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TB

Mycobacterial Infections in Patients Treated with Tumor Necrosis Factor Antagonists in South Korea

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Abstract
Background The aims of this study were to determine the incidence of tuberculosis (TB) and nontuberculous mycobacteria (NTM) lung disease in patients who were treated with tumor necrosis factor (TNF) antagonists in South Korea and to evaluate their clinical characteristics.
Methods We surveyed all patients ($N = 509$) who were treated with TNF antagonists at Severance Hospital, South Korea, between January 2002 and December 2011. We reviewed the patients' medical records and collected microbiological, radiographic, and clinical data, including the type of TNF blocker(s) used and the results of tuberculin skin tests and interferon-gamma release assays.
Results Rheumatoid arthritis (43.6 %) and ankylosing spondylitis (27.9 %) were the most common diseases in the patients treated with TNF antagonists. Patients received etanercept (33.4 %), infliximab (23.4 %), or adalimumab (13.2 %). The remaining patients received two or more TNF antagonists (30 %). Nine patients developed TB, and four patients developed NTM lung disease. After adjustment for age and sex, the standardized TB incidence ratio was 6.4 [95 % CI 3.1–11.7] compared with the general population. The estimated NTM incidence rate was 230.7 per 100,000 patients per year.
Conclusions Our results show that mycobacterial infections increase in patients treated with TNF antagonists. The identification of additional predictors of TB for the treatment of latent tuberculosis infection and the careful monitoring and timely diagnosis of NTM-related lung disease are needed for patients who receive long-term therapy with TNF antagonists.

Keywords *Mycobacterium tuberculosis* · Nontuberculous mycobacterium · Tumor necrosis factor antagonist

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Introduction

Tumor necrosis factor (TNF) plays an important role in the immune cell response and the inflammatory network. Treatment with TNF antagonists has been shown to be effective in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease, and psoriasis [1–4]. TNF antagonists have been used to treat patients with RA in South Korea since 2001, and the use of these drugs for the treatment of other diseases has increased. Four antibodies directed against TNF and one soluble TNF receptor agent are available for clinical use worldwide [5, 6]. Two antibodies directed against TNF, adalimumab and infliximab, and one soluble TNF receptor agent, etanercept, are currently used in South Korea.

Despite the satisfactory efficacy of TNF antagonists, tuberculosis (TB) and other granulomatous infections are important side effects of these agents [7–10]. Moreover, the incidence of TB in patients treated with these agents varies according to the disease, population, and the specific TNF antagonist used [11]. Consequently, it has been suggested that patients should be screened and treated for latent tuberculosis infection (LTBI) before the initiation of treatment with TNF antagonists [6].

Although several studies have reported that an increase in the risk of TB is associated with the use of TNF blockers, there is insufficient information on nontuberculous mycobacterial infections. Nontuberculous mycobacteria (NTM) are typically opportunistic pathogens and host susceptibility to pulmonary NTM-related disease can be influenced by immunosuppressive treatments and various pulmonary diseases [12–14]. A recent survey in the US suggested that TNF-blocker therapy is a predisposing factor for NTM infection [8]. Indeed, NTM infections are more common than TB in patients who receive TNF-blocker therapies [8]. However, unlike TB, there is no evidence of latent NTM infection. Thus, screening and preventing NTM-associated disease before and during TNF-blocker therapy might not be feasible [15]. In Korea, the burden of TB is intermediate, and the prevalence of LTBI is estimated to be 33 % [16]. In addition, there is persuasive evidence that the prevalence of NTM lung disease is increasing in Korea [17, 18]. Therefore, a survey of TB and NTM occurrence in patients exposed to TNF antagonists in Korea is needed. The aims of the present study were to determine the incidence of TB and NTM lung disease and to evaluate the clinical characteristics of patients with mycobacterial infections who are treated with TNF antagonists.

Patients and Methods

Study Design and Subjects

A retrospective, longitudinal cohort study was performed with patients who received TNF antagonists at Severance Hospital, which is a 2,000-bed university, tertiary, referral hospital in Seoul, South Korea. During the study period (January 2002–December 2011), 543 patients underwent treatment with TNF antagonists. Excluded from the study were those patients who were under 18 years of age ($N = 31$) or who visited the hospital only once ($N = 3$). Thus, we reviewed the medical records of 509 patients and collected microbiological, radiographic, and clinical data, which included the type of TNF antagonists used and the results of the tuberculin skin test (TST) and interferon-gamma (IFN-γ) release assay (IGRA). All follow-up data available until July 2012 were used. The study protocol was reviewed and approved by the Ethics Review Committee of Severance Hospital, Yonsei University Health System.

