Factors Affecting the Tuberculosis Risk in Patients Receiving Anti-Tumor Necrosis Factor- α Treatment

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Key Words

Tumor necrosis factor- α inhibitors · Tuberculosis · Risk factors

Abstract

Background: Tumor necrosis factor (TNF)- α inhibitors are known to increase the risk of tuberculosis (TB). **Objectives:** To examine the factors associated with an increased risk of TB in patients receiving anti-TNF- α treatment (aTNF- α -T). **Method:** Of 3,094 patients who received aTNF- α -T between 2003 and 2013, a total of 1,964 subjects with a follow-up time longer than 6 months were identified and included in this retrospective analysis. Potential risk factors for the development of TB in patients receiving aTNF- α -T were evaluated. **Results:** Of the 1,964 patients, 1,009 (51%) were male and 955 (49%) were female, with a mean age of 39.7 ± 13.9 years. The primary conditions requiring aTNF- α -T included ankylosing spondylitis ($n = 875$), rheumatoid arthritis ($n = 711$), Behçet's disease ($n = 83$), and others ($n = 295$). Sixteen patients [8 (50%) males and 8 (50%) females; 5 (31.2%) with pulmonary TB and 11 (68.8%) with extrapulmonary TB] developed TB, with a corresponding TB incidence of 466/100,000. No significant associations were found between age, gender, smoking history, pack-years of smoking,

isoniazid (INH) chemoprophylaxis, type of anti-TNF- α agent, use of other immunosuppressive drugs, and the risk of TB ($p > 0.05$). Multivariate logistic regression analysis showed a significantly higher risk of TB in patients diagnosed with Behçet's disease, and a significantly lower risk of TB in patients with a tuberculin skin test wheal ≥ 10 mm in diameter ($p < 0.05$). **Conclusion:** aTNF- α -T is associated with an increased risk of pulmonary or extrapulmonary TB, even when follow-up protocols and INH chemoprophylaxis are implemented, and TB often develops in the later stages of treatment. The risk of TB was higher in patients with Behçet's disease and lower in patients who had a strong tuberculin skin test reaction.

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Introduction

Tuberculosis (TB) is a major global public health problem, with one third of the world's population estimated to be infected with *Mycobacterium tuberculosis*. Although the primary site of involvement is the lungs (pulmonary TB; P-TB) in most cases, other organ systems may also be affected (extrapulmonary TB; EP-TB). Annually, 8.6 million people are infected, representing the second leading

cause of death from an infectious disease worldwide (after human immunodeficiency virus) [1]. Certain biological drugs that have been introduced recently, such as tumor necrosis factor (TNF)- α inhibitors, are known to increase the risk of TB [2–5]. TNF- α inhibitors are increasingly being used for the treatment of a number of immune-related diseases in clinical practice. These agents inhibit TNF- α , which is a key cytokine with an important role in the host defense against infections and in particular against *Mycobacterium* infections through a number of mechanisms. These mechanisms include: formation of granulomas; stimulation of dendritic cell maturation and antigen-specific T cell proliferation; increasing neutrophil adherence, phagocytic activity, and degranulation, and inhibition of the reactivation of dormant bacilli [6–10]. Several guidelines recommend 6 or 9 months of isoniazid prophylaxis (INH-Px) for the treatment of latent TB infections, based on studies which have reported up to a 10-fold increase in the risk of reactivation of latent TB in patients undergoing anti-TNF- α treatment (aTNF- α -T) and a decrease with appropriate chemoprophylaxis in the same group of individuals [6, 11–16].

One of every 4 individuals is estimated to be infected with *M. tuberculosis* in Turkey, with a TB incidence of 22/100,000 [17, 18]. On the other hand, limited data from this country regarding the incidence of TB in patients undergoing aTNF- α -T suggests an 11–40 times higher risk of TB compared to the general population [5, 19–22].

We aimed to determine the risk factors for TB in patients receiving aTNF- α -T in this study.

