

Retrospective Study

Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents

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Abstract

AIM: To evaluate the incidence and risk factors of Korean tuberculosis (TB) infection in patients with inflammatory bowel disease (IBD) undergoing anti-TNF treatment.

METHODS: The data of IBD patients treated with anti-TNFs in 13 tertiary referral hospitals located in the southeastern region of Korea were collected retrospectively. They failed to show response or were intolerant to conventional treatments, including steroids or immunomodulators. Screening measures for latent TB infection (LTBI) and the incidence and risk factors of

active TB infection after treatment with anti-TNFs were identified.

RESULTS: Overall, 376 IBD patients treated with anti-TNF agents were recruited (male 255, mean age of anti-TNF therapy 32.5 ± 13.0 years); 277 had Crohn's disease, 99 had ulcerative colitis, 294 used infliximab, and 82 used adalimumab. Before anti-TNF treatment, screening tests for LTBI including an interferon gamma release assay or a tuberculin skin test were performed in 82.2% of patients. Thirty patients (8%) had LTBI. Sixteen cases of active TB infection including one TB-related mortality occurred during 801 person-years (PY) follow-up (1997.4 cases per 100000 PY) after anti-TNF treatment. LTBI (OR = 5.76, 95%CI: 1.57-21.20, $P = 0.008$) and WBC count $< 5000 \text{ mm}^3$ (OR = 4.5, 95%CI: 1.51-13.44, $P = 0.007$) during follow-up were identified as independently associated risk factors.

CONCLUSION: Anti-TNFs significantly increase the risk of TB infection in Korean patients with IBD. The considerable burden of TB and marked immunosuppression might be attributed to this risk.

Key words: Tuberculosis; Anti-TNF; Korea; Inflammatory bowel disease; Latent tuberculosis infection; Risk factor

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Core tip: Anti-TNF antagonist therapy implies significant tuberculosis (TB) risk in inflammatory bowel disease (IBD) patients residing in areas with an intermediate burden of TB infection. The risk of susceptibility to TB under anti-TNF treatment is associated with latent TB infection and considerable immunosuppression. Rigorous and sustained assessment of TB infection should be implemented in Korean IBD patients undergoing anti-TNF therapy.

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INTRODUCTION

Anti-TNF agents are able to favorably change the natural course of inflammatory bowel disease (IBD), and these drugs are currently the most effective treatment to achieve sustained clinical remission and mucosal healing^[1]. Korea and other East Asian countries, once considered being a region in which

IBD was extremely rare, have had a rapidly increasing number of patients with IBD. The population-based Korean data showed that the mean annual incidence rates of Crohn's disease (CD) and ulcerative colitis (UC) increased from 0.05 and 0.34 per 100000 persons, respectively, in 1986-1990 to 1.34 and 3.08 per 100000, respectively, in 2001-2005^[2]. Anti-TNF agents such as infliximab and adalimumab have been used with gradually increasing frequency since they were approved for IBD treatment in the mid 2000s in Korea^[3-5].

One of the primary concerns regarding anti-TNF agents is an increased risk of tuberculosis (TB) infection. Despite a wide variation in TB rates among different countries, it has been reported that there was an approximately four-fold increased risk of TB in patients with rheumatoid arthritis (RA) treated with anti-TNF agents compared with those not treated with anti-TNF agents^[6,7]. For IBD patients, the current incidence of active TB after treatment with an anti-TNF inhibitor is approximately 1%-2%^[8,9]. The majority of TB cases occurred within 3-4 mo after anti-TNF therapy, suggesting that TB develops as a result of reactivation of latent disease rather than as a new infection^[9,10]. Furthermore, the clinical characteristics of TB infection in anti-TNF treated patients are markedly atypical, presenting a greater chance of disseminated and extra-pulmonary diseases^[11,12].

Although the incidence rate of TB infection in South Korea has been declining over recent decades, it remains one of the most common infectious diseases in the country. According to the World Health Organization, the incidence rate of TB in South Korea was 108 per 100000 inhabitants in 2012^[13]. Whereas the risk of TB in Korean patients with RA treated with infliximab has been reported^[14], there have been no reports on the incidence of TB infection in Korean IBD patients using anti-TNFs. Given that TB risks vary in different countries and with different diseases^[15], it would be noteworthy to identify the risk of TB infection due to anti-TNF therapy in Korean patients with IBD. The aim of this study was to evaluate the incidence of active TB infection and associated risk factors in Korean IBD patients treated with anti-TNF agents. Additionally, the clinical characteristics of TB infection in these subjects were estimated.

