의학석사 학위논문

Clinical characteristics of anti-TNF α agents-related tuberculosis in ankylosing spondylitis compared with rheumatoid arthritis

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ABSTRACT

Introduction: Ankylosing spondylitis (AS) is a rheumatic disease for which anti-TNF α agents are effective. Tuberculosis (TB) is one of the serious infectious complications of anti-TNF α agents. However, the clinical characteristics of anti-TNF α agents-related TB in AS are not well described. The objective of this thesis was to investigate the clinical characteristics of active TB in AS patients after anti-TNF α agents are prescribed.

Methods: All patients with AS or rheumatoid arthritis (RA) who took anti-TNF α agents were enrolled at Seoul National University Hospital between Jan 2001 and Aug 2011. The medical records were reviewed for all the patients. TB was defined as the presence of *M. tuberculosis* in culture and/or typical radiographic findings and/or clinical response to anti-TB medication. The clinical characteristics of AS patients who developed TB were compared with those of RA.

Results: Fourteen cases of TB were reported (AS, 7 out of 404 anti-TNF α agent treatment episodes; RA, 7 out of 277). The incidence rate of TB in AS for the anti-TNF α agent treated patients (600.2 per 100,000 person years) (95% CI 241.3-1236.3) was comparable with that of RA (771.6 per 100,000 person years) (95% CI 310.2-1589.9). Patients with AS and TB were younger with a significantly lower body mass index (BMI) than that of RA (19.9 ±2.6 vs 23.9 ±3.3, p= 0.027). In the multivariate analysis, a low BMI (OR 13.3, p=0.018, age and sex adjusted) was a significant risk factor for TB in the AS group. The time to TB in AS was longer than in RA (19.4 months vs 7.0 months, p=0.409). The proportion of extrapulmonary disease was similar for both groups (85.7% vs 85.7%). Prevalence of latent TB infection was estimated to be 31.1% vs 25.7% in the cohort of AS and RA patients, respectively. All 3

cases that developed TB despite treatment for latent TB were AS patients. **Conclusions:** When anti-TNF α agents are prescribed in AS, TB can develop as frequently as in RA. TB manifests later in AS than in RA by 1 year after initiation of anti-TNF α agents. Extrapulmonary TB was as prevalent as in RA. Cautious use of anti-TNF α agents with close surveillance for TB development should be exercised for a minimum of 1.5 years in AS.

Keywords: Ankylosing spondylitis, Rheumatoid arthritis, anti-TNF α agent, Tuberculosis

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LIST OF ABBREVIATIONS

AS ankylosing spondylitis

BMI body mass index

COPD chronic obstructive pulmonary disease

DMARDs disease modifying antirheumatic drugs

LTBI latent tuberculosis infection

RA rheumatoid arthritis

TB tuberculosis

TNF α tumor necrosis factor alpha

TST tuberculosis skin test

INTRODUCTION

Tumor necrosis factor alpha (TNF α) promotes inflammation in both physiologic and pathologic conditions. Since TNF α inhibitors are increasingly used for a number of autoimmune rheumatic diseases, more adverse events have been emerging. In immune defense, TNF α plays an essential role in forming and maintaining granulomas to confine mycobacteria from spreading causing latent tuberculosis infection (LTBI). As such, anti-TNF α agents increase the risk of reactivation of LTBI, possibly in a dose-dependent manner in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) (1-3). Interestingly, tuberculosis (TB) associated with anti-TNF α agents usually manifests within one year of the anti-TNF α treatment and often as extrapulmonary TB, suggesting the reactivation of the TB once confined in a granuloma. The incidence of new and reactivation of LTBI depends on the TB prevalence with a higher rate in endemic areas including South Korea with an intermediate TB burden (4).

Chronic, systemic inflammation in the joints is the main mechanism of RA and AS (5, 6). Although both respond well to anti-TNF α agents, the clinical and laboratory features are quite different. While both are characterized by peripheral erosive arthritis, the profound bone forming process in AS indicates a distinct immunopathologic process in the axial skeleton (7). Furthermore, AS is common in young individuals without any particular immunologic dysregulation whereas RA affects middle-aged people, accompanying systemic immunologic dysregulation which includes lymphocyte activation, autoantibody formation, and splenomegaly in some cases (8). Moreover, immunomodulating agents are rarely used in the treatment of AS while they are commonly used in the treatment of RA.

The aim of this thesis is to investigate the clinical characteristics, incidence and risk factors of TB in patients with AS who were treated with anti-TNF α agents compared to RA patients.

PATIENTS AND METHODS

1. Patients

A total of 336 AS patients and 222 RA patients who received anti-TNF α agents (etanercept, infliximab, adalimumab, golimumab and certorlizumab) at Seoul National University Hospital between Jan 2001 and Aug 2011 were included in this study. AS (n=986) and RA (n=2932) patients naïve to anti-TNF α agents were also recruited as comparison groups. All RA patients met the 1987 criteria for the classification of RA (9) and all AS patients met the 1984 modified New York criteria for AS (10). Follow-up was censored at the most recently completed follow-up or death, whichever came first.

Data on the patients were captured by reviewing the medical records. Demographic data and clinical information regarding age, sex, body mass index (BMI), disease duration, treatment duration of anti-TNF α agent, and use of concomitant DMARDs including methotrexate and steroids were obtained. Risk factors for TB were also obtained (history of diabetes mellitus, hypertension, end stage renal disease, osteoporosis, gastrectomy, peptic ulcer, human immunodeficiency virus infection, smoking, chronic obstructive pulmonary disease, and history of TB). The duration of anti-TNF α agents were the sum of the durations for each of the anti-TNF α agents.

