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Clinical characteristics and treatment responses of patients who developed tuberculosis following use of a tumor necrosis factor-α inhibitor

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Background/Aims: Individuals being treated with tumor necrosis factor (TNF)-α inhibitors are at increased risk of developing tuberculosis (TB). We determined the clinical characteristics and treatment response of patients who developed TB after using TNF-α inhibitors.

Methods: Patients with TB detected within 12 months of the initiation of TNF-α inhibitor treatment were included, if seen from January 1, 2000 to August 31, 2011. We retrospectively reviewed the clinical records, results of bacteriological examinations, and radiographs of the included patients and the response to anti-TB treatment.

Results: We indentified seven cases of TB in 457 patients treated with TNF-α inhibitors during the study period. TB developed a median of 123 days (range, 48 to 331) after the first dose of TNF-α inhibitor. Pulmonary TB, including TB pleuritis, was diagnosed in three patients and extrapulmonary TB in four. Favorable treatment outcomes were achieved in six of seven patients.

Conclusions: Among the TNF-α inhibitor users who contracted TB, extrapulmonary sites were common and the treatment response was satisfactory.

Keywords: Tumor necrosis factor-alpha; Tuberculosis; Mycobacterium

INTRODUCTION

Tuberculosis (TB) is a leading cause of mortality and morbidity worldwide. In 2010, there were 8.8 million incident cases of TB, 1.1 million deaths from TB among human immunodeficiency virus (HIV)-negative people, and an additional 0.35 million deaths from HIV-associated TB [1]. The majority of infected persons will develop a latent TB infection, and the infection will eventually reactivate in about 10% of these subjects, leading to active TB [2].

Tumor necrosis factor (TNF) and TNF receptors are important regulators of immune cell activation, proliferation, differentiation, survival, and apoptosis [3-5]. TNF-α is a key cytokine in the immune response to infection with *Mycobacterium tuberculosis* [6], and is critical for the formation and maintenance of the granuloma [7]. TNF-α, together with interferon (IFN)-γ, increases the phagocytic capacity of macrophages and enhances the killing of *M. tuberculosis* via the generation of reactive nitrogen and oxygen intermediates [8]. TNF-α, deficient mice are unable to control *M. tuberculosis* infection, and granulomas do not form properly in their lungs [9,10].

Several TNF-α inhibitors are used widely in the treatment of chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, and several other conditions [11-15]. Unfortunately,

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individuals treated with TNF-α inhibitors are reportedly at an increased risk of developing TB [11,14,16,17]. However, the characteristics and treatment results of subsequent TB cases have not yet been reported. In this study, we investigated the clinical characteristics and treatment responses of TB that developed after TNF-α inhibitor treatment.

METHODS

Study setting and patients

Patients with TB that was detected within 12 months of the initiation of TNF-α inhibitor treatment between January 1, 2000 and August 31, 2011 at Seoul National University Hospital, a tertiary referral hospital in South Korea, were included in the study. We excluded patients with any other risk factors for TB reactivation, such as HIV infection, silicosis, or other immunosuppressive treatment, including anticancer chemotherapy. Patients who used TNF-α inhibitors for less than 4 weeks were also excluded. TB was diagnosed using all clinical, radiological, microbiological, and pathological information collected during the diagnostic process and follow-up period. The study protocol was approved by the Ethics Review Committee of Seoul National University Hospital.

Data collection

We retrospectively reviewed the clinical records, results of bacteriological examinations, patient radiographs, and responses to anti-TB treatment. Patient clinical variables were analyzed using descriptive statistics. The results are expressed as means and standard deviations or median values with ranges.

RESULTS

Demographic and clinical characteristics of patients

During the study period, 457 patients were treated with TNF-α inhibitors in our hospital. Of these, 11 (2.4%) patients were diagnosed with TB. Four TB patients diagnosed more than 12 months after initiating TNF-α inhibitor treatment were excluded. In total, seven patients who were diagnosed with TB within 12 months of TNF-α inhibitor initiation were included in the analysis. The median patient age was 62 years (range, 32 to 67). Four of the patients were female and one had diabetes. Of the seven patients with TB, one completed a 9-month course of isoniazid prophylaxis before developing active TB.

Use of TNF-α inhibitors

Rheumatoid arthritis was the most common indication for TNF-α inhibitor use (three patients). TNF-α inhibitors were used in one patient each with Crohn's disease, ulcerative colitis, ankylosing spondylitis, and reactive arthritis. Infliximab was the most commonly prescribed (three patients). The median duration of TNF-α inhibitor use was 167 days (range, 42 to 1,704) (Table 1).

Table 1. Demographic and clinical characteristics of seven patients with tuberculosis (TB) that developed following tumor necrosis factor (TNF)-α inhibitor use

Characteristic	Value
Total patients	7
Age, yr	62 (32–67)
Female	4 (57.1)
Previous treatment	1 (14.3)
Underlying diseases	
Diabetes	1 (14.3)
Indication for TNF-α inhibitor	
Rheumatoid arthritis	3 (42.8)
Ankylosing spondylitis	1 (14.3)
Crohn's disease	1 (14.3)
Ulcerative colitis	1 (14.3)
Reactive arthritis	1 (14.3)
TNF-α inhibitor	
Infliximab	3 (42.8)
Adalimumab	1 (14.3)
Infliximab and etanercept	1 (14.3)
Adalimumab and etanercept	2 (28.6)
Duration of use, day	167 (42–1,704)
Number of doses administered	7 (2–123)

Values are presented as median (range) or number (%).