MATERIALS AND METHODS

This study was conducted in 13 referral hospitals in Gyeongsang province in the southeastern region of Korea. Two anti-TNF agents, infliximab and adalimumab, are currently approved to treat IBD in South Korea. Candidates approved for the use of anti-TNFs by the National Health Insurance Service were patients with a moderate to severe stage of IBD who failed to show response or were intolerant to conventional treatments, including steroids or immunomodulators^[4,5]. IBD patients treated with

Table 1 Baseline characteristics of patients treated with anti-TNF agent

	<i>n</i> = 376
Sex (male:female)	255:121
Age of diagnosis (yr)	27.9 ± 12.6
Age at the start of anti-TNFs (yr)	32.5 ± 13.0
Follow-up (mo)	81.6 ± 58.9
Diseases	
Crohn's disease	277 (73.7)
L1/L2/L3/L1+L4/L3+L4	48/60/157/4/8
B1/B2/B3	102/87/88
Perianal disease	160 (42.5)
Ulcerative colitis	99 (26.3)
E1/E2/E3	8/45/46
Previous anti-TB treatment	8 (2.1)
Diabetes Mellitus	12 (3.2)
Anti-TNF agents	
Infliximab	294 (78.2)
Adalimumab	82 (21.8)

Data are expressed as *n* (%) or mean ± SD. TB: Tuberculosis; UC: Ulcerative colitis.

either of these TNF antagonists from June 2003 to January 2014 were included in this study. Information regarding clinical and demographic characteristics such as sex, age of IBD diagnosis, disease duration, anti-TNF drug exposure period, location and behavior of CD, and extent of UC were obtained from medical records. For the risk factors for TB, diabetes mellitus (DM), previous TB infection, latent TB infection (LTBI), concomitant immunosuppressant at the start of anti-TNF therapy, and WBC count measured around the last follow-up day were recorded. When active TB infection developed after anti-TNF therapy, WBC counts at the time of TB diagnosis were counted. However, history regarding contact with active TB patients was not obtained. The study was approved by the ethics review committee of the Institutional Review Board of all of the hospitals participating in the study.

Definition of TB infection and screening modalities

According to the Korean Guidelines for Tuberculosis published in 2011, chest radiography, a tuberculin skin test (TST), and an interferon gamma release assay (IGRA) should be performed for LTBI screening before the initiation of anti-TNF therapy^[16]. Abnormal findings on chest radiography included apical densities, pleural scarring, and calcified granulomas. TST was performed according to the Mendel-Mantoux method using purified protein derivative (PPD). Skin induration with a diameter ≥ 10 mm at 48-72 h after the PPD inoculation on the forearm was considered positive^[17]. Two methods for IGRA are available in Korea: QuantiFERON®-TB Gold In-Tube (QFT-GIT; Cellestis, Carnegie, VIC, Australia) and T-SPOT®.TB (T-SPOT; Oxford Immunotec, Abingdon, UK). LTBI was defined as (1) cases of an abnormal chest X-ray without previous complete TB treatment or (2) positive results with TST or IGRA^[18]. The criteria for active TB infection were as follows: (1) typical symptoms with

isolation of *Mycobacterium tuberculosis* from a clinical specimen or (2) typical symptoms with radiological or histological findings of TB without culture or when a culture sample could not be obtained^[18]. Although there was no bacterial confirmation, these cases were regarded as active TB when the clinical symptoms and the radiological or histological findings improved with anti-TB therapy^[18]. The patients diagnosed with active TB before the initiation of anti-TNF therapy were not counted as the TB cases in the study.

Statistical analysis

The incidence rate of active TB was calculated using person-years (PY) and was expressed as new cases per 100000 PY. Differences in the categorical variables between the groups were assessed with the χ^2 test or Fisher's exact test. For comparisons of continuous variables, the Mann-Whitney test was used. To investigate the independent risk factors associated with active TB infection during anti-TNF therapy, a logistic regression analysis was performed using variables with statistically significant associations identified in a univariate analysis. Age and sex were also included as variables for a multivariate analysis because these are considered important risk factors of TB infection^[19,20]. A two-tailed *P* value < 0.05 was considered significant. The statistical analysis was performed with SPSS version 14.0 (SPSS, Chicago, IL, United States).