Study Population and Methods

Pharmacovigilance regulations in Turkey mandate that all patients be screened by chest physicians for TB risk before initiating aTNF- α -T. Between October 2003 and October 2013, a total 3,094 patients were screened for TB risk before initiation of aTNF- α -T for various autoimmune diseases at the Outpatient Unit, Department of Pulmonary Diseases, Cerrahpasa Faculty of Medicine, Istanbul University. Among these, 1,964 patients on regular aTNF- α -T with a follow-up time longer than 6 months were identified and included in this study. The screening was carried out in accordance with the consensus report on using TNF- α inhibitors endorsed by the Rheumatology Society of Turkey [23]. A tuberculin skin test (TST) was performed using the Mantoux method. A standard dose of 5 tuberculin units (0.1 ml) is injected intradermally and evaluated after 48–72 h. The TST result was reported in millimeters as the measured value. If the initial reaction was between 0 and 4 mm in diameter, the TST was repeated 1 or 2 weeks later to evaluate the booster phenomenon. In case of suspicion of active TB, a comprehensive work-up was performed that included a sputum smear and culture, a thorax CT, and a bronchoscopy; if need-

ed, further tests were carried out. INH-Px (300 mg/day) was given for 9 months if the screened patient had any of the following: a history of close contact with infectious cases within the past year, fibrotic changes consistent with TB on a chest X-ray (CXR) with no adequate history or documentation of a previous anti-TB treatment or a TST wheal ≥ 5 mm in diameter. In addition, INH-Px could be initiated at the discretion of the treating physician based on his/her clinical judgement. The aTNF- α -T was usually initiated 1 month after the start of INH-Px. Patients were followed up via regular visits performed every 3 months during the aTNF- α -T.

Since one of the primary objectives of this study was to evaluate the effect of INH-Px on the risk of TB, only those patients who had a follow-up time longer than 6 months under aTNF- α -T ($n = 1964$) were included.

Medical records of the patients were used to collect information on the following potential risk factors for TB: age, gender, smoking history, amount of smoking (<10 pack-years vs. ≥ 10 pack-years), primary disease, TST findings (anergic, wheal diameter <5 mm, wheal diameter 5–9 mm, and wheal diameter ≥ 10 mm), use of INH-Px, type of anti-TNF- α agent used, and use of other immunosuppressive agents such as methotrexate, azathioprine, and corticosteroids. Statistical analyses were performed using SPSS version 21.0 for Windows. A χ^2 test was used for comparison of categorical data. Continuous variables are reported as means $\pm$ SD or medians, and all categorical variables are expressed as numbers and percents of cases. The associated risk factors for TB were analyzed with multivariate logistic regression in order to define the most relevant predictive variables. The study protocol was approved by the Ethics Board of Cerrahpasa Medical School, Istanbul University (approval No. 83045809-3708).

Results

The mean follow-up time for the 1,964 participants was 27.9 ± 21.0 months (median 21). Of these, 1,009 (51%) were male and 955 (49%) were female, with a mean age of 39.7 ± 13.9 years. The primary diseases for aTNF- α -T were ankylosing spondylitis in 875 (44.6%), rheumatoid arthritis in 711 (36.2%), Behçet's disease in 83 (4.2%), and others in the remaining 295 (15%) patients. Fifty-seven patients (2.9%) had a previous history of TB; 886 patients [45.1%; 592 (66.8%) males and 294 (33.2%) females] were smokers (mean 14.8 ± 12.3 pack-years). The following anti-TNF- α agents were given to the patients: etanercept ($n = 760$; 38.7%), infliximab ($n = 684$; 34.8%), and adalimumab ($n = 520$; 26.5%). The demographic characteristics of the patients are shown in table 1.

Of 1,964 patients, 1,250 (63.6%) received INH-Px with the following indications: positive TST ($n = 1,162$; 93%), fibrotic changes consistent with TB on a chest CXR ($n = 34$; 2.7%), a history of close contact with infectious individuals within the past year ($n = 9$; 0.7%), and at the discretion of the physician ($n = 45$; 3.6%).

Table 1. Characteristics of the patients

	Values
Total patients, n	1,964
Mean age $\pm$ SD, years	39.7 $\pm$ 13.9
Gender	
Female	955 (49)
Male	1,009 (51)
Primary disease	
Ankylosing spondylitis	875 (44.6)
Rheumatoid arthritis	711 (36.2)
Behçet's disease	83 (4.2)
Others	295 (15)
History of TB	57 (2.9)
Smoking history	
Current smokers	886 (45.1)
Nonsmokers	1,036 (52.8)
Former smokers	42 (2.1)
Anti-TNF- α agents	
Etanercept	760 (38.7)
Infliximab	684 (34.8)
Adalimumab	520 (26.5)
Previous immunosuppressive drugs	
Prednisolone	703 (35.7)
Methotrexate	581 (29.5)
Azathioprine	82 (4.5)

Values are presented as numbers (%) unless otherwise stated.

