Incidence of Tuberculosis in Korean Patients with Rheumatoid Arthritis (RA): Effects of RA Itself and of Tumor Necrosis Factor Blockers

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ABSTRACT. ***Objective***. To elucidate the incidence rate and relative risk of tuberculosis (TB) in patients with rheumatoid arthritis (RA) and in patients with RA treated with tumor-necrosis-factor (TNF) blockers in Korea.

Methods. Using data from the Korean National Tuberculosis Association (KNTA) as a control and data from a single-center cohort of patients with RA, we conducted an evaluation of 1285 patients with RA not exposed to TNF blockers and reviewed medical records of 90 and 103 patients with RA treated with infliximab and etanercept, respectively, between 2001 and 2005.

Results. The mean incidence rate of TB, reported by the KNTA, was 67.2 per 100,000 person years (PY) from 2001 to 2004. In the TNF-blocker-naïve RA cohort, 9 cases of TB developed during 3497 PY of followup (257 per 100,000). In the infliximab-treated RA group, 2 cases of TB developed during 78.17 PY of followup (2558 per 100,000 PY), and there was no case of TB during 73.67 PY of followup in the etanercept-treated RA group. The risk of TB was higher in RA patients not treated with TNF blockers (sex- and age-adjusted risk ratio 8.9; 95% confidence interval 4.6-17.2), and in those treated with infliximab (sex- and age-adjusted risk ratio, 30.1; 95% confidence interval, 7.4–122.3) compared with the general Korean population.

Conclusion. The risk of TB infection is 8.9-fold higher in Korean patients with RA and 30.1-fold higher in RA patients treated with infliximab, compared with the general Korean population. (First Release Feb 15 2007; J Rheumatol 2007;34:706–11)

Key Indexing Terms:
TUBERCULOSIS RHEUMATOID ARTHRITIS INFLIXIMAB ETANERCEPT

Tumor necrosis factor (TNF) blockers have been used in patients with refractory rheumatoid arthritis (RA) in South Korea since 2001, and their application in ankylosing spondylitis, psoriatic arthritis, and RA is increasing.

Although a statistically significant increased risk of infectious diseases has not been detected in trials of TNF blockers, this possibility cannot be excluded[1-5]. The microorganisms responsible for the infectious complications associated with TNF blockers are generally intracellular pathogens or pathogens that commonly exist in a chronic, latent state[6]. The infection type causing the greatest concern is tuberculosis (TB). TNF plays a dominant role in protection against mycobacterial infection[7-8], and there is growing concern that frequent use of TNF blockers may increase vulnerability to TB[9-13].

TB is reemerging as an infectious disease in developed countries with a low TB burden, due to aging societies, increased immigration from developing countries, immunodeficiency caused by human immunodeficiency virus infection, and the use of immunosuppressive drugs including TNF blockers[14]. South Korea is classified as a country of intermediate TB burden, where the prevalence of latent TB infection is estimated to be 33%[15]. The Korean National Tuberculosis Association (KNTA) has reported on the annual incidence rate of TB in the general population from 2001 to 2004[16], and it is estimated that more than 65 cases of TB develop per 100,000 persons annually, which is markedly higher than the rates in other developed countries[17].

Vulnerability to infection and increased risk of TB in patients with RA, independent of TNF-blocker therapy, has been reported in Spain and Sweden[9,10,13]. Although hypothe-

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ses explaining these phenomena have been proposed, why RA patients are at risk of TB infection remains unclear.

Most studies on RA and TB, especially in patients with RA exposed to TNF blockers, have been conducted in developed countries with low TB burdens. In contrast, our study was conducted in a country with an intermediate TB burden; moreover, we examined the association between TB and the use of TNF blockers in patients with RA by comparing TB infection rates among the Korean population, RA patients in general, and RA patients exposed to TNF blockers.

MATERIALS AND METHODS

General population. The Korean Tuberculosis Surveillance System (KTBS) is an Internet-based reporting system serving 254 public health centers and 3 TB-specialized hospitals in the public sector, as well as 282 general hospitals, 636 hospitals, and 18,869 clinics in the private sectors, to report new TB patients to the Korean Center for Disease Control and Prevention (CDC) and the KNTA. It is mandatory for physicians to report active TB to the KTBS in Korea.

