Incidence of Tuberculosis Among Korean Patients with Ankylosing Spondylitis Who Are Taking Tumor Necrosis Factor Blockers

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ABSTRACT. ***Objective.*** To assess the incidence and relative risk of new tuberculosis (TB) infections in Korean patients with ankylosing spondylitis (AS) and patients with AS who are undergoing treatment with tumor necrosis factor (TNF) blockers.

Methods. New cases of TB were identified by reviewing the medical records of 919 patients with AS not treated with TNF blockers and those of 354 patients with AS treated with adalimumab (n = 66), infliximab (n = 78), or etanercept (n = 210) between 2002 and 2009. Reference data were obtained from the Korean National Tuberculosis Association.

Results. The mean incidence rate of TB was 69.8 per 100,000 person-years (PY) in the general population, 308 per 100,000 PY in the TNF blocker-naive AS cohort, and 561 per 100,000 PY in the TNF blocker-exposed AS cohort. The incidence rate of TB in the infliximab-treated AS cohort (540 per 100,000 PY) was higher than that in the adalimumab-treated AS cohort (490 per 100,000 PY). No cases of TB occurred in the etanercept-treated AS cohort. Comparing the relative risks of TB infections between the TNF blocker-exposed AS cohort and the TNF blocker-naive AS cohort, no statistically significant difference was identified (risk ratio 0.53; 95% CI 0.144–1.913).

Conclusion. The risk of TB was higher in the TNF blocker-naive AS cohort than it was in the general population. However, the risk of TB was not increased in the TNF blocker-exposed AS cohort compared with the TNF blocker-naive AS cohort. Among patients with AS, etanercept is associated with a lower risk of TB compared with monoclonal antibodies. (First Release Aug 15 2011; J Rheumatol 2011; 38:2218–23; doi:10.3899/jrheum.110373)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS TUMOR NECROSIS FACTOR BLOCKER
MYCOBACTERIUM TUBERCULOSIS

Currently, tumor necrosis factor (TNF) blockers are used in the treatment of many rheumatic diseases[1]. In patients with ankylosing spondylitis (AS) whose disease has proven refractory to nonsteroidal antiinflammatory drugs (NSAID) and/or disease-modifying antirheumatic drugs (DMARD), TNF blockers often significantly improve many of the symptoms and signs of AS. However, tuberculosis (TB) is the most important side effect in patients treated with these agents[2,3].

The overall incidence of TB in patients with rheumatic disease who are treated with TNF blockers varies by disease, population, and the specific TNF blocker used. For instance, while Korean patients with rheumatoid arthritis (RA) treated with infliximab faced a 30.1-fold greater risk of TB infection compared to the general Korean population[4], the risk among patients with RA in the United States was 9-fold higher[5]. Patients with various ethnicities and rheumatic diseases who were treated with etanercept demonstrated a lower risk of TB infections[6].

South Korea is considered a country with an intermediate TB burden — the reported prevalence of TB among patients with RA is markedly higher than in other developed countries[4]. While a comprehensive study of 36 global clinical trials regarding the use of adalimumab in 6 diseases (RA, AS, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, and Crohn's disease)[7] indicates that serious infections are significantly more common in RA and Crohn's disease, the exact prevalence of TB in patients with AS remains unknown. Accordingly, we assessed the incidence rate and relative risk (RR) of TB in 2 populations: patients with AS and patients with AS who were treated with TNF blockers.

MATERIALS AND METHODS

General population. The Korean Tuberculosis Surveillance System (KTBS) is a Web-based system used by 248 health centers throughout the country, as well as many other public and private health institutions, to report new TB cases to the Korean Center for Disease Control and Prevention (CDC) and the

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Korean National Tuberculosis Association (KNTA)[8]. Each year, the KNTA publishes the number of new TB cases and the incidence of TB, estimated by dividing the number of cases by the entire Korean population.

TNF blocker-naive AS cohort. A total of 3169 subjects with AS were recruited from Hanyang University Hospital for Rheumatic Diseases between 2002 and 2009. All individuals met the 1984 modified New York criteria for AS[9], and none had been previously exposed to TNF blockers. After excluding patients with missing data, a total of 919 were ultimately enrolled.