Sixteen patients [8 (50%) males and 8 (50%) females] developed TB (mean age 40.1 ± 14.6 years, range 25–74). Eight (50%) of them were in the INH-Px group. The annual incidence of TB in this patient group was 466/100,000.

Of the 16 TB cases identified, 5 (31.2%) had P-TB and 11 (68.8%) had EP-TB [military, $n = 4$ (25%); TB pleurisy, $n = 3$ (18.8%); intestinal TB, $n = 2$ (6.6%); TB of the ear, $n = 1$ (6.3%), and TB of the urogenital system, $n = 1$ (6.3%)]. All 16 patients were on aTNF- α -T at the time of the diagnosis of TB. The mean time between the initiation of aTNF- α -T and the TB diagnosis was 26.8 ± 17.1 months (range 1–60, median 26.5). TB developed in 3 (18.8%) patients during the first 12 months, in 3 (18.8%) patients between 12 and 18 months, and in 10 (62.4%) patients after 18 months. The characteristics of the 16 patients who developed TB during aTNF- α -T are shown in table 2.

A significantly lower proportion of patients with a TST wheal ≥ 10 mm in diameter (3/885) developed TB as compared to those with a TST wheal < 10 mm in diameter (12/1,079; $p = 0.027$).

The primary condition necessitating the use of aTNF- α -T in these 16 patients with a diagnosis of TB was ankylosing spondylitis in 8 (50%), rheumatoid arthritis in 4 (25%), Behçet's disease in 3 (18.8%), and Takayasu arteritis in 1 (6.3%) patient. TB was diagnosed in 8 of 875 (0.9%) ankylosing spondylitis patients, in 4 of 711 (0.5%) rheumatoid arthritis patients, and in 3 of 83 (3.6%) Behçet disease patients. A significantly higher proportion of patients with Behçet's disease were diagnosed with TB compared to patients with other conditions ($p = 0.028$). Thirteen of the 16 TB patients (81.2%) were also receiving at least one other immunosuppressive agent in addition to TNF inhibitors as follows: azathioprine, $n = 1$ (7.6%); prednisolone, $n = 6$ (46.2%); azathioprine + prednisolone, $n = 2$ (15.4%), and methotrexate, $n = 4$ (30.8%). TB occurred significantly more frequently among patients receiving azathioprine (3/82) than among those receiving other immunosuppressives (13/1,882; $p = 0.038$); however, it should be pointed out that azathioprine was prescribed only to patients with Behçet's disease. No association was found between use of methotrexate or steroids and TB development ($p > 0.05$).

There was also no association between TB development and the age and gender of the patients ($p > 0.05$) or the type of anti-TNF- α agent ($p > 0.05$). However, the rate of TB in patients treated with infliximab was approximately twice that of patients who received adalimumab or etanercept (the patient-years for etanercept were 23/10,000 compared to 52/10,000 for infliximab and 27/10,000 for adalimumab). Six (37.5%) of the 16 patients with TB were nonsmokers, while 10 (62.5%) were current smokers (mean 12.1 ± 10.4 pack-years, range 4–40). Three (60%) of the 5 patients with pulmonary TB were current smokers, while the corresponding figure was 7 (63.6%) among 11 patients with EP-TB. There was no statistically significant difference between current smokers and nonsmokers in terms of TB risk ($p > 0.05$). In addition, the smoking history length was not associated with an increased TB risk (< 10 vs. ≥ 10 pack-years, $p > 0.05$).

TB developed in 8 of 1,250 patients who received INH-Px (the TB incidence was 367/100,000) and in 8 of 714 patients who did not receive INH-Px (the TB incidence was 635/100,000), with the difference being insignificant ($p = 0.3$).

