# Characteristics Predicting Tuberculosis Risk under Tumor Necrosis Factor-α Inhibitors: Report from a Large Multicenter Cohort with High Background Prevalence

Bunyamin Kisacik, Omer Nuri Pamuk, Ahmet Mesut Onat, Sait Burak Erer, Gulen Hatemi, Yesim Ozguler, Yavuz Pehlivan, Levent Kilic, Ihsan Ertenli, Meryem Can, Haner Direskeneli, Gökhan Keser, Fahrettin Oksel, Ediz Dalkilic, Sedat Yilmaz, Salih Pay, Ayse Balkarli, Veli Cobankara, Gözde Yildirim Cetin, Mehmet Sayarlioglu, Ayse Cefle, Ayten Yazici, Ali Berkant Avci, Ender Terzioglu, Suleyman Ozbek, Servet Akar, and Ahmet Gul

***ABSTRACT.*** ***Objective.*** Screening strategies for latent tuberculosis (TB) before starting tumor necrosis factor (TNF)-α inhibitors have decreased the prevalence of TB among patients who are treated with these agents. However, despite vigilant screening, TB continues to be an important problem, especially in parts of the world with a high background TB prevalence. The aim of this study was to determine the factors related to TB among a large multicenter cohort of patients who were treated with anti-TNF.

***Methods.*** Fifteen rheumatology centers participated in this study. Among the 10,434 patients who were treated with anti-TNF between September 2002 and September 2012, 73 (0.69%) had developed TB. We described the demographic features and disease characteristics of these 73 patients and compared them to 7695 patients who were treated with anti-TNF, did not develop TB, and had complete data available.

***Results.*** Among the 73 patients diagnosed with TB (39 men, 34 women, mean age 43.6 ± 13 yrs), the most frequent diagnoses were ankylosing spondylitis (n = 38) and rheumatoid arthritis (n = 25). More than half of the patients had extrapulmonary TB (39/73, 53%). Six patients died (8.2%). In the logistic regression model, types of anti-TNF drugs [infliximab (IFX), OR 3.4, 95% CI 1.88–6.10, p = 0.001] and insufficient and irregular isoniazid use (< 9 mos; OR 3.15, 95% CI 1.43–6.9, p = 0.004) were independent predictors of TB development.

***Conclusion.*** Our results suggest that TB is an important complication of anti-TNF therapies in Turkey. TB chemoprophylaxis less than 9 months and the use of IFX therapy were independent risk factors for TB development. (First Release January 15 2016; J Rheumatol 2016;43:524–9; doi:10.3899/jrheum.150177)

*Key Indexing Terms:*
TUMOR NECROSIS FACTOR-A INHIBITORS TUBERCULOSIS REACTIVATION ISONIAZID

*From the Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Gaziantep University, Gaziantep; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Trakya University, Edirne; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Istanbul University; Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical School, Istanbul University; Division of Rheumatology, Department of Internal Medicine, Fatih Sultan Mehmet Research and Training Hospital; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Marmara University, Istanbul; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Uludag University, Bursa; Division of Rheumatology, Department of Internal Medicine, Hacettepe University Hospital; Division of Rheumatology, Department of Internal Medicine, Gulhane Military School of Medicine; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Pamukkale University, Ankara; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Ege University; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Katip Celebi University, Izmir; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Sutcu Imam University, Kahramanmaras; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Mayis University, Samsun; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Kocaeli University, Izmit; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Akdeniz University, Antalya; Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Cukurova University, Adana, Turkey.*

*B. Kisacik, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Gaziantep University; O.N. Pamuk, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Trakya University; A.M. Onat, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Gaziantep University; S.B. Erer, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Istanbul University; G. Hatemi, MD, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical School, Istanbul University; Y. Ozguler, MD, Division of Rheumatology, Department of Internal Medicine, Cerrahpasa Medical School, Istanbul University; Y. Pehlivan, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Uludag University; L. Kilic, MD, Division of Rheumatology, Department of Internal Medicine, Hacettepe University Hospital; I. Ertenli, MD, Division of Rheumatology, Department of Internal Medicine, Hacettepe*