RESULTS

In total, 376 IBD patients using anti-TNF agents were included in the study (255 males, mean age at the start of anti-TNF therapy of 32.5 ± 13.0 years, with 277 patients with CD and 99 patients with UC). The ileocolon (157, 56.7%) and non-stricturing non-penetrating type disease (102, 36.8%) were the most common location and behavior of CD, respectively. The majority of the UC patients had extensive disease (46, 46.5%). Eight patients (2.1%) had a previous TB infection history with successful anti-TB treatment. Infliximab and adalimumab were used in 294 (78.2%) and 82 (21.8%) patients, respectively. The baseline characteristics of the patients are described in Table 1.

Screening for latent TB infection before anti-TNF therapy

The screening outcomes prior to anti-TNF therapy are summarized in Table 2. A chest X-ray was taken before anti-TNF therapy in the majority of patients (356, 94.7%); 8 (2.2%) of the chest x-rays showed abnormal appearances, suggesting old pulmonary TB. Among these patients, 4 had a history of a complete course of anti-TB treatment for pulmonary TB infection. IGRA was performed in 276 (73.4%) patients, and the positivity rate was 5.8% (16/276). One hundred and thirty-one patients (34.8%) underwent TST before anti-TNF therapy, and the positivity rate was 9.2% (12/131). Both IGRA and TST were performed in 98 patients

Table 2 Screening outcomes for latent tuberculosis infection before anti-TNF agent

	<i>n</i> = 376, <i>n</i> (%)
Chest X-ray	
Done	356 (94.7)
Old tuberculosis	8/356 (2.2)
Negative	348/356 (97.8)
IGRA	
Unknown	9 (2.4)
Done	276 (73.4)
Positive	16/276 (5.8)
Negative	241/276 (87.3)
Indeterminate	19/276 (6.9)
Steroid or thiopurine at IGRA	214/276 (77.5)
QuantiFERON	247 (62.9)
Positive	14/247 (5.7)
Negative	218/247 (88.3)
Indeterminate	15/247 (6)
T-SPOT	29 (12.6)
Positive	2/29 (6.9)
Negative	23/29 (79.3)
Indeterminate	4/29 (13.8)
TST	
Unknown	10 (2.7)
Done	131 (34.8)
Positive	12/131 (9.2)
Negative	117/131 (89.3)
Steroid or thiopurine at TST	104/131 (79.4)
Screening tests for LTBI	
1 test (IGRA or TST)	211 (56.1)
2 tests (IGRA and TST)	98 (26.1)
Neither IGRA or TST	59 (15.7)
Latent tuberculosis infection	30 (8.0)

IGRA: Interferon gamma release assay; TST: Tuberculin skin test; LTBI: Latent tuberculosis infection.

(26.7%). The use of IGRA increased considerably from 34% in 2009 to 90.2% in 2013, whereas there was no significant change in the use of TST during the same period, with TST being performed in 30% and 39.8% of patients in 2009 and 2013, respectively. Using chest X-ray, IGRA and TST as screening measures, LTBI was confirmed in 30 patients (8.0%). Of these LTBI cases, 16 patients received prophylactic anti-TB medications. The patient flow diagram is shown in Figure 1. Immunosuppressants, such as steroids or thiopurine, were being administered at the time of IGRA and TST screening in 77.5% and 79.4% of patients, respectively.

Incidence and risk factors of active TB infection after anti-TNF agents

Sixteen cases of active TB infection occurred during the 801 PY follow-up period after anti-TNF exposure (1997.4 per 100000 PY). The median time from anti-TNF initiation to active TB infection was 28.7 wk (range, 8-142). The clinical characteristics of these patients are summarized in Table 3. Infliximab was used in 15 patients, whereas adalimumab was used in 1 patient. All of the patients except one (who had a chest X-ray only) underwent LTBI screening tests of IGRA (75%, 12/16) or TST (31.2%, 5/16) before