2. Definition of latent tuberculosis (LTBI).

LTBI was defined using the Korean guidelines for TB (Korean guidelines for tuberculosis, first edition, 2011). Cases with an abnormal chest radiograph suggesting healed TB such as apical fibronodular changes without adequate treatment of TB and/or positive TST (tuberculosis skin test) (induration diameter ≥ 10mm) or positive interferon γ releasing assay were regarded as LTBI.

3. Definition of tuberculosis infection

Patients were considered to undergo active TB if they had clinical symptoms suggesting active TB infection such as cough, fever, night sweats, weight loss/anorexia, hemoptysis with a positive result for acid fast bacillus smear test and/or positive culture result of *M. tuberculosis* and/or positive polymerase chain reaction results for *M.tuberculosis* and/or the presence of caseating granulomas from any specimens and/or an adequate response to anti-TB treatment. The site of infection was categorized as pulmonary or extrapulmonary. If a patient developed TB, the last anti-TNF α agent prescribed prior to the development of TB was regarded as a contributor to the event.

4. Study design

This was a retrospective study to investigate the clinical characteristics, incidence rate and risk factors of TB in AS patients treated with anti-TNF α agents compared with RA patients.

The clinical characteristics of TB were descriptively investigated in AS patients in comparison with RA. In addition to demographic factors, time to the occurrence of TB, location of infection and relationship with the latent infection were investigated.

The incidence of TB in 100,000 patient-years was calculated. In addition to comparing the incidence rates for TB between AS and RA, incidence rates in patients who were treated with anti-TNF α agents were compared with the incidence rates in patients naïve to anti-TNF α agents. To determine the risk factors for the development of TB, a direct comparison of risk factors between TB or non-TB patients was made between AS and RA. The predefined factors potentially predictive for the occurrence of TB were age, low BMI, diabetes

mellitus, malignancy, hypertension, hospitalization during anti-TNF α agent prescription, chronic renal disease, osteoporosis, gastrectomy/peptic ulcer, smoking history and chronic obstructive pulmonary disease. Significant risk factors included in the multivariate model were those associated in the univariate analysis with a significance level of $p<0.20$.

The study protocol was reviewed and approved by institutional review board of Seoul National University Hospital (IRB No H-1107-043-368).

5. Statistical analysis

Clinical characteristics of TB were descriptively compared.

The cumulative incidence rate was estimated using the Kaplan-Meier method. The incidence rates of TB were presented as events/100,000 person-years with 95% confidence intervals. The incidence rate ratios were calculated with the Poisson test, comparing AS patients with RA as the reference group and anti-TNF α agent treated patients with the anti-TNF α agent naïve patients (986 for AS and 2932 for RA).

To define the risk factors for TB, a comparison was made between the TB patients and non-TB patients in anti-TNF α agent treated patients.

To evaluate the risk factors, univariate analysis was performed first using chi-squared tests or Fisher's exact tests to compare categorical data and Student's t-test or Mann-Whitney test for continuous variables, respectively. Then, multivariate analysis was performed using significant risk factors from the univariate analysis.

All statistical analyses were performed with SPSS 19.0 for Windows (SPSS 19.0 Inc. IBM Company, Chicago, Illinois, USA).

RESULTS

Clinical characteristics of AS patients treated with anti-TNF α agents compared to RA

Anti-TNF α agents treated AS cohort included a total of 336 patients and anti-TNF α agents treated RA cohort included 222 patients (Table 1). For the 336 AS patients, a total of 404 anti-TNF α agents were prescribed (Table 1); 163 (40.3%) patients received etanercept, 150 (37.1%) adalimumab and 78 (19.3%) infliximab. In AS, 278 patients were prescribed one anti-TNF α agent while 58 (17.3%) patients were treated with more than 1 anti-TNF α agent. For the 222 RA patients, a total of 277 anti-TNF α agents were prescribed; 137 patients (48.7%) received etanercept, 75 (27.4%) adalimumab and 50 (18.1%) infliximab. In RA, 173 patients were prescribed one anti-TNF α agent, while 49 (22.1%) patients were treated with more than 1 anti-TNF α agent. The median follow-up duration (range) was 31.2 (15.8-51.6) months for AS and 31.9 (17.4-59.8) months for RA. Table 1 shows the baseline characteristics of the AS and RA patients treated with anti-TNF α agents. The AS cohort was younger, comprised less females, had been prescribed less DMARDs including methotrexate and prednisolone. Compared with the RA patients, AS patients were less likely to have comorbidities such as diabetes mellitus, hypertension, osteoporosis, chronic obstructive pulmonary disease or bronchiectasis (Table 2).

Table 1. Comparison of clinical characteristics between anti-TNF α agent treated AS and RA patients.