When patients who received INH-Px were assigned to 2 groups based on purified protein derivative (PPD) results as those with a wheal diameter ≥ 10 mm and those with a wheal diameter between 5 and 9 mm, a borderline insignificant difference was observed between the 2

Table 2. Characteristics of the 16 patients who developed TB

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Gender	Female	Male	Male	Female	Male	Male	Male	Female
Age, years	33	39	35	42	39	48	28	29
Smoking, pack-years	10	13	12	9	Nonsmoker	40	10	6
Primary disease	Ankylosing spondylitis	Ankylosing spondylitis	Behçet's disease	Takayasu arteritis	Ankylosing spondylitis	Ankylosing spondylitis	Behçet's disease	Ankylosing spondylitis
Anti-TNF- α agents	Infliximab	Infliximab	Infliximab	Infliximab	Adalimumab	Adalimumab	Infliximab	Etanercept
Duration of anti-TNF- α usage, months	60	49	48	14	29	24	35	8
TST wheal diameter, mm	0	0	8	0	7	10	9	0
INH usage	No	No	Yes (9 months)	No	Yes (9 months)	Yes (9 months)	Yes (9 months)	No
Clinical presentation	Fever, weight loss, night sweats, right pleural pain, and pleural effusion on CXR and thorax CT	Fever, weight loss, night sweats, left pleural pain, and pleural effusion on CXR and thorax CT	Tree-in-bud consolidation in the right upper lobe on thorax CT	Abdominal pain and ileus	Fever, weakness, weight loss, and miliary pattern on CXR and thorax CT	Fever, night sweats, right pleural pain, and pleural effusion on CXR and thorax CT	Weakness, weight loss, and miliary pattern on CXR and thorax CT	Consolidation on CXR in routine control and also on CT thorax
Diagnostic procedure	Thoracentesis	Thoracentesis	Bronchoscopy	Histopathologic examination of the resected tissue taken from the ileum by abdominal open surgery	Clinical + radiologic	Thoracentesis	Histopathologic examination of bone marrow aspiration	Thoracoscopic lung biopsy
Diagnosis	TB pleurisy	TB pleurisy	Culture (+), pulmonary TB	Intestinal TB	Miliary TB	TB pleurisy	Miliary TB	Pulmonary TB
Outcome	Treatment completed	Treatment completed	Treatment completed	Treatment completed	Treatment completed	Treatment completed	Treatment completed ^a	Treatment completed

	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16
Gender	Female	Male	Female	Male	Female	Female	Female	Male
Age, years	41	25	28	27	53	74	31	69
Smoking, pack-years	14	4	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker	3	Nonsmoker
Primary disease	Rheumatoid arthritis	Behçet's disease	Ankylosing spondylitis	Ankylosing spondylitis	Rheumatoid arthritis	Rheumatoid arthritis	Ankylosing spondylitis	Rheumatoid arthritis
Anti-TNF- α agents	Adalimumab	Infliximab	Etanercept	Etanercept	Infliximab	Etanercept	Infliximab	Infliximab
Duration of anti-TNF- α usage, months	31	24	12	7	1	12	36	39
TST wheal diameter, mm	>5	0	0	7	0	Not performed, history of TB diagnosis and treatment	11	10

Table 2 (continued)

	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16
INH usage	Yes (9 months)	No	Yes (9 months)	Yes (9 months)	No	No	Yes (9 months)	Yes (9 months)
Clinical presentation	Right ear pain	Fever, cough, sputum, weight loss, night sweats, consolidation on CXR and thorax CT	Fever, weakness, weight loss, miliary pattern on CXR and thorax CT	Consolidation on CXR in routine control	Abdominal pain, multiple lymphadenopathy in axileal and peritoneal areas on abdomen CT	Fever, cough, weakness	Fever, weakness, weight loss, miliary pattern on CXR and thorax CT	Anorexia, weight loss, night sweats, diffuse thickening of the cecum on abdominal CT
Diagnostic procedure	Ear operation: transcanal debridement and removal of granulated tissues in left middle ear under general anesthesia	Sputum examination	Clinical + radiologic	Sputum examination	Abdominal open surgery: multiple biopsies taken from the adnex and peritoneum under general anesthesia	Gastric lavage	Bronchoscopy, bronchial lavage culture (+)	Colonoscopy
Diagnosis	Pathology (+); ear TB	Smear (+); pulmonary TB	Miliary TB	Culture (+); pulmonary TB	Urogenital system TB	Recurrence of pulmonary TB	Miliary TB	Intestinal TB
Outcome	Treatment completed	Treatment completed	Treatment completed	Treatment completed	Treatment completed	Treatment completed	Treatment completed	Treatment completed

^a INH drug resistance was determined.