*University Hospital; M. Can, MD, Division of Rheumatology, Department of Internal Medicine, Fatih Sultan Mehmet Research and Training Hospital; H. Direskeneli, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Marmara University; G. Keser, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Ege University; F. Oksel, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Ege University; E. Dalkilic, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Uludag University; S. Yilmaz, MD, Division of Rheumatology, Department of Internal Medicine, Gulhane Military School of Medicine; S. Pay, MD, Division of Rheumatology, Department of Internal Medicine, Gulhane Military School of Medicine; A. Balkarli, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Pamukkale University; V. Cobankara, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Pamukkale University; G.Y. Cetin, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Sutcu Imam University; M. Sayarlioglu, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Mayis University; A. Cefle, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Kocaeli University; A. Yazici, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Kocaeli University; A.B. Avci, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Akdeniz University; E. Terzioglu, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Akdeniz University; S. Ozbek, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Cukurova University; S. Akar, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Katip Celebi University; A. Gul, MD, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Istanbul University.*

*Address correspondence to Dr. B. Kisacik, Gaziantep Universitesi, Tip Fakültesi Romatoloji Unitesi, 27100 Sahinbey, Gaziantep, Turkey. E-mail: bunyamin.kisacik@yahoo.com*

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Tumor necrosis factor inhibitors (anti-TNF) are a breakthrough in the treatment of inflammatory rheumatic diseases, especially rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Although the efficacy of these drugs is clinically verified and they are widely used, there are ongoing concerns about their side effects, especially the risk of infectious complications.

Because of the mechanism of action, anti-TNF treatment is shown to increase predisposition to infectious diseases, especially tuberculosis (TB)[1]. As a proinflammatory cytokine, TNF-α is associated with the protection mechanism against the major mycobacterium species, including *Mycobacterium tuberculosis, M. avium,* and *M. bovis*[2]. Disturbances of macrophage activation and granuloma formation are well-known pathological mechanisms predisposing to mycobacterial infections during anti-TNF treatment[3].

This risk may be especially pronounced in Turkey, where the background TB incidence is about 25–49 new cases in every 100,000 people[4]. Although recent screening and prophylactic measures have diminished the frequency of TB, TNF blockage might have more severe consequences compared with developed countries. Our retrospective data primarily analyzed the risk of TB infection in patients treated with anti-TNF drugs in Turkey.

## MATERIALS AND METHODS

*Patients*. Fifteen centers that are members of the Turkish Multicentered Investigators Platform in Rheumatology (TULIP) participated in our study. We collected the data retrospectively in our case-control study. We asked participating centers to fill out a standard form for TB characteristics of all cases who developed TB during or after anti-TNF therapies, and another form to record demographic and disease characteristics of all patients treated with anti-TNF agents until September 2012. These centers covered almost all regions of the country. A total of 10,434 patients were treated with licensed anti-TNF drugs including infliximab (IFX; since April 2002), etanercept (ETN; since January 2003), and adalimumab (ADA; since September 2004) in these centers between September 2002 and September 2012. Other biologics except rituximab (RTX) were not licensed in Turkey at that time. Because RTX has a very short history and very limited patient number, it was excluded from the data. The study protocol was approved by the local ethics committee of the principal institution.

*Data collection*. A standard form was used in all participating centers to record demographic features, socioeconomic status, anti-TNF, concomitant drugs, comorbid diseases, family history of TB, TB skin test (TST) results at anti-TNF onset, and duration of isoniazid (INH) use if latent TB was diagnosed among all of the center's patients treated with anti-TNF since September 2002. An additional form was used for patients who had developed TB, including questions about their TB features and prognosis.

According to Turkish guidelines, anti-TNF treatment candidates with latent TB (having a TST ≥ 5 mm and/or having chest radiographs suggestive of past TB and not having had adequate anti-TB treatment) should be treated with INH, initiated at least 4 weeks before the initiation of anti-TNF treatment, and should continue for 9 months. Patients who were not treated with INH for 9 months despite having latent TB were classified as "inadequate INH users".