	Ankylosing spondylitis	Rheumatoid arthritis	p-value
Number of patients	336	222	
Age, years	36.6 ± 12.3	51.9± 12.6	<0.001
Female, (%)	64 (19.0)	192 (86.5)	<0.001
BMI, kg/m^2	23.4 ± 6.1	22.8 ± 3.4	0.172
Use of anti-TNF α agents			
Number of anti-TNF α agents prescribed	404	277	
Nonswitcher, (%)	278 (82.7)	173 (77.9)	
2nd agent , (%)	48 (14.3)	43 (19.4)	0.187
3rd agent , (%)	10 (3.0)	6 (2.7)	
Etanercept (%)	162 (40.1)	135(48.7)	0.028
Adalimumab (%)	150 (37.1)	76 (27.4)	0.010
Infliximab (%)	78 (19.3)	50 (18.1)	0.691
Golimumab (%)	13 (3.2)	10 (3.6)	0.920
Certorlizumab (%)	0 (0)	5 (1.8)	0.007
Use of DMARDs			
Use of glucocorticosteroid (%)	61 (18.2)	156 (70.3)	<0.001
Prednisolone dose, mg/day	1.1 ± 2.9	4.4 ± 3.3	<0.001
Use of methotrexate (%)	84 (25.0)	165 (74.7)	<0.001
Methotrexate dose, mg/wk	3.4 ± 6.2	10.6 ± 7.2	<0.001
History of treated TB	19 (5.7)	12 (5.4)	0.867
Treated LTBI	104 (31.1)	56 (25.7)	0.180
Duration of anti-TNF α agent, months, median (Quartile 25-75)	24.1 (10.6-43.9)	14.9 (5.4-30.2)	<0.001
Disease duration, months, median (Quartile 25-75)	69.1 (43.3-116.2)	84.4 (45.4-129.1)	0.021
Follow-up duration, months, median (Quartile 25-75)	31.1 (17.6-63.3)	34.5 (15.7-52.2)	0.007

plus minus values are mean ± SD, BMI body mass index, DMARD disease modifying antirheumatic drug, TNF α tumor necrosis factor alpha, TB tuberculosis, LTBI, latent tuberculosis infection

Table 2. Comparison of comorbidity in anti-TNF α agent treated AS and RA patients.

	Ankylosing spondylitis (n=336)	Rheumatoid arthritis (n=222)	p-value
Diabetes mellitus	16 (4.8)	23 (10.4)	0.017
Hypertension	47 (14.0)	55 (24.8)	0.002
Gastrectomy/peptic ulcer	17 (5.1)	7 (3.2)	0.394
Chronic renal disease	8 (2.4)	7 (3.2)	0.601
Malignancy	8 (2.4)	11 (5.0)	0.150
Osteoporosis	11(3.3)	30 (13.5)	<0.001
Hospitalization	12 (3.6)	19 (8.6)	0.014
Smoking	26 (7.7)	26 (11.7)	0.137
COPD/bronchiectasis	8 (2.4)	24 (10.8)	<0.001

TNF α tumor necrosis factor alpha, COPD Chronic obstructive pulmonary disease

Clinical characteristics of TB that developed in patients treated with anti-TNF α agents

During 1,166.3 person-years of follow-up for AS and 907.2 person-years of follow-up for RA, 7 patients in each group developed TB (Table 3). AS patients who were infected with TB were significantly younger and had used DMARDs less when compared with RA, as expected from the baseline characteristics. Interestingly, AS patients with TB had a lower BMI than RA patients (p=0.027). The duration of disease and anti-TNF α agent treatment and comorbidities such as diabetes mellitus, malignancy, hypertension, hospitalization, chronic renal disease, osteoporosis, gastrectomy/peptic ulcer, smoking, and chronic obstructive pulmonary disease were not different between the AS and RA patients. The median time to development of TB from the exposure to anti-TNF α agents was 7.9 months for RA and 19.4 months for AS. It did not have any statistical significance (p=0.406, by Mann Whitney test) (Figure 1). The anti-TNF α agents, which had been prescribed when TB developed, are summarized in Figure 2.

Table 3. Comparison of clinical characteristics between anti-TNF α agent treated AS and RA patients who developed TB.

	Ankylosing spondylitis (n=7)	Rheumatoid arthritis (n=7)	p-value
Age, years, mean ± SD	35.9 ± 11.0	65.1 ± 3.1	<0.001
Female, (%)	2 (28.6)	6 (85.7)	0.103
BMI, kg/m^2, mean ± SD	19.9 ± 2.6	23.9 ± 3.3	0.027
Disease duration, months, median	38.3	48.3	0.239
Duration of anti-TNF α agent, months, median	13.8	6.7	0.968
Follow-up duration, months, median	28.1	19.6	0.942
Use of DMARDs			
No. of DMARD	0.7 ± 0.5	2.0 ± 1.0	0.021
Use of glucocorticosteroid (%)	1 (14.3)	4 (57.1)	0.266
Use of methotrexate (%)	2 (28.5)	7 (100)	0.010
Comorbidities			
Diabetes mellitus (%)	1 (14.3)	1 (14.3)	0.999
Hypertension (%)	1 (14.3)	3 (42.9)	0.383
Gastrectomy/peptic ulcer (%)	1 (14.3)	0 (0)	0.999
Chronic renal disease (%)	0 (0)	0 (0)	0.999
Malignancy (%)	0 (0)	0 (0)	0.999
Osteoporosis (%)	3 (42.9)	0 (0)	0.710
Smoking (%)	6 (85.7)	5 (71.4)	0.999
COPD/bronchiectasis (%)	1 (14.3)	1 (14.3)	0.710
History of TB (%)	1 (14.3)	1 (14.3)	0.999
Treated LTBI (%)	3 (42.9)	0 (0)	0.209

plus minus values are mean ± SD, BMI body mass index, DMARD disease modifying antirheumatic drug, TNF tumor necrosis factor α, TB tuberculosis