Table 3. Results of the multivariate logistic regression analysis

Feature	TB (+)	p*
TST wheal diameter ≥ 10 mm	3/845	0.027
Behçet's disease	3/83	0.003
Azathioprine user	3/82	>0.05

* p < 0.05 was considered statistically significant.

groups (3/885 for >10 mm and 4/277 for 5–9 mm; p = 0.05).

INH resistance was found in only 1 (12.5%) of the 8 patients who developed TB after INH-Px, but the subsequent treatment for TB in this patient was successful (case 7 in table 2).

In the multivariate regression analysis, Behçet's disease (p = 0.003) and having a TST wheal ≥ 10 mm in diameter (p = 0.027) were found to be associated with the development of TB infection. The effect of azathioprine use disappeared in the multivariate analysis (p > 0.05; table 3).

Discussion

TNF- α plays key role in the pathogenesis of TB through its involvement in almost all immunological and pathological responses of the host against *M. tuberculosis* [24, 25]. Therefore, an increased risk of developing P-TB, EP-TB, or disseminated forms of TB infection is expected in patients receiving aTNF- α -T [26–29]. Askling et al. [4] reported a 4-fold increased risk of TB in subjects with rheumatoid arthritis receiving aTNF- α -T from 1999 to 2004. In another report from Japan, TB was found to develop in 13 out of 4,000 patients receiving these agents [30]. In contrast, there is a relative scarcity of data on the prevalence of TB in patients receiving aTNF- α -T in Turkey [5, 19–22]. Hanta et al. [20] reported 3 patients developing TB out of 192 who received aTNF- α -T. Elbek et al. [5] concluded that aTNF- α -T is associated with a nearly 40-fold increased risk of TB after observing active TB in 2 of 240 subjects during the course of aTNF- α -T. Recently, Cagatay et al. [22] reported that 20 of 1,794 patients developed TB during such treatment. In our study, 16 of 1,964 patients who received aTNF- α -T for more than 6 months developed TB during an average follow-up period of 21 months, corresponding to an annual incidence

of 466/100,000, i.e. approximately 21 times the incidence of TB in Turkey (22/100,000) [18].

Several guidelines recommend patient assessment prior to the initiation of TNF inhibitors, with careful history taking regarding exposure to TB, TST, and CXR. These guidelines also recommend INH-Px (300 mg/day) for 6 or 9 months in patients diagnosed with latent TB [11, 12, 23]. Sichletidis et al. [31] reported the occurrence of active TB in 1 out of 3 patients despite INH-Px (patients with a TST wheal ≥ 10 mm in diameter received INH-Px for 6 months) during a 3-year follow-up. In contrast with the results reported by Sichletidis et al. [31], Manadan et al. [32] reported no active TB in patients who received INH-Px. Cagatay et al. [22] reported that 17 out of 20 TB cases developed TB in spite of INH-Px. Compared to all these studies, our study had a larger sample size. Among 16 patients who developed TB during 21 months of follow-up, TB developed despite INH-Px in 8 cases. Although no significant association between administration of chemoprophylaxis and TB development was found (8/1,250 among those who received INH-Px vs. 8/714 in those without INH-Px; $p = 0.3$), the TB incidence was lower among patients who received INH-Px (367/100,000) than among those who did not receive INH-Px (635/100,000). Since patients undergoing INH-Px represented a high-risk group, the absence of differences between INH users and INH nonusers in terms of the occurrence of TB, together with a lower TB prevalence among INH users, may be interpreted as an indication of the efficacy of INH-Px in reducing TB in high-risk groups. Also, in our study no patient developed TB during INH-Px, although no relationship was found between chemoprophylaxis and the risk of developing TB. This result is similar to the recently published study of Churchyard et al. [33], who examined workers in gold mines and found that, during the first 9-month period when INH was given, the incidence of TB was 58% lower in the INH cohort than in the control cohort but subsequently the TB incidence was similar in the 2 cohorts after INH-Px [33]. Clearly, more studies are warranted to shed more light on this issue. On the other hand, the 21 times higher TB incidence reported despite the use of follow-up protocols and INH-Px raises some doubts about the efficacy of the follow-up protocols and INH-Px implemented.