The KTBS acts as a country-wide data depository for consolidated information on TB. After person-based analysis, the KNTA reports the annual number of new TB cases that are reported to the KTBS, and the incidence of TB is estimated each year by dividing the number of cases by the Korean population.

RA patients not exposed to TNF blockers. We evaluated a cohort of 1285 RA patients meeting the criteria of the American College of Rheumatology[18] who attended a single clinical center. The cohort was constructed from 2001 to 2005, and no patient had been exposed to TNF blockers.

RA patients exposed to TNF blockers. Two TNF blockers are available for clinical use in Korea: infliximab and etanercept. RA patients refractory to conventional disease modifying antirheumatic drug therapy are candidates for TNF blockers. Among 193 patients with RA treated with TNF blockers, 90 patients were treated with infliximab and 103 patients with etanercept. The patients attended the same medical center between 2001 and 2005.

Data collection. As a reference, we used the mean incidence rate of TB in the general population from 2001 to 2004. To determine the relative risk (RR) of TB in RA patients with or without TNF blockers versus the general population, we reviewed all the medical records of RA patients. Clinical records in RA patients not exposed to TNF blockers were reviewed for sex, age, duration of RA, rheumatoid factor (RF), Health Assessment Questionnaire (HAQ), and risk factors such as a history of TB and the presence of diabetes mellitus (DM). However, we did not obtain baseline chest radiograph findings, contact active TB patients, or conduct tuberculin skin tests (TST).

For each patient exposed to TNF blockers, we gathered demographic information together with clinical characteristics of RA and factors related to TB infection such as DM, history of TB, TST, dosage of steroid, contact with active TB patients, and TB prophylaxis prior to TNF blocker therapy. Chest radiographic findings were also reviewed before initiation of TNF blockers. The frequency and duration of TNF blocker use were also surveyed (Table 1).

Definition of TB cases. The KTBS defines a TB case as a person with either (1) typical symptoms of TB and bacterial confirmation or (2) typical symptoms and radiological or histological findings, but without bacterial confirmation. A patient with RA treated with anti-TB medication because of symptoms or signs of TB and showing definitive improvement was defined as a new TB case irrespective of bacterial confirmation. Patients diagnosed with TB before the RA diagnosis were excluded. The TST was performed on the volar side of the forearm according to the Mantoux method. Induration was measured after 72 hours, with 10 mm of induration used as the cutoff for a positive test result.

Statistical analyses. To estimate incidence of TB among patients with RA not exposed and those exposed to TNF blockers, respectively, we divided the TB cases by the total and the TNF-blocker-specific number of patient-years of followup. We adjusted the potential confounding effects for sex and age when we compared the incidence rate of TB in the RA population with and without TNF blocker with that in the general population. The study population was divided into 2 age groups:≤ 30 and > 30 years.

The relative risk (RR) of TB was determined by logistic regression analyses, and the results are expressed as the RR with its 95% confidence intervals (95% CI). Variables were compared with Student's t test for continuous variables and the chi-square test for the categorical variables. Probability values of $p \leq 0.05$ were considered significant. The analyses were performed using SAS software (version 8.1, SAS Institute, Cary, NC, USA)

Table 1. Clinical characteristics of enrolled patients with rheumatoid arthritis (RA).

	TNF Blocker-Naïve (n = 1285)	TNF Blockers Infliximab (n = 90)	TNF Blockers Etanercept (n = 103)	p*
Women, %	88.5	84.4	86.4	NS
Age, yrs, mean (SD)	52.0 (12.2)	51.3 (13.8)	51.2 (12.2)	NS
Disease duration, yrs mean (SD)	13.9 (8.9)[a]	10.1 (8.0)[b]	9.1 (5.4)[b]	< 0.05
HAQ, mean (SD)	0.97 (0.67)[a]	1.02 (0.64)[a,b]	1.17 (0.69)[b,c]	< 0.05
Positive RF, %	90.0[a]	80.0[b]	76.5[b]	< 0.05
Diabetes mellitus, %	4.9[a]	6.7[a]	0.0[b]	< 0.05
Past TB history, %	10.3	10.0	9.7	NS
Chest radiography suggesting old TB, %	ND	4.4	1.9	NS
PPD positive, %	NA	29.6	33.7	NS
TB prophylaxis, %	NA	12.2	24.3	< 0.05
Steroid dosage, mg, mean (SD)	—	3.7 (3.5)	3.4 (2.6)	NS
MTX treatment, %	93.6[a]	91.1[a,b]	81.6[b]	< 0.05
Duration of TNF blocker therapy, mo, mean (SD)	NA	10.4 (9.0)	8.6 (6.4)	< 0.05
Patient-yrs exposure	—	78.2	73.7	—

* Statistical significances were tested by t test or ANOVA test between groups. [a,b,c] No significant difference between groups. SD: standard deviation; NS: not significant; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; TB: tuberculosis; PPD: purified protein derivatives; MTX: methotrexate; TNF: tumor necrosis factor.

