 150 patients who were followed up regularly during anti TNF alpha treatment. One of the patient was on the 5th year of treatment and the other one was on the 10th year of treatment. This rate is higher than the incidence of tuberculosis in our country (8). Hanta et al. (10) reported 3 patients who were diagnosed with tuberculosis in the 3-year follow-up of 192 patients with RA, AS and PSA. The rate of active TB in this study (1.5%) was similar with our findings (1.3%). However, our follow up duration was longer than these studies.

Age older than 60 years was independent risk factor for TB among patients with anti TNF alpha treatment in previous studies that were higher than that in our study (11-13).

Tuberculosis is more common among men than women worldwide (14). In our study one of the patient was male and one of the patients was female.

It is reported in the systematic meta-analyses that RA patients treated with anti TNF alpha had increased risk of TB (15). While several studies reported no significantly increased risk of TB infection when anti TNF alpha were used to manage patients with Crohn's disease, a systematic meta-analysis found that the risk of TB was increased by using anti TNF alpha inhibitors in patients with Crohn's disease (16-18).

Most of our patients that we follow up, had Crohn's disease. The reason of the detection of TB, only in Crohn's disease patients, may be due to the clustering of the Crohn's disease cases in our study. The increased number of TB cases among Crohn's disease patients in our study needs to be further addressed in future studies.

The risk of TB according to the classes of anti TNF alpha drugs was found to different. A higher TB risk with infliximab or adalimumab was reported than with etanercept (19). In a study published in 2007 it was found that the risk of TB of patients with RA was 8.9 times higher than the general population. This rate was found to be 30.1 times higher in patients with RA who were treated with infliximab (20). In our study, the patient who received etanercept was diagnosed with miliary tuberculosis.

Latent TB was reactivated despite a chemoprophylaxis in two (1.3%) of the patients.

Our national TB guideline recommends 9 months of isoniazid prophylaxis for the treatment of latent TB infections defined as having a PPD result ≥5 mm or a positive interferon gamma release test such as quantiferon TB, prior to initiation of anti TNF alpha therapy. It was pointed out that the TB chemoprophylaxis could be effective for as long as 19 years and it must be repeated in case of a close contact with active tuberculosis patient (8). The two patients developed active TB denied a close contact with an active TB cases, so the INH prophylaxis was not repeated.

Researchers reported the active TB cases despite INH prophylaxis during maximum 3 years follow up. Sichletidis et al. (21) found that eleven patients developed active TB among 45 patients. In another study of the total

of 255 patients whom were diagnosed with latent TB, 5 patients developed active TB after LTBI treatment and the maximum duration of time to TB after anti TNF alpha initiation was 73,2 months (22).

It was previously shown that the decreased number of lymphocytes is a risk factor for developing TB (23,24). Berhane et al. (25) reported that N/L ratio over 2.7 is a predictive parameter in diagnosis of pulmonary tuberculosis. One of our patient developed TB had a N/L ratio over 2.7 but the other did not. In our study the mean number of neutrophils, lymphocytes and N/L ratio was decreased significantly ($p<0.05$) after anti TNF alpha treatment but as the number of patients developed TB was small we could not show a relation between neither number of peripheral blood cells nor N/L ratio and developing TB.

Compared to the studies in the literature, we observed the patients for longer duration. TB developed in two patients among 124 patients who received INH prophylaxis. It is possible that long-term anti TNF alpha therapy may predispose patients to both de novo TB infection and reactivation of latent TB. Periodic regimens may be more effective for these patients.

Limitations: Only 2 of 150 patients developed tuberculosis so the risk for developing active TB could not be analyzed.

CONCLUSION

As a result of this study, we want to draw attention to the risk of TB development in an RD patient without latent TB. In an RD patient without latent TB, the risk of TB should be kept in mind even after 10 years. Regular monitoring should be considered for long term TNF antagonist therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee (235/June 11,2020).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: None.

Author Contributions: All of the authors declare that they have all participated in the design, execution, collection and analysis of the data and that they have approved the final version.

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