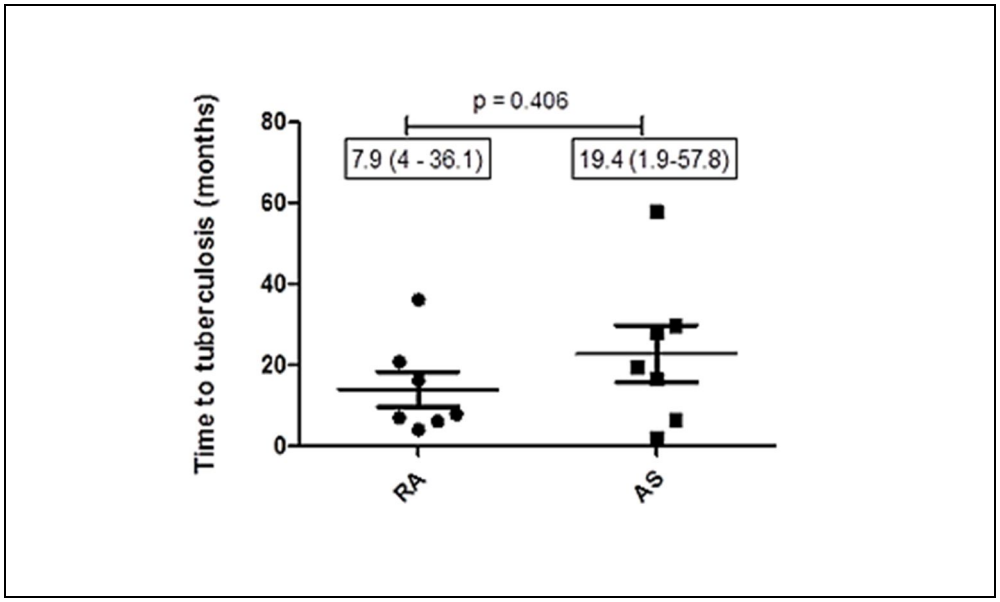


Figure 1. Comparison of time to occurrence of TB between AS and RA exposed to anti-TNF α agent

Median time (months) to tuberculosis (in the boxes) was 7.4 months in RA and 19.4 months in AS patients (p=0.406).

(A) (B)

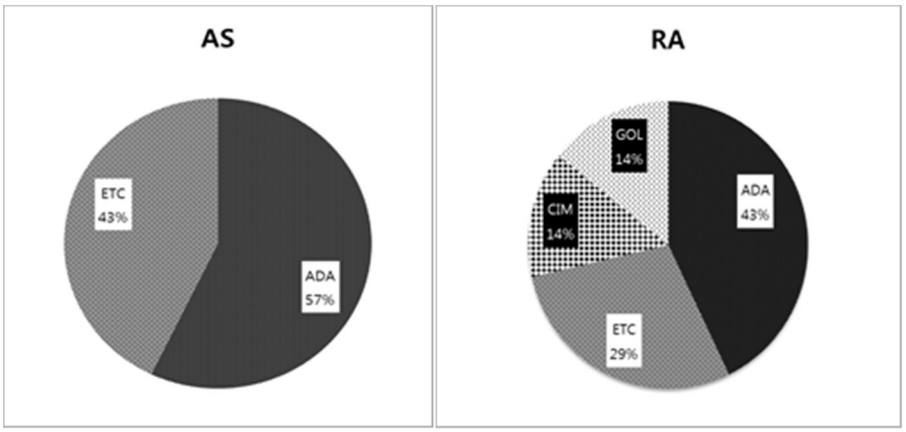


Figure 2. Anti-TNF α agent when TB developed.

(**A**) In the AS group, (**B**) In the RA group

Profiles of TB loci and treatment outcomes

Extrapulmonary TB was dominant in both groups. Among the 7 patients with TB in anti-TNF α agents treated AS cohort, 6 patients had extrapulmonary TB; the sites of extrapulmonary TB were as follows: 1 pericardial, 2 laryngeal, 2 pleural, and 1 disseminated. On the other hand, among the 7 patients with anti-TNF α agents treated RA patients, 6 patients had extrapulmonary TB; 2 peritoneal, 1 pleural, 1 lymphadenitis, and 2 disseminated disease (Table 4). The outcomes of TB are described in Table 5.

Table 4. Distribution of TB cases by anatomical site

Distribution (numbers)	Ankylosing spondylitis	Rheumatoid arthritis
Pulmonary	1	1
Extrapulmonary		
Pericardial	1	0
Peritoneal	0	2
Laryngeal	2	0
Pleural	2	1
Lymphadenopathy	0	1
Disseminated	1	2

Table 5. Outcomes of TB

	Ankylosing spondylitis (n=7)	Rheumatoid arthritis (n=7)
Hospitalization	3	6
ICU	0	3
Death	0	2

Latent tuberculosis (LTBI)

25.7% of RA and 31.1% of AS patients who received anti-TNF α agents had had LTBI and had received prophylactic anti-TB medication for about 6-9 months. Three patients with AS developed TB despite adequate treatment of LTBI. No RA patients developed TB when LTBI was treated.

Development and incidence rate of TB in AS and RA patients treated with anti-TNF α agents

The cumulative incidence of TB was similar between AS and RA patients who were treated with anti-TNF α agents (p=0.519 by log rank test). In the Poisson model, the incidence rate of TB was 600.2 per 100,000 person-years (95% confidence interval 241.3-1,236.6) in the AS cohort, while it was 711.6 per 100,000 person-years (95% confidence interval 310.2-1589.9) in the RA cohort.