Medical records for all enrolled subjects were reviewed for information regarding sex, age, disease duration, and risk factors for TB infection, including history of diabetes mellitus (DM), mean steroid dose, DMARD use, history of TB, recent contact with patients who have active TB, and abnormal chest radiographs suggestive of prior TB infection. Disease duration was calculated starting with date of initial symptom presentation. Tuberculin skin testing (TST) was not performed.

TNF blocker-exposed AS cohort. AS patients refractory to NSAID or DMARD received 1 of 3 TNF blockers: adalimumab, infliximab, or etanercept. Only subjects treated with TNF blockers for a period of at least 2 months were included in the cohort, and all subjects were recruited from the single medical center during the same timeframe. Subjects with missing data or who had been treated with > 2 TNF blockers were excluded. Of the 354 patients treated with TNF blockers, 66 received adalimumab, 78 infliximab, and 210 etanercept.

Prior to the initiation of TNF blocker therapy, demographic and clinical information regarding TB infection risk factors was obtained through a thorough review of the medical records (history of DM, mean steroid dosage, DMARD use, history of TB and TST, recent contact with patients with active TB, abnormal chest radiographs suggestive of a previous TB infection, and a history of anti-TB chemoprophylaxis). The duration and frequency of each TNF blocker were also documented.

Definition of TB cases. A "definite" case of TB, as defined by the KTBS, must meet 1 of the following criteria: (1) presentation with typical symptoms of TB and isolation of *Mycobacterium tuberculosis* from a clinical specimen, or (2) presentation with the typical symptoms and radiological or histological findings of TB, but culture has not been or cannot be obtained. A "clinical" case of TB is one in which the clinician judges that the clinical symptoms and/or radiological signs and/or histological findings are compatible with TB and that show definitive improvement with anti-TB medications. All individuals diagnosed with TB prior to being diagnosed with AS were excluded.

TST was performed by trained technicians on the volar side of the forearm, as per the Mantoux method. Tuberculin purified protein derivative (PPD) was injected intradermally, and any resulting induration was measured in millimeters 72 h after initial inoculation. Per KTBS guidelines, an induration of 10 mm or greater was considered positive.

Statistical analysis. To estimate the incidence of TB among patients with AS that had or had not been exposed to TNF blockers, we divided the TB cases by the total number of cases and by the TNF blocker-specific number of patient-years of followup. The RR of TB in patients with AS compared with that of the general population was calculated using crude analysis. To compare the RR of TB between the TNF blocker-specific AS cohort and the TNF blocker-naive AS cohort, Cox hazard survival regression analysis was performed. The OR of the specific clinical characteristics were calculated using binary logistic regression analysis for both the TNF blocker-exposed AS cohort and the TNF blocker-naive AS cohort. For the clinical characteristics with categorical variables, chi-squared and Fisher's exact tests were used to compare cohorts. For clinical characteristics with continuous variables, 1-way ANOVA and Tukey's multiple comparison tests were used for posthoc comparisons. All analyses were performed using SPSS v10 statistics package for Windows (SPSS, Chicago, IL, USA). In all cases, the null hypothesis was rejected at a significance level of 5% ($p < 0.05$).

RESULTS

Clinical features of patients with AS. Mean age, sex ratio, and disease duration did not differ significantly between TNF blocker-naive and TNF blocker-exposed AS cohorts (Table 1). Because etanercept was the first TNF blocker introduced in Korea, the etanercept-treated AS cohort was the largest.

Incidence rate of TB in the general population. As reported by the Korean CDC and the KNTA, the estimated mean incidence for all forms of TB between 2002 and 2009 was 69.8 cases per 100,000 person-years (PY), with pulmonary TB comprising about 83% of all cases. The estimated men-to-women ratio was 1.5:1, and the age distribution of TB showed a peak incidence rate in the elderly (> 70 yrs), followed by that of middle-aged adults, with young adults exhibiting the lowest incidence rate (data not shown).