An unexpected result of our study was the significantly lower occurrence of TB in patients with a TST wheal ≥ 10 mm in diameter (3/885) compared to those with a TST wheal < 10 mm in diameter (13/1,079; $p = 0.027$). This finding may be explained by the fact that all of these patients had chronic immune-related diseases and most of them also received immunomodulator drugs. A strong

reaction on a TST despite the presence of an immune-related disease and chronic illness may be considered a sign of a relatively better immune status, conferring protection for the patient. In these patients, generally an inadequate response to a TST is expected. When patients on INH-Px were categorized on the basis of PPD results as those with a skin reaction ≥ 10 mm in diameter and those with a reaction between 5 and 9 mm in diameter, no significant difference in terms of TB risk was found, suggesting that the low risk of TB in those with a PPD result ≥ 10 mm was not associated with INH-Px.

Of the 16 patients with an established diagnosis of TB, 5 (31.2%) had P-TB, while 11 (68.8%) had EP-TB. Similar to our results, Sichletidis et al. [31] reported that, of the 11 TB cases they identified despite chemoprophylaxis among patients receiving an anti-TNF agent, 6 (54.5%) had P-TB and 5 (45.5%) had EP-TB (nasopharyngeal TB, $n = 1$; oropharyngeal TB, $n = 1$; lymph node TB, $n = 1$; TB pleurisy, $n = 1$, and spleen TB, $n = 1$) [31]. This high occurrence of EP-TB indicates that, in patients receiving aTNF- α -T, a high index of suspicion should be maintained for P-TB and EP-TB when signs of infection are observed.

All 16 (100%) patients with an established diagnosis of TB were on aTNF- α -T at the time of diagnosis. The mean time between the initiation of aTNF- α -T and the TB diagnosis was 26.8 ± 17.1 months. TB was diagnosed during the first 12 months in 3 patients, between 12 and 18 months in 3 patients, and after 18 months in 10 patients. These data suggest an increased risk of TB during the late phase of the aTNF- α -T and give rise to a number of intriguing questions. For instance, can there be excessive immunosuppression in the long term in patients on aTNF- α -T, or could late TB infections occurring despite INH-Px be due to reinfections rather than latent infections, or should INH-Px be continued for more than 9 months? Certainly, further research is warranted to answer these questions.

Rheumatoid arthritis patients are known to have a higher risk of TB than the general population. Also agents used for the treatment of rheumatoid arthritis may further increase the risk of TB [34–36]. Recently, Kim et al. [37] reported that the TB incidence in ankylosing spondylitis and rheumatoid arthritis patients receiving aTNF- α -T is similar, and EP-TB was prevalent in both conditions. On the other hand, a higher risk of TB was observed in patients diagnosed with Behçet's disease in our study ($p = 0.003$), consistent with some previous reports suggesting an association between an elevated TB risk and Behçet's disease [38, 39]. This maybe related to the fact that Behçet's disease generally involves large and small

blood vessels, facilitating TB infection through a ventilation-perfusion mismatch subsequent to microclotting.

A differential risk of TB was reported for different anti-TNF- α agents, with more cases reported for monoclonal antibodies compared to receptor proteins (etanercept, 35/100,000; infliximab, 144/100,000, and adalimumab, 240/100,000) [38]. Wallis et al. [16] reported a 3-fold increased risk of TB with infliximab treatment compared to etanercept. However, in our study the TB incidence was comparable between the 3 anti-TNF- α agents (the patient-years for etanercept were 23/10,000 as compared to 52/10,000 for infliximab and 27/10,000 for adalimumab; $p > 0.05$). Also, there was no relationship between age, gender, and the risk of TB ($p > 0.05$).

The potential strengths of our study include the fact that it represents one of the largest and longest studies investigating TB and related risk factors in patients receiving aTNF- α -T.

However, its retrospective design with the absence of an appropriate control group, the absence of interferon- γ release assay testing for TB in addition to TST, and the absence of data on compliance with INH treatment are among its limitations.