RESULTS

Clinical features of patients. Table 1 shows the baseline demographics, HAQ, DM, medication history, and variables related to TB. The tuberculin skin test was not applied routinely to the TNF blocker naïve RA patients included in our study, and hence the TST-positive rate could not be compared between RA patients not exposed and exposed to TNF blockers. The patients treated with infliximab were treated longer and were half as likely to have received prophylaxis compared with those treated with etanercept. No patient had contact with active TB patients during the period of TNF blocker treatment.

Incidence rate of tuberculosis. The estimated incidences of all forms of TB reported by the Korean CDC and the KNTA were (in cases per 100,000) 72.1 in 2001, 67.2 in 2002, 64.0 in 2003, and 65.4 in 2004, with a mean of 67.2. Pulmonary TB comprised about 88.7% of all cases of TB. The estimated male-to-female risk ratio was 1.6, and the age distribution of TB showed a peak incidence rate in the elderly (> 60 yrs) followed by young adults, with middle-aged patients exhibiting the lowest incidence rate; this distribution is similar to that in developing countries with a high TB burden.

The patients with RA not exposed to TNF blockers were followed up for 3,497 person-years (PY). The estimated TB infection rate was 257 per 100,000 PY; 7 of the 9 cases of TB that developed during followup were pulmonary TB (77.8%), which is similar to the percentage of 88.7% for the general population. Characteristics of the patients with TB are summarized in Table 2.

Two cases of TB developed during followup in the 90 patients with RA treated with infliximab (2,558 cases per 100,000 PY). The information of the 2 patients is presented in Table 3.

Relative risk of active TB in RA patients. Nonexposure to TNF blockers resulted in a 8.9-fold increase in the risk of TB (95% CI, 4.6-17.2) compared with the general population.

Relative risk of active TB in RA patients treated with TNF blocker versus the general population. Exposure to infliximab increased the likelihood of TB infection 30.1-fold (95% CI, 7.4–122.3) compared with the general population. No patient with RA exposed to etanercept developed active TB.

DISCUSSION

We found that the risk of TB was higher in RA patients than in the general population. Patients exposed to infliximab had an additional risk of TB, which developed within 1 year after the initiation of infliximab therapy, but we found no cases of TB in patients exposed to etanercept

TB is significantly more common in Korea than in other developed countries. Moreover, the actual incidence of TB in Korea may be higher than the reported incidence rate (67.2 per 100,000) due to the possibility of underreporting of TB, even though reporting active TB is mandatory for physicians in Korea, the accuracy could be improved by promoting the reporting of rates of TB cases to the KTNS. In the US, the incidence rate was 5.1 per 100,000 in 2003 and is in decline[19]. Even in Spain, which has one of the highest incidence rates of TB in Europe, there were only 21 cases of TB per 100,000 in 2000[10].

Patients with autoimmune rheumatic diseases, especially systemic lupus erythematosus (SLE), are thought to be at increased risk for infections, including TB[20,21]. Immune disturbance due to both the disease itself and to associated immunosuppressive agents is likely to explain the higher risk of TB. The results for RA have been conflicting: in Spain and Sweden risk of TB infection is 4- and 2-fold higher in RA patients, respectively, while rate of TB in RA patients in a US study was not increased[9,13,22]. A survey conducted in Korea from 1979 to 2000 compared the incidence of TB infection in SLE and RA patients. Although significantly lower than that for SLE, the estimated incidence rate of TB in RA patients was 230 per 100,000[23]. However, the incident rate was not compared with that in a general population in the survey. In the present study, 257 cases of TB were estimated per 100,000 PY from 2001 to 2004, which is similar to that in the previous study.

Table 2. Characteristics of 9 TB cases found in patients with RA not exposed to TNF blockers.