Incidence rate of TB in the TNF blocker-naive AS cohort. There were 10 incident cases of TB during 3247 PY of followup (308 per 100,000 PY). The risk of TB in this cohort was 4.3-fold higher than that in the general Korean population. The mean age for all TB cases was 31.1 years, with young adults exhibiting the highest incidence rate (Table 2). The estimated men-to-women ratio was 5.4:1. One of the 10 cases had a history of TB. The mean interval between AS onset and diagnosis of active TB was 7.3 years (range 1–19 yrs). The overall rate of extrapulmonary TB was 20%, which is comparable to the general population.

Incidence rate of TB in the TNF blocker-exposed AS cohort. Three cases of TB developed during 1784 PY of followup (561 per 100,000 PY). The RR of TB in the TNF blocker-exposed AS cohort was not statistically significant compared with that of the TNF blocker-naive cohort (RR 0.53, 95% CI 0.144–1.913). To assess the risk factors for TB in patients with AS treated with TNF blockers, a logistic regression analysis was performed comprising 919 TNF blocker-naive subjects and 354 TNF blocker-exposed subjects (Table 1). This analysis revealed TB in the TNF blocker-exposed AS cohort to be negatively associated with HLA-B27 positivity (OR 0.17, 95% CI 0.037–0.731; $p = 0.013$).

In the adalimumab-treated AS cohort, 1 case of TB developed during 204 PY of followup (308 per 100,000 PY). The risk for TB in the adalimumab-treated AS cohort was 7.0-fold higher than that in the general population and 1.33-fold higher (95% CI 0.170–10.437) than the respective risk for the TNF blocker-naive AS cohort. In the infliximab-treated AS cohort, 2 cases of TB developed during 366 PY of followup (540 per 100,000 PY), resulting in a risk for TB that was 7.7-fold higher than that in the general population and 1.57-fold higher (95% CI 0.344–7.184) than the respective risk in the TNF blocker-naive AS cohort. In the etanercept-treated AS cohort, there was no case of TB during 1214 PY of followup. Additional information regarding the 3 patients diagnosed with TB is presented in Table 2.

DISCUSSION

Per our results, the TNF blocker-naive AS cohort between 2002 and 2009 had a 4.3-fold higher risk of TB compared with

Table 1. Clinical characteristics of enrolled patients with ankylosing spondylitis (AS). Data are percentages unless otherwise indicated.

Characteristic	TNF Blocker-naive, n = 919	TNF Blocker Adalimumab, n = 66	TNF Blocker Infliximab, n = 78	TNF Blocker Etanercept, n = 210	p*	TNF Blocker Total, n = 354	OR (95% CI)	p**
Men/women	84.3/15.7	86.4/13.6	88.5/11.5	81.9/18.1	0.543	84.2/15.8	—	—
Age, yrs, mean ± SD	34.6 ± 10.4	33.3 ± 10.3	36.7 ± 11.6	35.9 ± 10.2	0.085	35.5 ± 10.5	—	—
Disease duration, yrs, mean ± SD	10.2 ± 8.7††	11.6 ± 9.0††	11.5 ± 7.3††	13.3 ± 6.9††	< 0.0001	12.6 ± 7.4	0.93 (0.833–1.034)	0.175
HLA-B27-positive	92	84.4	89.7	82.4	< 0.0001	80.0	0.17 (0.037–0.731)	0.013
Peripheral arthritis	35.8	51.5	70.5	49.7	< 0.0001†	54.2	2.20 (0.507–9.572)	0.291
Enthesitis	28.9	21.2	25.6	26.2	0.641†	25.1	—	—
Diabetes mellitus	1.3	1.5	1.3	0.5	0.652†	0.8	—	—
MTX treatment	22.6	40.9	61.5	49	< 0.0001	49.7	0.52 (0.122–2.239)	0.381
SSZ treatment	40.3	68.2	65.4	59.2	< 0.0001	61.6	1.26 (0.262–6.101)	0.771
Steroid dosage, mg/day, mean ± SD	0.80 ± 1.50	2.90 ± 2.59	2.50 ± 4.20	2.20 ± 3.18	< 0.0001	2.4 ± 3.3	1.00 (0.750–1.324)	0.982
TB history	3.7	6.1	3.8	8.1	0.046	6.8	0.98 (0.098–9.793)	0.986
Chest radiography suggesting old	2.6	9.1	2.6	4.8	0.027	5.1	8.67 (0.920–81.628)	0.059
TB-positive TST before TNF blocker therapy	—	37.9	47.4	32.9	< 0.0001	—	—	—
TB prophylaxis	—	50.0	46.2	42.4	0.307†	—	—	—
Duration of TNF blocker therapy, mo, mean ± SD	—	13.7 ± 8.4††	34.1 ± 24.9††	39.0 ± 14.1††	< 0.0001	—	—	—
Patient-yrs exposure	—	75.4	221.7	682.5	< 0.0001	—	—	—