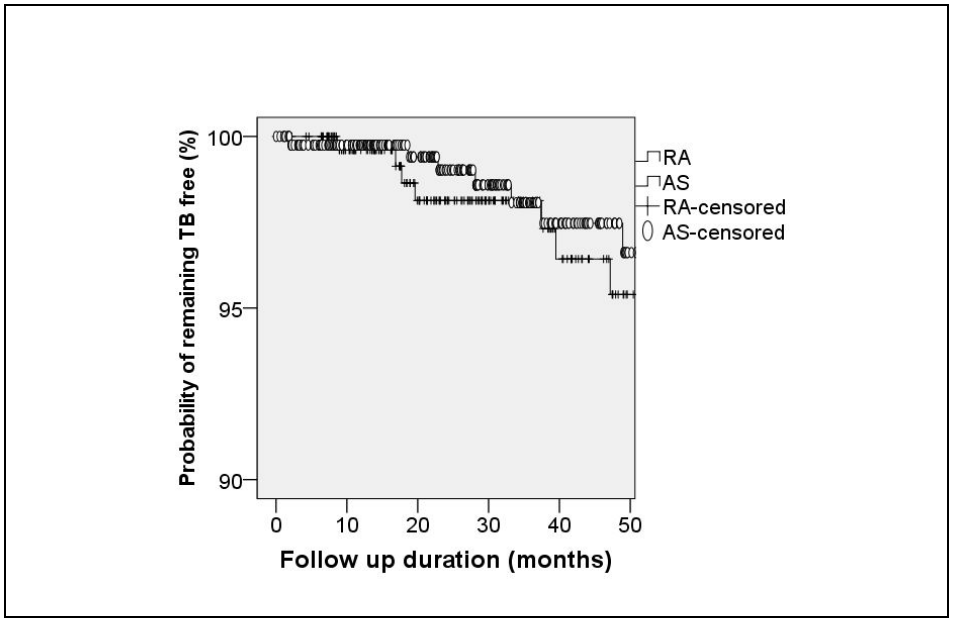


Figure 3. Kaplan-Meier analysis of the cumulative rate of TB stratified by disease type

The difference was not statistically significant (p=0.519, Log rank test) between AS and RA. However, median times (months) to tuberculosis was 7.4 months in RA and 19.4 months in AS patients (p=0.406).

Tuberculosis incidence in the AS and RA cohorts naïve to anti-TNF α agents

The incidence rates of TB were also calculated among patients who were not treated with any anti-TNF α agents. In AS, a total of 8 patients developed TB during a total follow-up time of 6,497 person-years (123.1/100,000 person-years), while 46 patients developed TB in RA during a total follow-up time of 21,572 person-years (213.2/100,000 person-years). The incidence rate for TB was higher in the anti-TNF α agent treated AS and RA patients than in the anti-TNF α agent naïve patients. The incidence of TB was 4.9 times higher in the AS patients treated with anti-TNF α agents and 3.6 times higher for the RA groups (Table 6).

Table 6. Incidence rates of TB in anti-TNF α agent treated or anti-TNF α agent naïve AS and RA

TB Incidence rate /100,000 pyrs				
	Anti-TNF α agent naïve	Anti-TNF α agent exposed	IRR	p-value
AS	123.1 (531-242.5)* (n=8/986)	600.2 (241.3-1,236.6)* (n=7/336)	4.87	0.0007
RA	213.2 (156.1-284.4)* (n=46/2932)	771.6 (310.2-1,589.9)* (n=7/222)	3.61	0.0007
IRR	0.577	0.777		
p-value	0.146	0.637		

*95% confidence interval, TNF α tumor necrosis factor alpha, IRR Incidence rate ratio, RA rheumatoid arthritis, AS ankylosing spondylitis TB tuberculosis

Risk factors for TB

In the univariate analysis, a lower BMI (p=0.008) in AS and older age in RA (p=0.001) were significant risk factors for TB (Table 7, Table 8). A low BMI below 22 kg/m^2 (OR 13.3, 95% CI 0.01-0.63, p=0.018) in AS and older age (OR 1.14, 95% CI 1.04-1.25, p=0.006) in RA were still significant risk factors for TB in the age, sex adjusted multivariate analysis (Table 9).

AS patients who developed TB were about the same age as the patients in the AS control group (35.9±11.0 vs 36.6±12.4, p=0.865). AS patients with TB had a lower BMI score (19.9±2.6 vs 23.6±6.4, p=0.008) (Table 7). In contrast, TB developed in RA patients who were 13 years older (65.1±3.1) than the patients in the RA cohort naïve to anti-TNF α agents (51.4±12.6, p=0.001) (Table 8). The cumulative probability for TB free was not different between AS and RA in etanercept (p=0.989), adalimumab (p=0.920) (Figure 4) or golimumab users (p=0.317) tested by the Log Rank test. TB was not detected in infliximab users in these cohorts.

Table 7. Risk factors for the development of TB in anti-TNF α agent treated AS.

	TB (n=7)	Non TB (n=329)	p-value*
Age, years, mean ± SD	35.9±11.0	36.6±12.4	0.865
Female, (%)	2 (28.6)	62 (18.8)	0.622
BMI, kg/m^2, mean ± SD	19.9±2.6	23.6±6.4	0.008
Disease duration, months, median	53.6±43.0	82.5±57.8	0.127
Follow-up duration, months, median	27.3±15.0	35.0±21.6	0.227
No. of DMARD	0.7±0.5	0.8±0.7	0.503
Use of glucocorticosteroid (%)	1 (14.3)	60 (18.2)	0.789
Use of methotrexate (%)	2 (28.6)	82 (24.9)	0.826
Diabetes mellitus (%)	0 (0.0)	16 (4.9)	0.551
Hypertension (%)	1 (14.3)	46 (14.0)	0.982
Gastrectomy/peptic ulcer (%)	0 (0.0)	17 (5.2)	0.538
Chronic renal disease (%)	0 (0.0)	8 (2.4)	0.677
Malignancy (%)	0 (0.0)	8 (2.4)	0.677
Hospitalization (%)	0 (0.0)	12 (3.6)	0.607
Osteoporosis (%)	0 (0.0)	11 (3.3)	0.623
Smoking (%)	0 (0.0)	26 (7.9)	0.439
COPD/bronchiectasis (%)	0 (0.0)	8 (2.4)	0.677
History of treated TB (%)	0 (0.0)	19 (5.9) (5 missing)	0.510
Treated LTBI (%)	3 (42.9)	101 (30.9) (2 missing)	0.499

*Mann Whitney test, plus minus values are mean ± SD, BMI body mass index, DMARD disease modifying antirheumatic drug, TNF tumor necrosis factor α, TB tuberculosis

Table 8. Risk factors for the development of TB in anti-TNF α agent treated RA.