Sex/age, yrs	Disease Duration, yrs	RF	DMARD	Steroid, mg/day	DM	Past History of TB	Method of Diagnosis	Location of TB
F 68	40	–	MTX, BC, CYC	5	–	+	AFB +	Pulmonary
F 32	10	+	MTX, HCQ, SSZ	0	–	–	Clinical	Pulmonary
F 67	13	+	MTX, gold	5	–	+	AFB +	Pulmonary
F 58	13	+	SSZ	5	–	+	AFB +	Pulmonary
F 24	5	+	MTX, HCQ	1.25	–	–	AFB +	Pulmonary
F 39	6	+	MTX, HCQ, SSZ	0	–	–	AFB +	Pulmonary
F 62	5	+	Mizoribine	2.5	–	–	Culture +	Disseminated
F 53	25	+	Leflunomide	5	–	–	Clinical	Meninges
F 74	2	+	MTX, SSZ	2.5	–	+	Clinical	Pulmonary

DMARD: disease-modifying antirheumatic drug; DM: diabetes mellitus; MTX: methotrexate; BC: bucillamine; CYC: cyclosporine; HCQ: hydroxychloroquine; SSZ: sulfasalazine; AFB: acid-fast bacilli.

Table 3. Characteristics of TB occurring in RA patients treated with infliximab.

Sex,Age, yrs	Method of Diagnosis	Location	TST	Chest X-ray	prophylaxis	DMARD	Steroid	Dm	Duration of Therapy, mo
F 51	Biopsy	Pulmonary	+	Bronchiectasis	No	MTX, CYC, BC	—	—	8
M 34	AFB +	Miliary	–	NL	No	MTX, HCQ, SSZ	5 mg/day	–	4

DMARD: disease-modifying antirheumatic drug; DM: diabetes mellitus; TST: tuberculin skin test; NL: normal.

The rate of TB infection is about 9 times higher in RA versus the general population, but the factors contributing to this increased TB risk are unclear.

A past history of TB was present in 4 out of 9 RA patients who developed TB (44.4%); this was higher than in RA patients who did not have TB (10.0%), suggesting that a past history of TB is an important risk factor for TB development in RA. A previous study into the clinical characteristics of TB in patients with SLE in Korea showed an analogous result: a past history of TB was significantly more likely in SLE patients who developed TB than in those who did not develop TB[23].

Infliximab is a chimeric antibody against TNF-α used for treatment of rheumatologic diseases and Crohn's disease[24,25]. Although infliximab exerts definite clinical effects, there are many case reports and studies showing an increased risk of TB in patients exposed to infliximab in developed countries. Studies conducted in the US, Spain, and France have found that infliximab increased the risk of TB, with more than half of the cases being extrapulmonary[10,11,13,26-28]; whereas a study conducted in Sweden found that pulmonary TB predominated[9]. Combining our results with those of previous studies reveals that when the incidence rate of TB is higher in the general population, the incidence rate of TB in RA patients is higher with or without TNF blockers (Figure 1).

Etanercept is a fusion protein consisting of 2 soluble p75 TNF-α receptors linked to a human immunoglobulin Fc portion. A study conducted in Sweden found that an increased risk of TB is related to the use of both infliximab and etanercept[9]. TEMPO (The Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) showed no case of TB in over 2 years of treatment[29]. Our results are similar to previous studies in that RA increases the risk of TB and infliximab endows an additional risk within the first year after initiation of infliximab treatment. Although there was no case of TB in RA patients exposed to etanercept in our study, this does not mean that etanercept is not related to an increased risk of TB, because the followup period of this study was short (8.6 ± 6.4 months); a study with longer followup may reveal a relationship between etanercept therapy and the risk of TB.

Differential modes of action of the 2 classes of TNF blockers may explain the difference in the development of TB.