Diagnosis of Active TB and NTM-Related Lung Disease

A diagnosis of TB was made if *Mycobacterium tuberculosis* (*M. tuberculosis*) was isolated in the culture of any clinical specimen or if *M. tuberculosis* DNA was detected in any clinical specimen by polymerase chain reaction analysis. Patients with a high clinical likelihood of active TB and a negative mycobacterial culture finding but who had good clinical and radiographic responses to anti-TB treatment were also included as active TB patients. NTM lung disease was defined according to the 2007 diagnostic criteria proposed by the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) [19]. We defined TB and NTM lung disease as mycobacterial infections that occurred during treatment with TNF antagonists if they were diagnosed during the period of anti-TNF treatment or within 3 months of the discontinuation of TNF antagonist treatment.

TST and IGRA

The TST was performed on the volar side of the forearm, according to the Mantoux method, with a 2-TU dose of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark). A positive result was adjudged when the transverse diameter of the induration was >10 mm after 48–72 h using the ballpoint method.

The QuantiFERON-TB Gold In-Tube test (QFT-GIT test; Cellestis Ltd., Carnegie, Victoria, Australia) has been used in our hospital since December 2006. This test was performed according to the manufacturer's instructions. The QFT-GIT test was considered positive for an IFN-γ response to the TB antigen tube that was significantly above the nil IFN-γ IU/mL value (≥0.35 IU/mL).

Statistical Analysis

Data are expressed as numbers (percentages) and medians (interquartile range). Standardized incidence ratios (SIRs) for TB were calculated to compare the incidence of TB in patients who received TNF antagonists with that in the Korean general population [9]. Data on the incidence of TB in the general population were provided by the Korean Tuberculosis Surveillance Center, and an estimate of the total population was obtained from the Korean National Statistical Office. The observed number of TB cases among patients who were treated with TNF antagonists was divided by the expected number of TB patients who received TNF antagonists. The expected number of TB patients treated with TNF antagonists was extrapolated from the incidence of TB for the general population in 2007 (the midpoint of 2002–2011). The expected number of TB patients was calculated by multiplying the TB incidence for the general population in 2007 by the number of patients who took TNF antagonists. The ratios were adjusted for both age and sex. All tests were two-sided, and $p < 0.05$ was considered to indicate statistical significance. Data

were gathered and analyzed using the SAS ver. 9.2 software (SAS Institute Inc., Cary, NC, USA).

Results

Clinical Features of Patients Exposed to TNF Antagonists

Table 1 provides a general description of the patients who were exposed to TNF antagonists. In total, 509 patients received anti-TNF therapy in our hospital between January 2002 and December 2011. The median age of the patients was 43 (range = 18–85) years, and there were 268 female patients (52.7 %). RA (43.6 %) and AS (27.9 %) were the most common diseases in the patients treated with TNF antagonists. Inflammatory bowel diseases, including Crohn's disease (16.3 %), ulcerative colitis (2.0 %), and Behcet's disease (2.2 %), were the main diseases that were treated with TNF antagonists. Etanercept (33.4 %) was the most commonly administered TNF antagonist among those patients who received a single TNF antagonist. Overall, 119/436 (27.3 %) patients showed a positive TST, while 63/203 (31.0 %) patients showed a positive result in the IGRA. Treatment for LTBI was implemented in 146 patients (28.7 %). The median duration of follow-up was 34.92 (range = 0.12–120.96) months.

Table 1 Clinicopathologic characteristics of the patients who received treatment with TNF antagonists