	TB (n=7)	Non TB (n=215)	p-value*
Age, years, mean ± SD	65.1±3.1	51.4±12.6	0.001
Female, (%)	6 (85.7)	186 (86.5)	0.952
BMI, kg/m^2, mean ± SD	23.9±3.3	22.8±3.4	0.398
Disease duration, months, median	103.4±97.5	93.4±60.2	0.797
Follow-up duration, months, median	26.7±14.4	41.4±28.5	0.037
No. of DMARD	2.0±1.0	1.8±0.9.	0.577
Use of glucocorticosteroid (%)	4 (57.1)	152 (70.7)	0.441
Use of methotrexate (%)	7 (100.0)	158 (73.8) (1 missing)	0.118
Diabetes mellitus (%)	0 (0.0)	23 (10.7)	0.362
Hypertension (%)	3 (42.9)	52 (24.2)	0.261
Gastrectomy/peptic ulcer (%)	0 (0.0)	7 (3.3)	0.628
Chronic renal disease (%)	0 (0.0)	7 (3.3)	0.628
Malignancy (%)	0 (0.0)	11 (5.1)	0.540
Hospitalization (%)	4 (57.1)	15 (7.0)	<0.001
Osteoporosis (%)	1 (14.3)	29 (13.5)	0.952
Smoking (%)	0 (0.0)	26 (12.1)	0.329
COPD/bronchiectasis (%)	1 (14.3)	23 (10.7)	0.764
History of treated TB (%)	0 (0.0)	12 (5.6)	0.521
Treated LTBI (%)	0 (0.0)	56 (26.4) (3 missing)	0.116

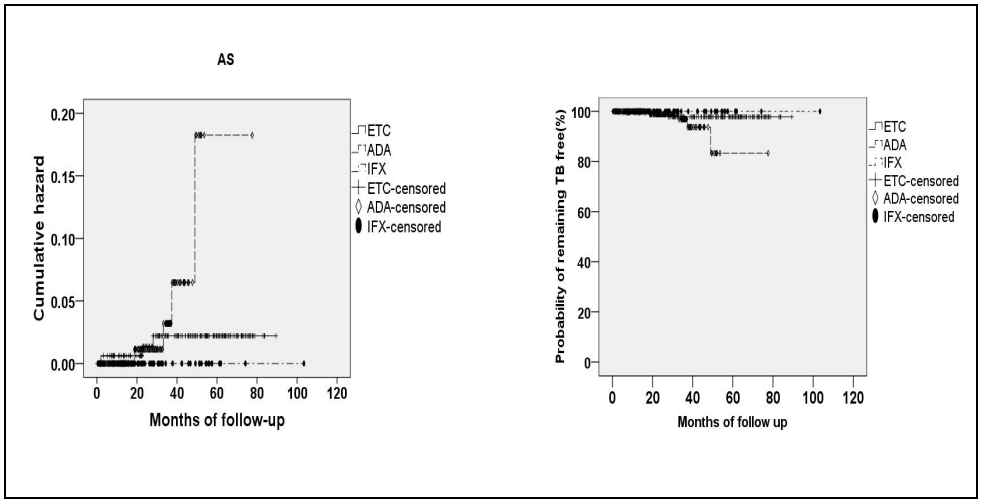
*Mann Whitney test plus minus values are mean ± SD, BMI body mass index, DMARD disease modifying antirheumatic drug, TNF tumor necrosis factor α, TB tuberculosis

Table 9. Age, sex-adjusted predictors of active TB in anti-TNF α agent exposed AS and RA patients, multivariate analysis.

Predictor variable	Odds ratio	95% confidence interval	*p*-value
Ankylosing spondylitis			
Age	0.99	0.93-1.06	0.895
BMI < 22kg/m^2	13.3	0.01-0.63	0.018
Female sex	1.2	0.21-6.43	0.825
Rheumatoid arthritis			
Age	1.14	1.04-1.25	0.006
BMI < 22kg/m^2	0.84	0.14-5.01	0.845
Female sex	1.15	0.09-9.15	0.903

BMI body mass index, TNF tumor necrosis factor α, TB tuberculosis

(A)



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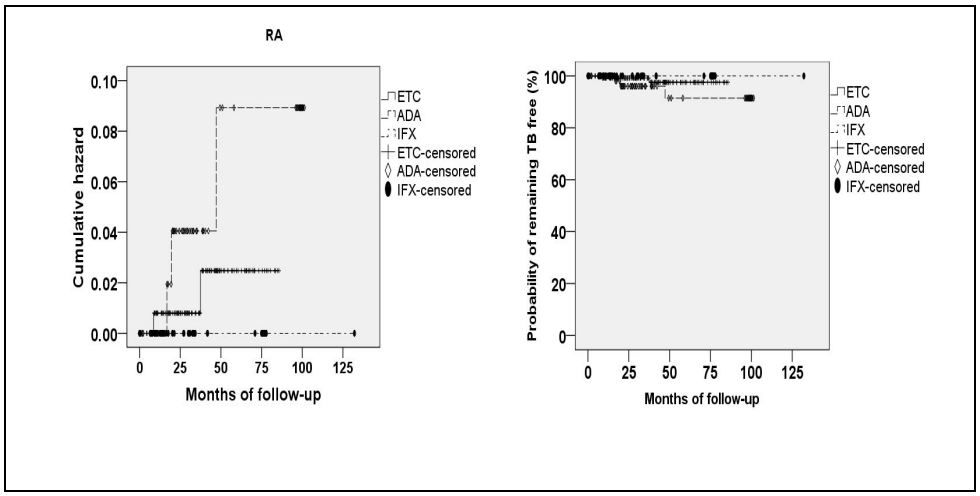

Figure 4. Kaplan-Meier analysis of the cumulative rate of TB stratified by types of anti-TNF α agents.