In conclusion, our results suggest that aTNF- α -T increases the risk of P-TB and EP-TB despite the implementation of follow-up protocols and INH-Px, and that TB often develops during the late phase of such treatment. Although INH-Px appears to reduce the TB risk in high-risk subjects, TB development despite Px in some patients raises questions about the duration of the Px in high-risk groups in populations with a high prevalence of TB infection. The risk of TB was higher in patients with Behçet's disease and lower in patients who had a strong reaction to the TST. Patients receiving aTNF- α -T should be monitored closely for TB even at the late phases of the therapy.

References

- 1 World Health Organization: Global Tuberculosis Report 2013. http://www.who.int/tb/publications/global_report/en/ (accessed June 21, 2014).
- 2 Schiff MH, Burmester GR, Kent JD, Pangan AL, Kupper H, Fitzpatrick SB, Donovan C: Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;65:889–894.
- 3 Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD; BIOBADASER Group: Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003;48:2122–2127.
- 4 Askling J, Forde CM, Brandt L, Baecklund E, Bertilsson L, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, Romanus V, Klareskog L, Feltelius N: Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum* 2005;52:1986–1992.
- 5 Elbek O, Uyar M, Aydin N, Borekci S, Bayram N, Bayram H, Dikensoy O: Increased risk of tuberculosis in patients treated with antitumor necrosis factor alpha. *Clin Rheumatol* 2009;28:421–426.
- 6 Mutlu GM, Mutlu EA, Bellmeyer A, Rubinstein I: Pulmonary adverse events of anti-tumor necrosis factor-alpha antibody therapy. *Am J Med* 2006;119:639–646.
- 7 Vordermeier HM: T-cell recognition of mycobacterial antigens. *Eur Respir J Suppl* 1995; 20:657–667.
- 8 Flynn JL, Goldstein MM, Chan J, Triebold KJ, Pfeffer K, Lowenstein CJ, Schreiber R, Mak TW, Bloom BR: Tumor necrosis factor-alpha is required in the protective immune response against *Mycobacterium tuberculosis* in mice. *Immunity* 1995;2:561–572.
- 9 Stenger S: Immunological control of tuberculosis: role of tumour necrosis factor and more. *Ann Rheum Dis* 2005;64(suppl 4):24–28.
- 10 Engele M, Stossel E, Castiglione K, Schwerdtner N, Wagner M, Bolcskei P, Rollinghoff M, Stenger S: Induction of TNF in human alveolar macrophages as a potential evasion mechanism of virulent *Mycobacterium tuberculosis*. *J Immunol* 2002;168:1328–1337.
- 11 American Thoracic Society: Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;61:221–247.
- 12 British Thoracic Society Standards of Care Committee: BTS recommendations for assessing risk and for managing *Mycobacterium tuberculosis* infection and disease in patients due to start anti-TNF- α treatment. *Thorax* 2005;60:800–805.
- 13 Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Bréban M, Pallot-Prades B, Poupelin S, Sacchi A, Chichemanian RM, Bretagne S, Emilie D, Lemann M, Lortholary O, Mariette X; Research Axed on Tolerance of Biotherapies Group: Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum* 2009;60:1884–1894.
- 14 Brassard P, Kezouh A, Suissa S: Antirheumatic drugs and the risk of tuberculosis. *Clin Infect Dis* 2006;43:717–722.
- 15 Wallis RS: Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. *Lancet Infect Dis* 2008;8:601–611.
- 16 Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO: Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004;38:1261–1265.
- 17 Kiter G, Uçan ES: Prevention of tuberculosis. *Toraks* 2001;2:85–90.
- 18 World Health Organization: Turkey – tuberculosis profile. 2011. https://extranet.who.int/sree/Reports?op=Replet&name=/WHO_HQ_Reports/G2/PROD/EXT/TBCountryProfile&ISO2=TR&outtype=html (accessed June 21, 2014).
- 19 Doğan C, Kırıl N, Cömert SS, Fidan A, Çağlayan B, Salepci B: Tuberculosis frequency in patients taking TNF-alpha blockers. *Turks Toraks Derg* 2012;13:93–98.
- 20 Hanta I, Ozbek S, Kuleci S, Kocabas A: The evaluation of latent tuberculosis in rheumatologic diseases for anti-TNF therapy: experience with 192 patients. *Clin Rheumatol* 2008; 27:1083–1086.
- 21 Cagatay T, Aydin M, Sunmez S, et al: Follow-up results of 702 patients receiving tumor necrosis factor-alpha antagonists and evaluation of risk of tuberculosis. *Rheumatol Int* 2010;30:1459–1463.