initiating anti-TNF treatment. Fifteen patients (93.8%) were taking immunosuppressants, including steroids or azathioprine, within 1 wk of the screening tests, and 4 patients had LTBI. Among the 4 LTBI cases, 2 patients received prophylactic treatment of either isoniazid for 9 mo or isoniazid plus rifampicin for 3 mo, and one patient had a previous complete anti-TB medication history for active pulmonary TB. The majority of the patients (15/16, 93.8%) were taking steroids or azathioprine when the active TB diagnosis was made. We conducted a univariate analysis to identify the risk factors of TB infection during anti-TNF treatment in IBD patients (Table 4). The positive rate of screening for LTBI in the TB infection group was higher than in the non-TB infection group (25% vs 7.2%, $P = 0.031$). A WBC count < 5000 mm³ was more often observed in the TB infection group than in the non-TB infection group (62.5% vs 31.9%, $P = 0.015$). There was no significant difference between the groups regarding disease type, DM, anti-TNF agents, and immunomodulator use at the start of anti-TNF treatment. A multivariate analysis using logistic regression after adjustment for age and sex demonstrated that LTBI (OR = 5.76, 95%CI: 1.57-21.20, $P = 0.008$) and white blood cell (WBC) count < 5000 mm³ during follow-up (OR = 4.5, 95%CI: 1.51-13.44, $P = 0.007$) were significant independent risk factors for active TB infection during anti-TNF agent therapy (Table 5).

One 24-year-old male patient with CD undergoing infliximab treatment died 55 d after miliary TB diagnosis because of devastating acute renal failure. His chest X-ray had been normal, and TST had shown a negative result. He was taking steroids at the time of the TST.

Clinical features of active tuberculosis infection during treatment with anti-TNF agents

Fever (43.8%) was the most common clinical manifestation, followed by cough, dyspnea, abdominal distension, fatigue and chest pain. The most frequent sites of infection were the lung, lymph node and pleura, in that order. Miliary TB was observed in 6 (37.5%) patients. The majority of the patients (81.3%) showed extra-pulmonary TB, indicating an atypical presentation of TB infection. The clinical characteristics of active TB infections are shown in Figures 2A and 2B.

DISCUSSION

In this study, the incidence rate of TB infection was 1997.4 per 100000 PY in IBD patients exposed to anti-TNF inhibitors, and this risk was associated with LTBI confirmed by the screening tests and with leukopenia (WBC < 5000 mm³) during the follow-up period. These rates are much higher than the rates found in Western studies^[7,9,11]. The remarkably high incidence of TB in this study might be related to the large burden of TB in the general population. South Korea has been

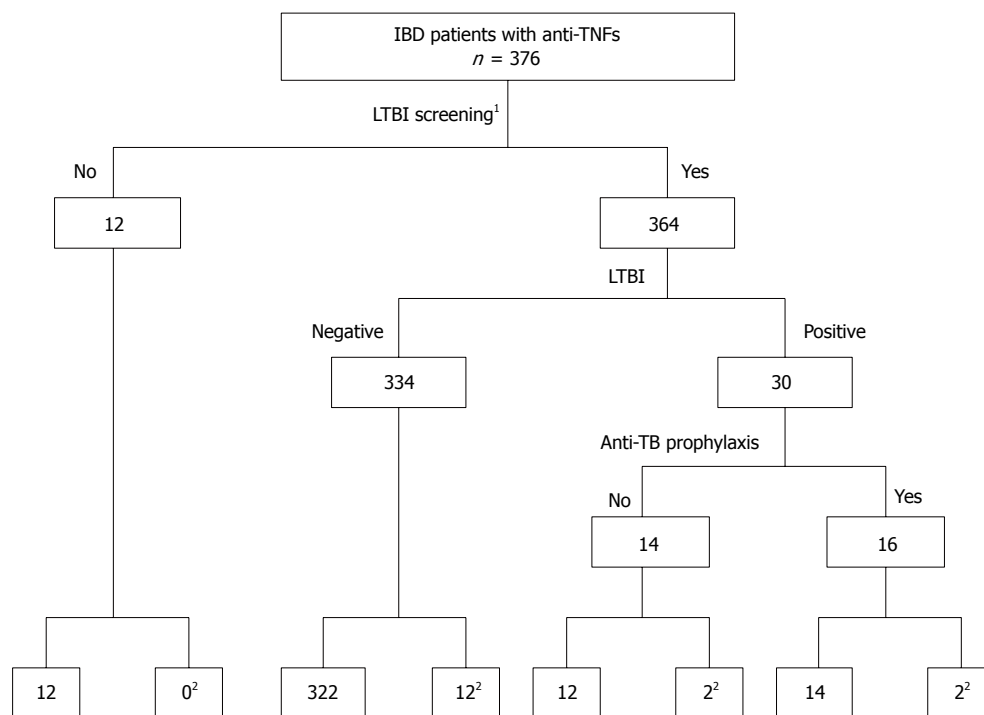


Figure 1 Flow diagram of patients, illustrating screening outcomes. ¹Chest X-ray, tuberculin skin test, or interferon gamma release assay; ²Development of active tuberculosis infection after anti-TNF therapy. LTBI: Latent tuberculosis infection.