The cumulative rate for TB was highest in the adalimumab user in AS(A) and RA (B) followed by etanercept user. There was no TB in the infliximab user.

DISCUSSION

In this study, the occurrence of TB in AS patients taking anti-TNF α agents was found to be comparable to RA despite the different baseline characteristics, including younger age, less DMARDs, corticosteroids and low frequency of comorbidities, regardless of the specific types of anti-TNF α agents. Extrapulmonary TB was prevalent in AS which was similar to RA. The risk of TB in AS patients increased 4.87 times after taking anti-TNF α agents while it increased 3.61 times in RA patients. The increased risk of TB in AS seems to be caused by new infections while it was caused by the reactivation of latent TB in RA, considering the delayed occurrence of TB in AS. The major risk factor for TB was a low BMI in AS, while it was old age in RA.

A lower prevalence of TB in AS patients naïve to anti-TNF α agents rather than in RA patients is evident in this study. The systemic nature of the disease, more complicated organ involvement and more prevalent use of immunosuppressants in RA suggest a greater prevalence of TB in RA cases than in AS cases after introduction of anti-TNF α agents. However, results of this study showed a similar occurrence of TB. It is also interesting that the risk of TB was more increased in AS patients than in RA patients (OR 4.87 vs 3.61). The results suggest that anti-TNF α agents can override all the risk factors known to be related to TB infection such as human immunodeficiency virus infection, silicosis, diabetes, gastrectomy, chronic renal failure, malignancies, organ transplantation, smoking, low BMI score, pulmonary disease (11-15), and absence of proper prophylactic treatment for LTBI (16, 17). More to the point, a lower prevalence of risk factors for TB in AS patients may lead physicians to ignore the development of TB in them.

Extrapulmonary TB prevailed (85.7%) in both AS and RA patients in the current study. In the general population, 80% of TB manifests as pulmonary disease (1, 18). In contrast, Keane et al reported that in anti-TNF α agent exposed patients, 57% patients had extrapulmonary TB and 25% patients had disseminated disease (19). Similarly, high rates of extrapulmonary TB associated with TNF blockade treatment have been reported (20, 21). Extrapulmonary diseases are associated with delayed diagnosis and more adverse effects from anti-TB therapy (22). In general, a pulmonary evaluation is warranted in patients suspected of TB. However, one should also carefully evaluate extrapulmonary tissues such as the lymph nodes, bones/joints, skin, gastrointestinal, genitourinary tract, and neurologic system when caring for patients exposed to anti-TNF α agents. It is known that less interferon γ, TNF α, interleukin-10, and interleukin-6 are secreted in Mycobacterium TB-infected macrophages in cases with extrapulmonary manifestations than in those with pulmonary cases (23) suggesting global immune defects in patients with extrapulmonary TB. This study suggests that anti-TNF α agents can cause global immune dysfunction. Changed cytokine profiles with TNF blockade in AS tissue may act against anti-TB mechanism (24) since TNF α , is a core cytokine that maintains granulomas (25, 26). Otherwise, susceptibility to *M. tuberculosis* may originate from a reduction in CD8+ T cell function (27), rather than TNF blockade itself considering that counter-regulatory TNF increases in the T cells of AS (28).

This study suggests difficulty in diagnosing TB in AS patients exposed to anti-TNF α agents. A high false negativity in the interferon γ releasing assay or TST has been reported in patients who took immunosuppressants (29). In addition to selecting the risk group, present study confirmed the later development of TB in this group could make the diagnosis even more difficult.

TB was found to develop 1 year later in AS patients exposed to anti-TNF α agents compared to RA patients.

This study suggests that the major cause of TB in AS exposed to anti-TNF α agents is new infections rather than the reactivation of latent infections as in RA. First, it took 19.4 months to develop TB in AS patients after introduction of anti-TNF α agents, while it took a median time of 7.4 months in RA. Development of TB within 1 year of receiving anti-TNF α agents suggests reactivation of LTBI in patients exposed to anti-TNF α agents (25, 26). Therefore, more than 1 year in AS suggests a new infection rather than reactivation. Second, TB developed after adequate prophylaxis of LTBI in the AS cases. LTBI was detected in around 30% of the patients in the current cohort. Korea belongs to country of moderate risk for TB (3) and TB is strictly controlled by the government. Patients who are going to receive anti-TNF α treatment are tested with routine TST or interferon γ releasing assay, and chest radiography before initiation of the therapy and patients with LTBI are adequately treated with prophylactic anti-TB medication. Three patients from the AS group, who completed prophylactic treatment against TB developed TB later, while there was no cases of TB among the RA patients who received adequate prophylactic treatment, suggesting new infection rather than reactivation in AS.