* One-way ANOVA, mean ± SD, $p < 0.05$ and chi-squared test, n (%), $p < 0.05$. ** Binary logistic regression analysis. †† Nonsignificant difference between groups based on Tukey's multiple comparison test. † Fisher's exact test, n (%), $p < 0.05$. TNF: tumor necrosis factor; MTX: methotrexate; SSZ: sulfasalazine; TB: tuberculosis; TST: tuberculin skin test.

Table 2. Clinical characteristics of new TB infections occurring in patients with ankylosing spondylitis.

Patient	Age, yrs	TNF Blocker	Disease Duration, yrs	Peripheral Arthritis	HLA-B27	DM	DMARD	Mean Steroid, mg/day	History of TB	Old TB on CXR	TST	Prophylaxis	Interval to Active TB*, mo	Diagnosis Method	TB Type
1	32 F	—	25	+	+	—	MTX + SSZ	2.5	—	—	ND	ND	228	AFB (+) CXR (+)	Pulmonary
2	45 M	—	15	—	—	—	—	0	+	+	ND	ND	132	CXR (+)	Pulmonary
3	31 M	—	10	+	ND	—	SSZ	5	—	—	ND	ND	14	CXR (+)	Pulmonary
4	30 F	—	10	+	+	—	SSZ	0	—	—	ND	ND	36	AFB (+)	Pulmonary
5	43 M	—	6	+	+	—	—	0	—	—	ND	ND	1	CXR (+)	Pulmonary
6	37 M	—	6	—	ND	—	SSZ	0	—	—	ND	ND	60	CXR (+)	Pulmonary
7	29 M	—	3	—	+	—	SSZ	0	—	—	ND	ND	15	CXR (+)	Pleurisy
8	45 F	—	17	—		—	—	0	—	—	ND	ND	192	TB-PCR (+)	Intestine
9	41 M	—	21	+	+	—	MTX + SSZ	0	—	—	ND	ND	108	CXR (+)	Pulmonary
10	30 M	—	12	—	ND	—	—	1.25	—	—	ND	ND	96	CXR (+)	Pulmonary
1	42 M	Infliximab	17	+	+	—	MTX + SSZ	5	—	—	—	INH 9 mo	177 (27)**	CXR (+)	Pleurisy
2	27 M	Infliximab	5	+	+	—	SSZ	5	—	—	—	ND	41 (16)	Chest CT (+)	Miliary
3	27 M	Adalimumab	16	+	—	—	MTX + SSZ	0	+	+	ND	ND	186 (12)	Chest CT (+)	Pulmonary

* Interval between onset of AS and diagnosis of active TB. ** ( ) Interval between starting TNF blockers and diagnosis of active TB. TB: tuberculosis; TNF: tumor necrosis factor; DM: diabetes mellitus; DMARD: disease-modifying antirheumatic drug; CXR: chest radiograph; TST: tuberculin skin test; MTX: methotrexate; SSZ: sulfasalazine; ND: not done; AFB: acid-fast bacilli; TB-PCR: polymerase chain reaction for *M. tuberculosis*; INH: isoniazid; CT: computed tomography scan.