Table 3 Clinical characteristics of patients developing active tuberculosis infection after anti-TNF agent

No.	IBD	Sex	Age of anti-TNFs (yr)	Anti-TNFs	Previous TB treatment	Screening IGRA	Screening TST	IS at screening	Prophylaxis	Interval to TB infection (wk)	IS at TB diagnosis	Extra-pulmonary TB	No. of involvement organ
1	CD	F	21	IFX	No	ND	ND	None	ND	83	CS + AZA	No	1
2	CD	M	24	ADA	No	+	ND	CS	INH	22	None	Yes	1
3	CD	M	24	IFX	No	-	ND	CS + AZA	ND	35	AZA	Yes	3
4	CD	M	42	IFX	Yes	-	ND	CS	ND	46	CS + AZA	Yes	6
5	CD	F	34	IFX	Yes	-	ND	AZA	ND	23	AZA	Yes	1
6	CD	M	29	IFX	No	-	ND	AZA	ND	10	AZA	Yes	5
7	CD	M	41	IFX	No	ND	-	AZA	ND	12	AZA	Yes	1
8 ¹	CD	M	24	IFX	No	ND	-	CS	ND	8	CS	Yes	4
9	CD	M	27	IFX	No	ND	-	AZA	ND	22	AZA	No	1
10	CD	M	23	IFX	Yes	+	-	AZA	ND	8	CS + AZA	Yes	1
11	CD	M	21	IFX	No	-	Unknown	CS + AZA	ND	129	CS + AZA	Yes	3
12	UC	M	32	IFX	No	+	ND	AZA	INH + RFP	40	AZA	Yes	4
13	UC	M	70	IFX	No	-	ND	AZA	ND	142	AZA	No	1
14	UC	M	21	IFX	No	-	ND	CS + AZA	ND	52	AZA	Yes	3
15	UC	M	56	IFX	No	-	ND	AZA	ND	47	AZA	Yes	2
16	UC	F	25	IFX	No	+	-	AZA	ND	12	AZA	Yes	2

¹This patient died 55 d after miliary tuberculosis diagnosis due to devastating acute renal failure. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; IFX: Infliximab; ADA: Adalimumab; ND: Not done; TB: Tuberculosis; IGRA: Interferon gamma release assay; TST: Tuberculin skin test; IS: Immunosuppressant; CS: Corticosteroid; AZA: Azathioprine; INH: Isoniazid; RFP: Rifampin.

reported to have an intermediate burden of TB with an incidence, mortality and prevalence of 108, 5.4 and 146 per 100000 persons, respectively, in 2012^[13]. For reference, the incidence, mortality, and prevalence of TB in the United States were 3.6, 0.14, and 4.7 per 100000 persons, respectively, in the same year^[13]. The incidence rates were also considerably high in Korean ankylosing spondylitis (AS) or RA patients using anti-TNF agents, with the rates ranging from 540 to 2558 per 100000 PY, which is similar to the observations in

our study^[14,18]. To the best of our knowledge, this is the first study to evaluate the risk of TB infection in a large number of Korean IBD patients undergoing anti-TNF therapy.

Although the Korean Guidelines for TB in 2011 recommend TST or IGRA as screening tests before initiating anti-TNF agents, TST and IGRA were used in only 34.8% and 73.4% of patients, respectively, in the present study. This low compliance of screening tests might be partly attributed to the patients who

Table 4 Univariate analysis of risk factors for active tuberculosis infection after anti-TNF therapy *n* (%)

	TB infection + (<i>n</i> = 16)	TB infection - (<i>n</i> = 360)	<i>P</i> value
Age at anti-TNF (yr)	26 (21-70)	30 (11-76)	0.808
Female	3 (18.8)	118 (32.8)	0.287
Diseases			0.772
Crohn's disease	11 (68.8)	266 (73.9)	
Ulcerative colitis	5 (31.3)	94 (26.1)	
Diabetes mellitus	1 (6.3)	11 (3.1)	0.411
Anti-TNF agent			0.212
Infliximab	15 (93.8)	279 (77.5)	
Adalimumab	1 (6.3)	81 (22.5)	
LTBI	4 (25)	26 (7.2)	0.031
IM at anti-TNF agent	13 (81.3)	228 (63.3)	0.187
WBC count < 5000 mm ³	10 (62.5)	115 (31.9)	0.015

LTBI: Latent tuberculosis infection; IM: Immunomodulator.