Anti-TNF α agents treated AS patients had 4.9 times higher incidence of TB than anti-TNF α agents naïve patients. The similar risk of TB between anti-TNF α agent naïve versus exposed patients in a previous report (30) is apparently related to the inclusion of a large number (60%) of patients given etanercept. *M. tuberculosis* bacilli enter the bodies of patients by inhalation process in an endemic area and is engulfed by alveolar macrophages. Activated alveolar macrophages secrete TNF which can kill or limit the

propagation of the TB pathogen by forming granulomas, causing the patient to be in a state of latent infection. Since TNF blockade can alter this process, TB risk is increased in patients exposed to anti-TNF α agents (16). During 40 months of follow-up, TB incidences were increased in the patients exposed to anti-TNF α agents than in the naïve patients in both the AS and RA cohorts in this study.

Monoclonal antibody agents were reported to be more susceptible to TB risk than receptor agents in a post-marketing physician-reporting database by the US FDA (26). In this study, the incidence of TB tended to be higher in adalimumab followed by etanercept users. There were no cases of TB in infliximab users but the number of patients were lower (n=163 for etanercept, n=150 for adalimumab and n=78 for infliximab). It is consistent in that the risk of TB is higher for patients receiving anti-TNF α monoclonal antibody therapy than for those receiving soluble TNF receptor therapy (17).

A low BMI (< 22 kg/m^2) was found to be an independent risk factor for TB after adjusting for age and sex in AS while old age was found to be a risk factor in RA. A BMI below 18.5 kg/m^2 increases the risk by 2 to 3 times. This result is consistent with a previous report that an increase in body weight lowers the risk of TB (31). Considering new infections as the cause of TB in this group of patients, a low BMI may be related to a poor nutritional status, which is one of major risk factors for TB (32). It is recommended that patients with low BMI prescribed anti-TNF α agents should be carefully followed-up for over a year for TB.

In conclusion, the incidence of TB in AS patients was comparable with that of RA patients. New infection rather than reactivation of TB is suggested as the primary cause of infection. Extrapulmonary TB was prevailed in AS just as in RA. Physicians should be vigilant for surveillance for

extrapulmonary TB for more than 1-2 years after initiation of treatment with anti-TNF α agents in AS.

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국문 초록

서론: 종양 괴사 인자 억제제는 강직성 척추염을 효과적으로 치료하지만, 결핵의 발생은 종양 괴사 인자 억제제의 가장 위험한 감염성 합병증의 하나이다. 그러나, 강직성 척추염에서 종양 괴사 인자 억제제 사용과 관련한 결핵의 임상적 특징은 잘 보고되어 있지 않다. 이에 종양 괴사 인자 억제제 연관 결핵의 발생과 임상적 특징을 조사하고자 하였다.

방법: 2001 년 1 월부터 2011 년 8 월까지 서울대 병원에서 치료 받은 강직성 척추염환자와 질환 대조군인 류마티스 관절염 환자를 대상으로 하여 의무기록을 후향적으로 조사하였다. 활동성 결핵은 *M. tuberculosis* 가 검체에서 확인되거나 전형적인 영상 소견을 보이거나 항 결핵 약제에 효과적으로 반응한 경우로 정의하였다. 종양 괴사 인자 억제제를 투여받거나 받지 않은 강직성 척추염 환자와 류마티스 관절염환자에서 발생한 결핵의 특징을 분석하였다.

결과: 종양 괴사 인자 억제제를 투여받은 강직성 척추염군 336 명 가운데 7 명의 활동성 결핵이, 류마티스 관절염군 222 명 가운데 7 명의 활동성 결핵이 발생하였다. 이에 결핵 발생률은 강직성 척추염의 경우 십만인년당 600.2(95% 신뢰구간 241.3-1,236.3)로 류마티스 관절염의 결핵발생률인 십만인년당 771.6(95% 신뢰구간 310.2-1,589.9)와 비슷하였다. 결핵이 발생한 강직성 척추염 환자는 류마티스 관절염 환자에 비해서 통계적으로 유의하게 나이가 젊고, 낮은 체질량 지수를 보였다 (19.9±2.6 vs 23.9±3.3, p= 0.027). 다변량 분석에서도 역시 낮은 체질량 지수가 결핵 발생에 유의한 위험인자였다 (교차비 13.3, p=0.018, 연령, 성비 보정후). 추적 관찰

기간동안 결핵의 발생까지의 시간은 강직성 척추염에서 보다 길었다 (19.4 개월 대 7.0 개월 p=0.409). 폐외 결핵의 비율은 비슷하였다 (85.7% vs 85.7%). 잠복 결핵의 유병률은 강직성 척추염에서 31.1%, 류마티스 관절염 환자에서 25.7%였다. 잠복결핵이 적절하게 치료되었음에도 강직성 척추염 환자 3 명에서는 활동성 결핵이 발생한 것으로 보고 되었다.

결론: 결론적으로, 종양 괴사 인자 억제제를 처방하는 경우, 강직성 척추염에서도 류마티스 관절염과 비슷한 비율로 활동성 결핵이 발생할 수 있다. 다만, 종양 괴사 인자 억제제를 처방한 뒤 류마티스 관절염 환자보다 1 년 가까이 늦게 결핵이 발생하였다. 폐외 결핵의 발생 빈도는 류마티스 관절염 환자에서 발생한 종양 괴사 인자 억제제 연관 결핵의 양상과 비슷하였다. 강직성 척추염 환자에서 종양 괴사 인자 억제제를 처방할 때에는 적어도 18 개월이상 결핵의 발생에 대한 면밀한 추시와 주의가 필요하다.

주요어: 강직성 척추염, 류마티스 관절염, 종양 괴사 인자 억제제, 결핵

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