*Statistical analysis*. Comparisons of categorical data between groups were made using the chi-square test or Fisher's exact test. The Student t test was used to analyze continuous data. Possible factors related to TB development were evaluated by Spearman correlation for continuous variables and ϕ coefficient for dichotomous or nominal variables.

Logistic regression analysis was used to explore the factors associated with TB development in patients who used anti-TNF agents. Data of 7695 out of 10,434 patients with accurate and complete laboratory and clinical data were included in our analysis, together with the 73 patients who had developed TB. The variables that were significantly associated with the development of TB in univariate analysis ($p < 0.05$) were included in the regression model. Selected for the univariate analysis were the demographic and socioeconomic characteristics (age, sex, ethnicity, marital status, health insurance, monthly income), drugs used, comorbid conditions, family history of TB, TST result in mm, and the duration of TB prophylaxis. No variables were forced into the model unless significantly associated in the univariate analysis.

Kaplan-Meier curve was used to show the time to TB development after initiation of anti-TNF drugs and log-rank test was used to compare the groups. All statistical tests were 2-tailed and a p value < 0.05 was considered statistically significant. The statistical analysis was carried out using Statistical Package of Social Science (SPSS), version 13.

## RESULTS

*Patients with TB*. Among the total 10,434 patients treated with anti-TNF drugs between September 2002 and September 2012, 73 patients (0.69%, M/F: 39/34) had developed TB (Table 1). Six patients out of 73 TB cases (8.2%) died during followup. Of those 6 cases, 4 patients were receiving ETN and 2 patients were receiving ADA. Among the 6 patients who died, 4 patients had pulmonary and 2 patients had extrapulmonary TB. Four of them were

*Table 1*. The characteristics of patients receiving anti-TNF therapy who developed (n = 73) and did not develop TB (n = 7695). Values are n (%) unless otherwise specified.

| Characteristics | Patients with TB, n = 73 | Patients without TB, n = 7695 | p |
|---|---|---|---|
| Male/female | 39/34 | 3634/4061 | 0.346 |
| Age, yrs, mean ± SD | 43.6 ± 13 | 43.4 ± 13.6 | 0.870 |
| Duration of anti-TNF use, mos, mean ± SD | 18.6 ± 18.5 | 25.9 ± 23.1 | 0.001 |
| TST positivity | 38 (52.1) | 4205 (55.2) | 0.897 |
| TST not performed | 11 (15.1) | 619 (8.1) | 0.03 |
| INH prophylaxis | 43 (58.9) | 5661 (74.3) | 0.003 |
| Patients who used INH regularly | 35 (81.4) | 5255 (92.8) | 0.011 |
| Steroid use | 32 (43.8) | 3804 (49.9) | 0.412 |
| Diseases | | | |
| Rheumatoid arthritis | 25 (34.2) | 2808 (36.5) | |
| Ankylosing spondylitis | 38 (52.1) | 3898 (50.6) | |
| Psoriatic arthritis | 4 (5.6) | 457 (6.04) | |
| Behçet disease | 5 (6.8) | 124 (1.56) | |
| Other disease | 1 (1.4) | 408 (5.3) | |
| Anti-TNF, n | | | |
| Infliximab | 46 | 2684 | |
| Adalimumab | 14 | 2238 | |
| Etanercept | 13 | 2773 | |

TNF: tumor necrosis factor; TB: tuberculosis; TST: TB skin test; INH: isoniazid.

not screened for latent TB before starting the TNF-α antagonist, and 2 patients had not received INH treatment despite positive TST results (Table 2).

When compared, 73 patients with TB were in whole similar disease groups; number and frequency for AS, RA, psoriatic arthritis, Behçet disease (BD) and vasculitis were 38 (0.97%), 25 (0.87%), 5 (4%), and 1 (0.24%), respectively. The TNF-α antagonists that these patients were receiving at the time of TB were IFX in 46 patients, ETN in 13 patients, and ADA in 14 patients. The median time for occurrence of TB since the initiation of anti-TNF treatment was 13 months with IFX (range 1–96 mos), 13 months with ADA (range 3–36 mos), and 7 months with ETN (range 4–60 mos, $p > 0.05$).