that of the general population. Patients with rheumatic diseases are vulnerable to infections because of the intrinsic immune dysregulation associated with the disease processes, the immunosuppressive therapies used, and other associated comorbidities[10,11]. After the introduction of TNF blockers, the incidence of TB increased significantly among patients with

autoimmune diseases[3]. TNF-α is critical for the host immune response against intracellular bacteria, particularly TB[12,13], as this cytokine plays a central role in macrophage activation, cell recruitment to the sites of infection, granuloma formation, and the maintenance of granuloma integrity[14,15,16]. Moreover, the release of TNF-α in response to TB infection is believed to have several beneficial effects. *In vitro* studies suggest that TNF-α promotes macrophage phagocytosis, thereby increasing mycobacteria destruction[17] and inducing granuloma formation, all of which ultimately serve to sequester the invading mycobacteria and inhibit further dissemination[13]. Further, TNF-α-induced granuloma formation is important for survival after primary infection[18,19,20]. In patients with latent tuberculosis infections (LTBI), iatrogenic TNF-α neutralization by monoclonal antibodies may result in the dissolution of intact granulomas, the release of viable mycobacteria, and disease reactivation[21].

While the increased risk of TB in patients treated with TNF blockers has already been well established in reports from multiple countries[4,5,22,23,24,25], most data derive from studies of patients with RA who were treated with infliximab or etanercept. Our study, which focuses on patients with AS treated with TNF blockers, also reveals similar patterns to those seen in previous RA cohorts[4]. Compared with a TNF blocker-naive RA cohort in Korea[4], the mean age (4th decade vs 6th decade), total percentage of patients with DM (1.3% vs 4.9%), and the percentage of patients treated with methotrexate (23.5% vs 93.6%) were all lower in our TNF blocker-naive AS cohort. These differences provide a possible explanation for why fewer TB cases occurred in our cohort than in the RA cohort.

Nonetheless, the risk of TB in the TNF blocker-naive AS cohort was found to be 4.3-fold higher than that in the general Korean population, especially among young individuals. While the exact cause for this discrepancy remains unclear, data from 1 prospective study[26] indicate that nonspecific subclinical pulmonary involvement (manifested as apical fibrosis, interstitial lung disease, bronchiectasis, or emphysema) occurs frequently in AS, particularly in early AS. Another recent retrospective analysis[27] also suggests that TB is the most frequent pulmonary infection in patients with AS and commonly presents with apical lung fibrosis. Still, the exact causal mechanism resulting in increased risk of TB among patients with AS remains unknown.

To identify specific risk factors of TB in patients with AS receiving TNF blockers, clinical characteristics from 919 TNF blocker-naive and 354 TNF blocker-exposed subjects were compared using a logistic regression analysis. However, no significant association (except HLA-B27 positivity) was identified between the 2 cohorts. We contend that this occurred because of the relatively small sample size and followup period, and strict TST surveillance for LTBI as well as appropriate anti-TB chemoprophylaxis, which likely further reduced the TB incidence rate in the TNF blocker-exposed AS cohort. Additionally, the most common TNF blocker prescribed was etanercept, accounting for 59% of all cases, and study participants taking etanercept had a TB incidence rate of zero.

In the infliximab-treated AS cohort, 1 of 2 TB cases showed positive TST conversion, progressing from an initial negative result to a strong reactive result (> 15 mm). This particular individual was treated with infliximab for 16 months, then miliary TB was diagnosed. Notably, the median time from the first infliximab dose to TB diagnosis was 21.5 months (range 16 to 27 mo), longer than the interval in other studies. In patients with RA, the median interval from initiation of infliximab treatment to LTBI reactivation was 3 months[28]. We contend that the TB cases in our cohort may not have resulted from the reactivation of LTBI but instead represent the progression of new infections that occurred throughout treatment[1]. In the adalimumab-treated AS cohort, 1 TB case had a history of pulmonary TB, which was later diagnosed as being in complete remission after a 6-month course of anti-TB medication. At the time of adalimumab initiation, this subject had undergone neither TST nor additional prophylactic TB treatment, as he had already finished a full course of anti-TB therapy. In this case, the median time from first adalimumab dose to TB diagnosis was 12 months. No cases of TB occurred in the etanercept-treated AS cohort. Our finding that etanercept is associated with a lower risk of TB compared to those of monoclonal antibodies supports most data from other RA cohort studies in Korea and other countries[4,5,23,25,29].