- 22 Cagatay T, Bingol Z, Yegin Z, Okumus G, Kiyani E, Arseven O, Erkan F, Gulbaran Z, Erelel M, Ece T, Kilicaslan Z: Clinical characteristics of tuberculosis patients who were on therapy of tumor necrosis factor alpha antagonists. *Chest* 2014;145:137A.
- 23 Keser G, Direskeneli H, Akkoç N, et al: Rheumatology Research and Education Foundation's Consensus Report on using TNF- α inhibitors. 2005. <http://www.romatoloji.org/Romatizma.asp?RAED=RaporveKilavuzlar&SubShf=IIRAEDUzlasi> (accessed April 14, 2013).
- 24 Lasco TM, Cassone L, Kamohara H, Yoshimura T, McMurray DN: Evaluating the role of tumor necrosis factor-alpha in experimental pulmonary tuberculosis in the guinea pig. *Tuberculosis* 2005;85:245–258.
- 25 Philips JA, Ernst JD: Tuberculosis pathogenesis and immunity. *Annu Rev Pathol Mech Dis* 2012;7:353–384.
- 26 Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM: Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;345:1098–1104.
- 27 Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, Vinh DC: Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis* 2003;3:148–155.
- 28 Toussiot E, Wendling D: The use of TNF-alpha blocking agents in rheumatoid arthritis: an overview. *Expert Opin Pharmacother* 2004;5:581–594.
- 29 Roberts L, McColl GJ: Tumour necrosis factor inhibitors: risks and benefits in patients with rheumatoid arthritis. *Intern Med J* 2004;34:687–693.
- 30 Imaizumi K, Sugishita M, Usui M, Kawabe T, Hashimoto N, Hasegawa Y: Pulmonary infectious complications associated with anti-TNF alpha therapy (infliximab) for rheumatoid arthritis. *Intern Med* 2006;45:685–688.
- 31 Sichletidis L, Settas L, Spyrtos D, Chloros D, Patakas D: Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. *Int J Tuberc Lung Dis* 2006;10:1127–1132.
- 32 Manadan AM, Joyce K, Sequeira W, Block JA: Etanercept therapy in patients with a positive tuberculin skin test. *Clin Exp Rheumatol* 2007;25:743–745.
- 33 Churchyard GJ, Fielding KL, Lewis JJ, Coetzee L, Corbett EL, Godfrey-Faussett P, Hayes RJ, Chaisson RE, Grant AD; Thibela TB Study Team: A trial of mass isoniazid preventive therapy for tuberculosis control. *N Engl J Med* 2014;370:301–310.
- 34 Carmona L, Hernández-García C, Vadillo C, Pato E, Balsa A, González-Alvaro I, Belmonte MA, Tena X, Sanmartí R; EMECAR Study Group: Increased risk of tuberculosis in patients with rheumatoid arthritis. *J Rheumatol* 2003;30:1436–1439.
- 35 Yamada T, Nakajima A, Inoue E, Tanaka E, Hara M, Tomatsu T, Kamatani N, Yamanaka H: Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan. *Ann Rheum Dis* 2006;65:1661–1663.
- 36 Brassard P, Lowe AM, Bernatsky S, Kezouh A, Suissa S: Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. *Arthritis Rheum* 2009;61:300–304.
- 37 Kim HW, Park JK, Yang JA, Yoon YI, Lee EY, Song YW, Kim HR, Lee EB: Comparison of tuberculosis incidence in ankylosing spondylitis and rheumatoid arthritis during tumor necrosis factor inhibitor treatment in an intermediate burden area. *Clin Rheumatol* 2014;33:1307–1312.
- 38 Efthimiou J, Hay PE, Spiro SG, Lane DJ: Pulmonary tuberculosis in Behçet's syndrome. *Br J Dis Chest* 1988;82:300–304.
- 39 Coelho PC, da Silva JA, Romeu JC, da Costa JC, de Queiroz MV: Simultaneous appearance of Behçet's disease and pulmonary tuberculosis. *Clin Exp Rheumatol* 1994;12:692.