Thirty-four cases (46.6%) out of 73 patients with TB were diagnosed with pulmonary TB, and 39 cases (53.4%) with extrapulmonary TB. Extrapulmonary TB types included pleural (13 patients), lymph node (8 patients), miliary (7 patients), peritoneal (6 patients), bone (2 patients), joint (1 patient), bladder (1 patient), and intestinal TB (1 patient).

Thirty-eight of the patients (52%) had positive TST at the onset of anti-TNF treatment. INH was started in 43 patients (59%) and 35 of them completed 9 months of INH treatment.

*Comparison with patients who did not develop TB*. A total of 7695 patients who had not developed TB and who had complete and reliable data were compared with the 73 patients who developed TB (Table 1). The median followup for these 7768 patients was 20 months (range 1–96 mos). The mean age and sex of the patients who developed TB and who did not were similar. The number of patients who did not have a TST at the onset of anti-TNF treatment was higher (11/73, 15% vs 619/7695, 8.4%, $p = 0.03$), and the number of patients who had INH treatment ($p = 0.003$) and who completed 9 months of INH treatment were lower in the TB group ($p = 0.011$).

The frequency of TB was significantly higher among patients with BD compared with the other diseases ($p = 0.007$; Table 3). The frequency of TB was higher in patients who received IFX (1.27%) than in patients who received

*Table 2*. Demographic features of patients who died.

| Deceased Patients | Age/Sex | Diagnosis | TNF-α Antagonist | TST | Completed Isoniazid Treatment | TB Type |
|---|---|---|---|---|---|---|
| Patient 1 | 67/F | RA | ETN | Positive | No | Pulmonary |
| Patient 2 | 70/F | RA | ADA | ND | No | Extrapulmonary |
| Patient 3 | 34/M | AS | ETN | ND | No | Pulmonary |
| Patient 4 | 61/F | RA | ADA | Negative | No | Extrapulmonary |
| Patient 5 | 32/M | AS | ETN | Positive | No | Pulmonary |
| Patient 6 | 47/F | RA | ETN | Negative | No | Pulmonary |

TNF-α: tumor necrosis factor-α; TB: tuberculosis; TST: TB skin test; RA: rheumatoid arthritis; AS: ankylosing spondylitis; ETN: etanercept; ADA: adalimumab; ND: not done.

*Table 3*. Frequency of tuberculosis (TB) according to rheumatologic condition.

| Diseases | TB/Control Group, n/N | % |
|---|---|---|
| Ankylosing spondylitis | 38/3898 | 0.97 |
| Rheumatoid arthritis | 25/2808 | 0.89 |
| Psoriatic arthritis | 4/457 | 0.87 |
| Behçet disease | 5/124 | 4 |
| Other disease | 1/408 | 0.24 |

ETN (0.3%) and ADA (0.57%, $p < 0.001$ and $p = 0.008$, respectively; Table 4). Although TB was more frequent in patients who received ADA compared with ETN, the difference was not statistically significant ($p = 0.08$).

In correlation analysis, TB development was related to disease category, type of anti-TNF drug used, lack/irregularity of TB prophylaxis, and the duration of TB prophylaxis. In the logistic regression model, types of anti-TNF agent (IFX, OR 3.4, 95% CI 1.88–6.1, $p = 0.001$) and insufficient prophylaxis (< 9 mos, OR 3.15, 95% CI 1.43–6.9, $p = 0.004$) were independent predictors of TB development among patients treated with anti-TNF.

Thirteen cases (17.8%) out of 73 TB cases were treated with anti-TB therapy for a year and then, because of the progressive characteristics of the underlying diseases, anti-TNF therapies were reinitiated (9 patients ETN, 3 patients ADA, and 1 patient IFX). However, 3 cases (23%) that were reconsidered for anti-TNF therapy (1 IFX, 1 ETN, and 1 ADA) experienced TB recurrence and their therapy had to be terminated. The time to TB recurrence in these patients was 9 (IFX), 12 (ETN), and 13 months (ADA).

The time to TB occurrence among patients who were receiving their second anti-TNF was similar to those who had TB while receiving their first anti-TNF agent. Concerning TST positivity, there was no significant difference between patients without TB reactivation and those with TB reactivation.