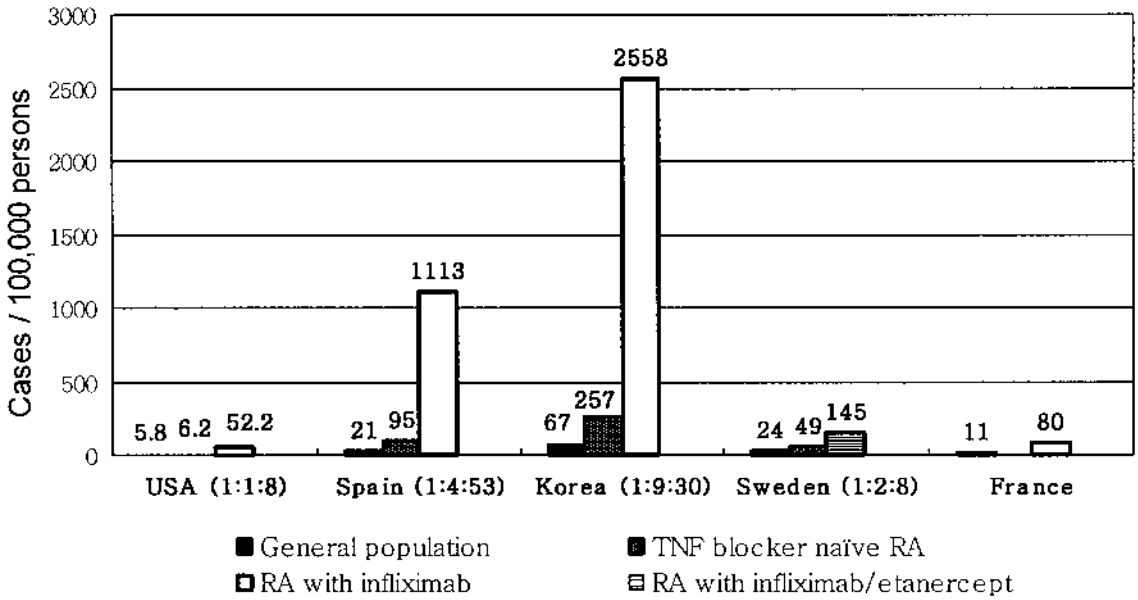

Figure 1. Comparison of incidence rate and relative risk of tuberculosis (TB). Values in parentheses are the relative risks of TB in rheumatoid arthritis (RA) patients with or without infliximab compared to the incidence rates of TB in the general population. The Swedish data include infliximab- and etanercept-treated RA patients, and the French data do not include the incidence rate of TB in RA patients not exposed to tumor necrosis factor blockers.

Method of administration, dosage, and half-life were also suggested as causes for differing incidence rates between infliximab and etanercept[30-32].

In our study, the rate of TB prophylaxis was lower in infliximab-treated patients than in patients treated with etanercept, which may explain the increased risk of TB in infliximab-treated RA patients: Only one of the 2 TB patients exhibited a positive TST. In the START (Safety Trial for RA with Remicade Therapy), 7 patients developed active TB but none of them were TST-positive[1], which casts doubt on the reliability of the TST. New infection of TB from other active TB patients is a possibility, but a false-negative TST may be attributable to RA increasing anergy to skin-test antigens[33], and these patients usually taking immunosuppressive drugs. We consider that a stricter cutoff size for the induration after the TST or a more reliable screening test is necessary before the initiation of TNF blockers. Assessing immune responses to antigens highly specific for TB that are not found in patients vaccinated with bacillus Calmette Guerin may be a more specific alternative to the TST[15,34,35].

Previous studies have revealed that active TB can develop early after the initiation of treatment with infliximab, with the longer term risk of TB after infliximab remaining high[10,11,13]. Two patients in the present study developed active TB less than 1 year after the initiation of infliximab treatment, which is consistent with the previous studies and suggests that caution is required in the early period after the initiation of infliximab treatment.

One of the limitations of our present study relates to the possible underestimation of the true rate of TB in the general population. The KTBS is affected by the rate at which patients utilize medical centers and by the reporting rate of TB by medical centers. Therefore, the RR of TB in RA patients with or without infliximab treatment might be overestimated. The small sample size, short term followup period, difference in TB prophylaxis rate, lack of chest radiograph information in TNF blocker naïve patients, and retrospective nature without case control also limit the significance of this study: the small sample size mandated that subjects be divided into only 2 age groups; and the duration of etanercept treatment was 8.6 ± 6.4 months, which is shorter than the known median interval between the initiation of etanercept treatment and the diagnosis of TB[12].

Given the relatively small number of TB cases in the TNF blocker group, the confidence intervals are quite wide. It is difficult to state with certainty the actual increased risk. But our results suggest that stricter surveillance for latent TB is essential before infliximab treatment is applied in countries with intermediate and high TB burdens. Longterm followup studies are also needed to determine the RR of TB in etanercept-treated patients.

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