Characteristic	Patients ($N = 509$)
Age [median (range)] (years)	43 (18–85)
Gender, female	268 (52.7 %)
BMI [median (IQR)]	21.50 (19.38–24.37)
History of TB	30 (5.9 %)
Diabetes mellitus	36 (7.1 %)
Hypertension	79 (15.5 %)
Main diagnosis	
Adult-onset still's disease	5 (1.0 %)
Ankylosing spondylitis	142 (27.9 %)
Behcet's disease	11 (2.2 %)
Crohn's disease	83 (16.3 %)
Graft versus host disease	5 (1.0 %)
Juvenile rheumatoid arthritis	7 (1.4 %)
Psoriasis	10 (2.0 %)
Rheumatoid arthritis	222 (43.6 %)
Ulcerative colitis	10 (2.0 %)
Others[a]	14 (2.8 %)
TNF antagonist	
One TNF antagonist	356 (70.0 %)
Adalimumab	67 (13.2 %)
Etanercept	170 (33.4 %)
Infliximab	119 (23.4 %)
Two or more TNF antagonists	153 (30.0 %)
Duration of TNF antagonist median (IQR) months	13.0 (6.0–33.5)
TST, positive (total $N = 436$)	119 (27.3 %)
IGRA, positive (total $N = 203$)	63 (31.0 %)
TB prophylaxis	146 (28.7 %)
Patient-years [median (IQR)]	2.91 (1.33–5.33)
Patient-years (months) [median (range)]	34.92 (0.12–120.96)

BMI body mass index, *IQR* interquartile range, *TB* tuberculosis, *TNF* tumor necrosis factor, *IGRA* IFN-γ release assay, *TST* tuberculin skin test

[a] Others includes unspecific arthritis, psoriatic arthritis, fibromyalgia syndrome, hemophagocytic syndrome, scleritis, sclerosing mesenteritis, seronegative spondyloarthropathy, undifferentiated spondyloarthropathy

Clinical and Demographic Characteristics of the Nine TB Patients

Of the 509 patients studied, 9 (1.8 %) developed TB during or after treatment with TNF antagonists. Table 2 gives the characteristics of these nine TB patients. Six patients developed TB during anti-TNF treatment (infliximab, $N = 3$, etanercept, $N = 1$, and more than one agent, $N = 2$). Since it was included in the multiple agent regimen, infliximab was administered to two thirds of the TB patients who were treated with TNF antagonists. The median time from initiation of TNF antagonist administration to development of TB was 8 (range = 2–24) months. Of the nine patients with TB, eight were diagnosed with pulmonary TB and one with extrapulmonary TB. Four patients had a positive TST and four patients had a positive IGRA. Three of the four patients with positive TST received isoniazid treatment for LTBI. Among them, one patient was diagnosed based on the positive mycobacterial culture of sputum and showed no resistance to isoniazid. One patient had a mixed infection with TB and NTM. This patient was diagnosed with *Mycobacterium abscessus*-associated lung disease before the diagnosis of TB. Eight of the patients with TB were treated with first-line anti-TB medication and successfully completed the full course of anti-TB treatment. One patient died during the anti-TB treatment due to complications associated with underlying Crohn's disease.

Clinical and Demographic Characteristics of the Four NTM Patients (Table 3)

Four patients were diagnosed as having NTM lung disease after treatment with TNF antagonists. Two patients had received etanercept, one patient had received infliximab, and one patient had received both adalimumab and etanercept. The duration of treatment with TNF antagonists

Table 2 Clinical and demographic characteristics of nine TB patients during or after treatment with TNF antagonists

Case	Age/sex	History of TB	DM	TNF antagonists received	Duration of TNF antagonist treatment (months)	From TNF antagonist to TB onset (months)	Main diagnosis	Prophylaxis	TST	IGRA	TB diagnosis method	TB treatment outcome
1[a]	42/F	+	–	Etanercept	24	24	RA	–	–	nd	Clinical	Cure
2	41/M	–	–	Etanercept + infliximab	2	2	AS	–	+	nd	Culture	Cure
3	31/F	–	–	Infliximab	2	62	AOSD	–	–	nd	Culture	Cure
4	52/F	–	+	Adalimumab + etanercept	23	23	RA	+	+	+	Culture	Cure
5	32/M	–	–	Etanercept	2	54	AS	+	+	+	Clinical	Cure
6	40/M	–	–	Infliximab	1	2	Crohn's disease	–	nd	+	Culture	Death d/t main disease
7	25/M	–	–	Infliximab	18	13	Crohn's disease	–	–	nd	Culture	Cure
8	32/F	–	–	Infliximab	2	4	Crohn's disease	+	+	nd	Clinical	Cure
9[b]	51/M	–	–	Infliximab	1	26	Behcet's disease	–	–	+	Culture	Cure

AS ankylosing spondylitis, *AOSD* adult-onset still's disease, *DM* diabetes mellitus, *IGRA* IFN-γ release assay, *nd* not done, *RA* rheumatoid arthritis, *TB* tuberculosis, *TNF* tumor necrosis factor, *TST* tuberculin skin test