The different pharmacologic mechanisms of action among TNF blockers may account for the varying rates of LTBI, particularly between the 2 monoclonal antibodies and etanercept. Specifically, etanercept binds only trimeric soluble TNF (sTNF) and releases sTNF faster than do monoclonal antibodies. Conversely, both infliximab and adalimumab bind trimeric as well as monomeric sTNF, forming significantly more stable complexes. Moreover, etanercept binds sTNF and transmembrane TNF-α (tmTNF-α) at equal ratios, while monoclonal antibodies are able to bind both forms of TNF molecules at once[1,30]. In particular, infliximab can bind tmTNF-α much more tightly than can the other agents, and facilitates macrophage and monocyte lysis through antibody- and complement-mediated cytotoxicity[13,16]. Further, the effect of bolus dosing and high peak levels of infliximab may additionally increase the risk of infection[12,31]. Accordingly, infliximab likely disturbs the host's ability to suppress TB infection significantly more than do either of the other 2 agents[12].

According to the South Korean guidelines published in 2004[32], all patients must be screened for LTBI by TST, chest radiography, physical examination, and interview prior to receiving TNF blocker therapy. Under these guidelines, patients exhibiting positive TST (defined as an area of induration with a diameter ≥ 10 mm) are recommended to receive isoniazid at a dose of 4 to 6 mg/kg/day for 9 months. Additionally, all patients with intermediate TST (defined as an

area of induration between 5 mm and 10 mm) with a history of incompletely treated TB, untreated exposure to TB, or a documented episode of TB are also recommended to receive anti-TB chemoprophylaxis 1 month prior to starting TNF blocker therapy. Due to anergy to cutaneous delayed hypersensitivity resulting from deficient cell-mediated immunity (either from the underlying disease itself or because of immunosuppressive treatments)[33], patients with RA undergoing treatment with immunosuppressive agents often exhibited false-negative TST results[34]. As such, a reactivation of LTBI has been increased in patients with RA treated with TNF blocker[12]. In a recent study by Inanc, *et al*[35], patients with AS who were treated with immunosuppressive agents, as well as untreated patients, rarely showed false-negative TST results, compared with the results of similar populations of patients with RA. However, we previously reported that, even after starting TNF blocker therapy, the positive TST conversion rate was significantly higher in patients with AS than it was in patients with RA, which could represent either new TB infection or reactivation of LTBI[36]. The TST has a low specificity as the PPD used for TST shares antigens with Bacillus Calmette-Guérin (BCG) and several nontuberculous mycobacteria (NTM)[37]. Interferon-γ (IFN-γ) assays use antigens that are highly specific for *M. tuberculosis* and that are not present in NTM[38]. As a result, IFN-γ assays are now suggested as supplementary tests for the diagnostic exclusion of LTBI in Korea, where BCG vaccination for newborn babies and children is still recommended[13,34,39,40].

Our study has several notable limitations. The study design was retrospective, without case control, and the patient data regarding smoking were incomplete. The rate of TB in the general population may not be accurate. It was reported by KNTA, which is dependent on the quality of the information and case reporting activities of the private sector. Additionally, the sample sizes were small and a longer followup period was needed. Nonetheless, our study represents some of the first research to specifically focus on the relative risk of TB among patients with AS treated with TNF blockers.

The risk of TB in Korean patients with AS was relatively lower than in Korean patients with RA, and higher than in the general Korean population. However, when the risk for TB was compared between the TNF blocker-exposed AS cohort and the TNF blocker-naive AS cohort, no significant difference was identified. These results were obtained partially through strict surveillance for LTBI with TST, chest radiography, and medical history, and through low usage of immunosuppressive drugs and a low rate of concomitant diseases with AS. Additionally, our data strongly suggest that, among patients with AS, etanercept is associated with a lower risk of TB infection compared with monoclonal antibodies. Given these data, TNF blockers seem relatively safe options for the treatment of AS if proper surveillance remains an essential prerequisite prior to starting TNF blocker therapy. Serial TST with adjuvant IFN-γ assays and proper anti-TB chemoprophylaxis would likely further reduce future reactivation of LTBI or new TB infections in Korean patients with AS.

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