## DISCUSSION

Anti-TNF agents have been very effective in the inhibition of the progression of rheumatic diseases, especially RA and AS, since their approval by the US Food and Drug Administration (FDA) and their introduction to the clinical setting.

*Table 4*. Frequency of TB according to the anti-TNF drug.

| Anti-TNF Drugs | TB/all Patients, n/N | % |
|---|---|---|
| IFX* | 46/3614 | 1.27 |
| ETN | 13/4369 | 0.3 |
| ADA** | 14/2451 | 0.57 |
| Total | 73 (10,434) | 0.69 |

* TB frequency in patients using IFX was significantly higher than in patients receiving ETN ($p < 0.001$) and ADA ($p < 0.008$). ** The difference between ADA and ETN was not statistically significant ($p = 0.08$). TB: tuberculosis; TNF: tumor necrosis factor; IFX: infliximab; ETN: etanercept; ADA: adalimumab.

However, anti-TNF drugs in the market have a black box warning for TB and other opportunistic infections. Our analysis of 73 TB cases (0.69%) collected among 10,434 patients from 15 different centers further underlines the increased TB risk in patients receiving anti-TNF therapy, especially in countries with an increased background prevalence of TB. According to regression model analysis, using INH for less than 9 months and the use of IFX were independent risk factors for TB development.

The mechanism of latent TB reactivation by anti-TNF is not fully understood. However, some studies revealed the involvement of TNF in mediating mycobacterial infections through the reactivation of macrophage and T lymphocytes[5]. Anti-TNF drugs are classified into 2 groups as monoclonal antibodies (IFX or ADA) and soluble TNF receptor (ETN), depending on their mechanism of TNF-α inhibition. Although all anti-TNF agents treat through TNF-α blockade, their indications and adverse event profiles vary according to the drug type. For instance, while IFX and ADA are indicated in the treatment of Crohn disease, ETN is not indicated[6,7,8]. These clinical differences between the drugs cannot be explained only by the neutralization of soluble TNF-α. Mitoma, *et al* evaluated the clinical effects of these anti-TNF agents by analyzing their biologic activities on transmembrane TNF-α. All of the anti-TNF agents were bound to transmembrane TNF-α, but IFX and ADA exerted almost equal complement-dependent cytotoxic activities while ETN showed considerably lower activity[9].

The first alert regarding the increased TB risk with anti-TNF therapy was issued by the Adverse Event Reporting System of the FDA. TB was seen at a rate of 144 per 100,000 patients receiving IFX per year and 35 per 100,000 patients receiving ETN per year. TB frequency was 5.2–6.8 per 100,000 cases per year in the general US population[2]. Most of the latest data concerning the TB frequency in patients treated with anti-TNF therapy arose from registry studies. The first results of the Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER) registry covering 2000–2002 reported 17 TB cases (IFX 17/1578, ETN 0/1540) among of 3118 patients treated with anti-TNF drugs[10]. In the second edition of the same registry, 15 new TB cases were reported among 5198 patients treated with anti-TNF drugs. Interestingly, none of these cases had been treated with the correct chemoprophylaxis against TB before anti-TNF therapy was initiated[11].

Using the British Society for Rheumatology Biologics Register, a national prospective observational study enrolled 7664 anti-TNF–treated severe RA cases. The study reported 10 cases developing TB (7 IFX, 2 ETN, and 1 ADA), and of these, 7 had extrapulmonary presentation[12]. The French Research Axed on Tolerance of Biotherapies (RATIO) registry reported 69 validated TB cases. Of them, 36 (52.1%)

had received IFX, 28 (40.5%) had received ADA, and 5 (7.2%) had received ETN. IFX usage has the major risk among monoclonal anti-TNF drugs for patients in the RATIO registry[13].

The patient profile of our group was relatively different from other registries. In our group, 36% of the patients had RA and 50% had AS compared with 75% RA and 11% AS in the Danish Biologic Registry[14], 64% RA and 13% AS in the BIOBADASER[15], and 75% RA and 13.2% AS in the Australian Rheumatology Association Database[16]. The main reason behind this difference could be the reimbursement conditions in Turkey, which require the use of 3 disease-modifying antirheumatic drugs before anti-TNF therapy in RA treatment.