[a] Patient with extrapulmonary tuberculosis

[b] Patient having mixed infection with TB and NTM

ranged from 1 to 30 months. All four patients were diagnosed with NTM lung disease after discontinuation of the TNF antagonists; the median time from the discontinuation of the agents to diagnosis of NTM lung disease was 17 (range = 5–32) months. However, all the patients continued to take other immunosuppressive agents, including prednisolone and methotrexate, when NTM-related lung disease developed. Of the four patients, two were diagnosed as being infected with *M. abscessus*, one with *M. avium*, and one with *M. intracellulare*. Chest CT showed that two of the patients had the nodular bronchiectatic form and one had the fibrocavitary form of the disease. The two patients with lung disease associated with *M. avium* and *M. intracellulare* infections were treated with clarithromycin, rifampin, and ethambutol; one of them died during the treatment due to aggravation of pneumonia. The remaining two patients with *M. abscessus*-related lung disease were followed stationary, without treatment.

Incidences of TB and NTM After Exposure to TNF Antagonists

The incidence of TB after exposure of TNF antagonists was 519.0 per 100,000 patients per year. Table 4 gives the incidence ratio adjusted for sex and age. The overall incidence of TB in patients who were treated with TNF antagonists, adjusted for sex and age, was significantly higher than that in the general population (SIR 6.4, 95 % CI 3.1–11.7). The estimated incidence of NTM lung disease after exposure to TNF antagonists was 230.7 per 100,000 patients per year.

Discussion

Several studies have reported on the relationship between TB and TNF antagonists [9, 11, 20, 21]. In the present study, the estimated incidence of TB for patients who were exposed to TNF antagonists was 519.0 per 100,000 patient-years. When we adjusted for age and sex, this was 6.4 times higher than the incidence of TB in the general population. This result confirms the results of previous studies that addressed the higher incidence of TB in patients who received TNF antagonists [9–11]. In addition, we found that NTM lung disease could occur in patients who were treated with TNF antagonists. However, the number of patients with NTM lung disease was lower than the number of patients with TB in our study population.

The risk for TB development in patients who receive TNF-α inhibitors is relatively well known [9–11]. TNF-α is a potent proinflammatory cytokine that plays an important role in immunity to intracellular bacteria, particularly TB [22]. TNF-α inhibitors can inhibit the formation of granulomas and can interfere with innate immune responses, such as phagolysosomal maturation and monocyte apoptosis during TB [23]. As the presence of TNF-α is essential for the formation and maintenance of the granuloma, the use of a TNF-α inhibitor may result in the reactivation of

Table 3 Clinical and demographic characteristics of four NTM patients after treatment with TNF antagonists

Case	Age/sex	History of TB	DM	TNF antagonists received	Duration of TNF antagonist treatment (months)	From TNF antagonist to NTM onset (months)	Main diagnosis	Prophylaxis	NTM species	TST	IGRA	Radiologic profile	Immune suppressant
1	62/F	–	–	Etanercept	30	49	RA	–	*M. abscessus*	–		Bronchiectasis	Methotrexate, prednisolone
2	68/M	–	–	Adalimumab + Etanercept	4	9	RA	–	*M. intracellulare*	–	–	Consolidation, fibrosis	Prednisolone
3	74/F	+	–	Etanercept	12	27	RA	–	*M. avium*	–		Bronchiectasis	Prednisolone
4[a]	51/M	–	–	Infliximab	1	33	Behcet's disease	–	*M. abscessus*	–	+	Fibrosis, cavitation	Prednisolone

TB tuberculosis, *DM* diabetes mellitus, *TNF* tumor necrosis factor, *NTM* nontuberculous mycobacteria, *TST* tuberculin skin test, *IGRA* IFN-γ release assay, *RA* rheumatoid arthritis