Table 2. Characteristics of tuberculosis (TB) that developed following tumor necrosis factor (TNF)-α inhibitor use

Characteristic	Value
Total patients	7
Involved organ	
Pulmonary	
Lung	2 (28.6)
Pleura	1 (14.3)
Extrapulmonary	
Pericardium	1 (14.3)
Gastrointestinal	1 (14.3)
Musculoskeletal	1 (14.3)
Disseminated	1 (14.3)
Interval between the first dose of TNF-α inhibitor and the development of TB, day	123 (48–331)
Interval between the last dose of TNF-α inhibitor and the development of TB, day	25 (3–80)
Diagnosis of TB	
Culture proven	3 (42.8)
Positive TB-PCR using sputum or tissue	2 (28.6)
Diagnosed clinically	2 (28.6)
Treatment regimen	
HRE (Z)[a]	5 (71.4)
HRE and levofloxacin	2 (28.6)
Treatment duration, day	280 (182–1,142)
Follow-up duration after closing anti-TB treatment, day	286 (28–902)
Response to treatment	
Improved	6 (85.7)
Premature cessation of treatment	1 (14.3)
Died	0 (0)
Failed	0 (0)

Values are presented as median (range) or number (%).
PCR, polymerase chain reaction.
[a]Isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z).

Results of tuberculin skin tests and IFN-γ release assays

Tests for latent TB infection were performed in five of the seven patients. The tuberculin skin test was negative in one patient. In addition, IFN-γ release assays performed in four patients were negative.

TB developed after using TNF-α inhibitors

TB developed a median of 123 days (range, 48 to 331) after the first dose of TNF-α inhibitor. The median number of TNF-α inhibitor doses before developing TB was 16 doses (range, 2 to 123). TB was diagnosed a median of 25 days (range, 3 to 80) after the last dose of

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TNF-α inhibitor. TB was diagnosed in three patients based on sputum *M. tuberculosis* culture, in one patient with TB-polymerase chain reaction of a sputum specimen, and in three other patients based on symptoms, compatible chest radiograph findings, and clinical responses to anti-TB medication. Pulmonary TB, including TB pleuritis, was diagnosed in three patients and extrapulmonary TB, including disseminated TB, was diagnosed in four. The extrapulmonary sites were the pericardium, intestine, and bone (Table 2).

Anti-TB treatment and responses

All patients were treated with combinations of first-line anti-TB medications. The median treatment duration was 280 days (range, 182 to 1,142). In two patients, levofloxacin was used instead of pyrazinamide due to abnormal liver function.

Of the three patients with pulmonary TB, two were cured following treatment, and confirmed by negative sputum conversion in one patient. In the other patient, treatment was completed without evidence of aggravation or recurrence. Three of four patients with extrapulmonary TB improved clinically and radiographically with treatment. In one patient, however, the anti-TB treatment was stopped prematurely after 130 days of medication, because of worsening of ulcerative colitis (Table 2).

DISCUSSION

In this study, we found that active TB developed within 12 months of TNF-α inhibitor initiation in 7 of 457 patients (1.5%). Pulmonary TB, including TB pleuritis, was diagnosed in three patients and extrapulmonary TB was diagnosed in the other four. Since extrapulmonary TB constitutes 18.9% of all TB in South Korea [18], the proportion of extrapulmonary TB among TNF-α inhibitor users was somewhat higher than expected. In fact, an earlier study that showed a higher risk of TB developing in TNF-α inhibitor users also showed that extrapulmonary TB constituted 56% of the TB cases [19]. It is possible that the high proportion of extrapulmonary TB among TNF-α inhibitor users is associated with inadequate compartmentalization of viable mycobacterial bacilli by granulomas due to TNF-α antagonism [10].

The treatment responses of TB in the TNF-α inhibitor users were satisfactory. Favorable outcomes were achieved in all but one patient, who could not take anti-TB medication because of worsening ulcerative colitis. This concurs with the favorable treatment responses of other immunocompromised TB patients, such as those with HIV infection [20], organ transplant [21,22], and long-term steroid users [23].

Although the use of TNF-α inhibitors is regarded as one of the indications of treatment for latent TB infection [24-26], only one of the seven patients in our series started a 9-month course of isoniazid prophylaxis before initiating TNF-α inhibitor treatment. A possible explanation is that the official Korean guidelines recommending the treatment of latent TB in TNF-α inhibitor users were published in 2011 [27]. Most of the patients in our study started TNF-α inhibitors before the guideline was publish.

In summary, we showed that among TNF-α inhibitor users who contracted TB, extrapulmonary sites were common and the treatment responses were satisfactory.

KEY MESSAGE

1. We found seven cases of tuberculosis (TB) from 457 patients treated with tumor necrosis factor (TNF)-α inhibitors during study period of 12 years.
2. Among TNF-α inhibitor users who contracted TB, extrapulmonary site were commonly involved.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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