One of our interesting observations was the relatively high frequency of TB among patients with BD treated with TNF-α antagonists. This may be because these patients were younger, more active, and usually employed, causing them to be more exposed to mycobacteria compared with other patient groups such as patients with RA. It was previously observed that the frequency of TB is significantly higher among the first-degree relatives of patients with BD compared with first-degree relatives of patients with familial Mediterranean fever, systemic lupus erythematosus, and healthy controls[17]. Moreover, the mean number of siblings was also significantly higher in patients with BD compared with the other groups. Although we did not formally assess this, another reason for increased TB could therefore be a more crowded living environment and lower socioeconomic conditions of patients with BD, as shown previously[18]. On the other hand, there may be immunologic factors rendering patients with BD and their relatives more prone to infection with mycobacterium TB. Whether the increased frequency of TB among patients with BD receiving TNF-α antagonists is related to social factors and increased exposure to mycobacteria or a genetically determined immunological susceptibility deserves further attention.

Genetic studies of TB have been widely reported. Some of these studies focused on *HLA* genes. Hwang, *et al* and Hafez, *et al* have evaluated the TB-associated *HLA* genes and the *HLA-B5* gene, which were positively associated with the frequency of BD and were also found to be associated with TB. Considering these studies, the high frequency of TB among patients with BD may signal the potential association between these 2 syndromes[19,20].

Another interesting finding in our study was the TB recurrence in patients who reinitiated treatment with anti-TNF drugs after completing anti-TB treatment. In 13 patients who developed TB, anti-TNF therapy was terminated, 12 months of anti-TB treatment was completed, and anti-TNF therapy was reinitiated. TB recurrence was observed in 3 (23%) of these patients. Currently, there is no consensus on reinitiating anti-TNF treatment following anti-TB therapy. The guidelines of the British Thoracic Society suggest concomitant use of anti-TB therapy during anti-TNF treatment[21]. Denis, *et al* conducted a longterm followup study of 21 patients diagnosed with TB during anti-TNF treatment, and anti-TNF was reinitiated in 6 of them[22]. TB recurrence was not observed in any of these cases. Caution is required when making a decision to reinitiate anti-TNF treatment in such patients, especially in countries with high TB prevalence.

During our followup, 6 out of 73 patients with TB (8.2%) had died. The study conducted by Denis, *et al* revealed 4.8% mortality among all TB cases[22]. Mortality among patients with TB without anti-TNF use is reported to be between 6.6% and 31.8%. The higher mortality rate is related to human immunodeficiency virus positivity. Larger series are needed to draw conclusions on the relative mortality increment with anti-TNF treatment[23,24,25]. We found that INH prophylaxis less than 9 months is an independent risk factor for TB infection. In a recent metaanalysis, Stagg, *et al* reported that 6 or 9 months of INH or 3 months of rifampin treatment have similar efficacy for TB prophylaxis. However, the most important variable determining the TB risk is lack of drug compliance and irregular chemoprophylaxis[26].

Our study had some limitations. It is based on retrospective data gathered from several centers. Interpreting TST results and chest radiograph findings by different physicians seems to be a limitation. Another limitation is that although TB seems to be more frequent in patients with BD, there is a limited number of patients treated with BD to make a firm conclusion. Also, because of the retrospective design of our study, there were patients with missing data regarding reliable TST results, socioeconomic variables, or family history of TB. Therefore, we were able to include 7695 patients with reliable data among the total pool of 10,434 patients who used TNF-α antagonists. Finally, interferon-γ release assays were not performed in many of the patients, which made it impossible for us to comment on its potential benefit over TST in patients who were candidates for anti-TNF therapy.

TB is still an important risk for patients receiving anti-TNF therapy. Patients' adherence to INH treatment is important for preventing the reactivation of latent TB. INH treatment for less than 9 months and the use of IFX therapy were the only independent risk factors for TB development. Reinitiating anti-TNF therapy after completing anti-TB therapy in patients who developed TB during anti-TNF therapy may result in TB recurrence in about a quarter of the patients.

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