[a] Patient having mixed infection with TB and NTM

LTBI. The screening and treatment of LTBI are recommended in the clinical guidelines for the use of TNF-α inhibitors. Sixty patients (11.8 %) in the present study did not receive screening or treatment for LTBI before they received TNF-α inhibitors, although none of them developed active TB. Thus, clinicians need to pay more attention to screening and treatment of LTBI before administering TNF-α inhibitors. In addition, nine patients developed active TB after treatment with TNF-α inhibitor, even though more than 90 % of the patients in our population who had a positive TST or IGRA received treatment for LTBI. Three of these patients were treated with isoniazid for LTBI before receiving treatment with TNF-α inhibitor. It has been reported that the development of TB during TNF-α inhibitor treatment shows a biphasic pattern, i.e., early TB development after 2–3 months of treatment and late TB development after more than 20 months of treatment [24]. The reactivation of LTBI and newly acquired TB infection during TNF-α inhibitor treatment have been implicated in this biphasic emergence of TB among patients treated with TNF-α inhibitors. Likewise, in our patients, only half of the TB patients were diagnosed at 2–4 months of treatment with TNF-α inhibitors. Therefore, additional predictors of TB development, such as serial monitoring of IGRA for patients with long-term TNF-α inhibitor therapy, are needed, especially in TB-endemic areas.

Although there are emerging data on the increasing incidence of NTM infection among patients who receive TNF antagonist therapy [8, 25], there is still insufficient information regarding the relationship between NTM infection and TNF-α inhibitors. NTM-related diseases in impaired hosts have been reported [26], but this is not considered to be reactivation of latent infection with NTM and is, instead, related to an unrecognized active disease or de novo exposure while on immunosuppressive medications [27]. TNF antagonists were shown in a mouse model to alter resistance to *M. avium* complex infection and increase the NTM burden [28]. In addition, six children from the Mediterranean region who had disseminated NTM infections were reported to show defective TNF-α production in response to endotoxin [29]. In the present study, four patients were diagnosed with NTM lung disease after exposure to TNF-α inhibitors. Two of these patients had underlying lung disease, such as COPD and fibrosis, before TNF-α inhibitor therapy, although we cannot be certain that they had NTM lung disease before TNF-α inhibitor therapy or newly acquired NTM infection thereafter, since no screening process for NTM lung disease was performed before the TNF-α inhibitor therapy. Given the long period of time between the start of TNF-α inhibitor therapy and the diagnosis of NTM lung disease, as well as the progression of underlying structural disease or newly

Table 4 Observed numbers and standardized incidence ratios of patients with TB

Subgroup	Patients (*N*)	Duration of patient observation (patient-years)	Observed	Expected[a]	Standardized incidence ratio	95 % CI, low	95 % CI, high
Sex							
Male	236	783	5	0.78	6.4	2.4	14.2
Female	264	934	4	0.63	6.3	2.0	15.3
Age range (years)							
20–29	87	268	1	0.22			
30–39	121	489	3	0.32			
40–49	105	344	3	0.20			
50–59	89	311	2	0.21			
60–69	58	172	0	0.18			
≥70	40	133	0	0.28			
Overall	500	1,717	9	1.41	6.4	3.1	11.7

TB tuberculosis, *CI* confidence interval

[a] To estimate "expected TB," the sex- and age-specific patient notification rates for all forms of TB in 2007 were extrapolated

developed lung inflammation, the NTM lung disease was probably newly acquired after therapy with the TNF-α inhibitor. Given the increase in NTM lung disease in many countries, including Korea [17, 18], careful monitoring and timely diagnosis of NTM lung diseases are important for patients who receive long-term treatment with TNF-α inhibitors. Timely diagnosis relies on chest imaging studies, mycobacterial culturing, and examination of respiratory symptoms.

The present study has several limitations. It was a retrospective survey at a single referral medical center, and we could not know all the risk factors for mycobacterial infections. For each patient, the follow-up period was different, and this period of time might be too short to detect mycobacterial infection in some patients. Some patients did not undergo the TST or IGRA or receive TB prophylaxis. Regardless of the TNF antagonist administered, underlying diseases and immunosuppressive agents might increase the risk for mycobacterial infections. In our cohort, four patients with NTM lung disease were diagnosed after the discontinuation of TNF-α inhibitors. This means that the NTM lung disease could not be affected by the TNF-α inhibitors alone but rather by other immunosuppressive agents, such as methotrexate and prednisolone. However, many studies have demonstrated a relationship between TNF antagonists and infections [6–9, 11].

In summary, the risk of TB was 6.4 times higher for patients who were treated with TNF antagonists compared with the Korean general population, and NTM lung disease developed after treatment with TNF antagonists. The identification of additional predictors of TB with treatment for LTBI, as well as careful monitoring and timely diagnosis of NTM lung disease, are needed for patients who are receiving long-term anti-TNF therapy.

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Conflict of interest The authors have no conflict of interest to disclose.

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