were taking anti-TNF agents in the early period when LTBI screening before the use of TNF blockers was not strictly performed in Korea. A study from the USA also showed a low rate (65%) of LTBI screening prior to initiating anti-TNF therapy in IBD patients, and the authors reported that the initiation of treatment prior to 2006 was a risk factor for screening failure^[21]. In our study, the use of IGRA rose significantly over time from 34% in 2009 to 90.2% in 2013. However, the rate of TST remained low throughout the study period, reflecting the low preference for TST due to insufficient accuracy of TST for LTBI screening, particularly in Korea, where Bacille Calmette-Guerin (BCG) vaccination is mandatory, which might influence TST results. A lack of specificity for pathogenic *Mycobacterium tuberculosis* is a limitation of TST, and this might be due to cross-reactivity with the BCG vaccination and environmental mycobacteria^[22,23]. Therefore, IGRA might be more appropriate as a LTBI screening test in countries using routine BCG vaccination, such as Korea^[24].

One important finding of the present study was the low positivity rates of each screening test (5.8% for IGRA and 9.2% for TST). There appear to be different positivity rates of LTBI screening tests between patients with different diseases. For example, the TST and IGRA positivity rates of RA patients were relatively high, up to 23% and 31.6%, respectively^[25], whereas the rates of IBD patients were 12.5%-16% and 7.2%-9%, respectively^[26,27], which are similar to our results. Although the cause of the difference between the studies is unclear, the different patient age ranges and the varying use of concomitant immunosuppressants during screening might be plausible explanations. IBD patients are typically younger than RA patients, and age is strongly associated with the positivity of TST as a result of longer exposure to *Mycobacterium tuberculosis*^[26]. Additionally, approximately 80% of patients in the present study were taking steroids or thiopurine during the screening tests, which could lead to low positive

Table 5 Multivariate analysis of risk factors for active tuberculosis infection after anti-TNF therapy

	OR	95%CI	<i>P</i> value
Age at anti-TNF	0.98	0.94-1.02	0.346
Female	1.95	0.53-7.18	0.328
LTBI	5.76	1.57-21.20	0.008
WBC count < 5000 mm ³	4.50	1.51-13.44	0.007

LTBI: Latent tuberculosis infection; WBC: White blood cell.

results for the tests. Immunosuppression has been known to negatively affect the outcomes of TST and IGRA, resulting in low sensitivity of these screening tests^[26]. Therefore, the ideal time for LTBI screening would be prior to the initiation of immunosuppressant therapy.

There has been no study on the risk factors for the development of TB infection during anti-TNF therapy because the number of TB cases is too small for a precise assessment. We identified positive LTBI and a WBC count < 5000 mm³ as independent risk factors for active TB infection during anti-TNF therapy. Patients with LTBI were more likely to have active TB infection than patients without LTBI (OR = 5.76, 95%CI: 1.57-21.20, *P* = 0.008) (Table 5). This result is not surprising because LTBI is likely to progress to active TB in immunocompromised patients, such as those taking anti-TNF inhibitors^[17]. There is clear evidence suggesting that chemoprophylaxis with screening for LTBI considerably reduces the TB reactivation rate^[28,29]. However, we should consider that chemoprophylaxis for suspected LTBI prior to anti-TNF therapy does not entirely avoid the development of active disease^[30]. It has been reported that chemoprophylaxis is only moderately effective^[28,30]. In the present study, we could not find a prophylactic effect of anti-TB medications; 12.5% (2/16) of patients with LTBI who took prophylactic anti-TB medication still developed active TB, whereas 14.3% (2/14) of patients with LTBI who did not take prophylaxis had active TB during anti-TNF therapy (Figure 1). Although the exact reason for the lack of efficacy of prophylaxis in this study is unclear, the emergence of drug-resistant TB in Korea might be a possible explanation^[31,32].

Guidelines recommend delaying to begin anti-TNF for at least 3 wk when LTBI is confirmed^[16,33]. Anti-TNF agents can be started early in some inevitable cases for disease control. Given that LTBI positivity is a significant risk factor for the development of active TB and there seems to be the lack of efficacy of chemoprophylaxis for that, we should consider seriously undertaking the balance between the risk and the benefit before initiating anti-TNF agents in IBD patients with positive result for LTBI. If anti-TNF is used in these patients, more strict and complete anti-TB prophylaxis measures should be followed by rigorous monitoring for the development of active TB.

Our result showing leukopenia as an independent

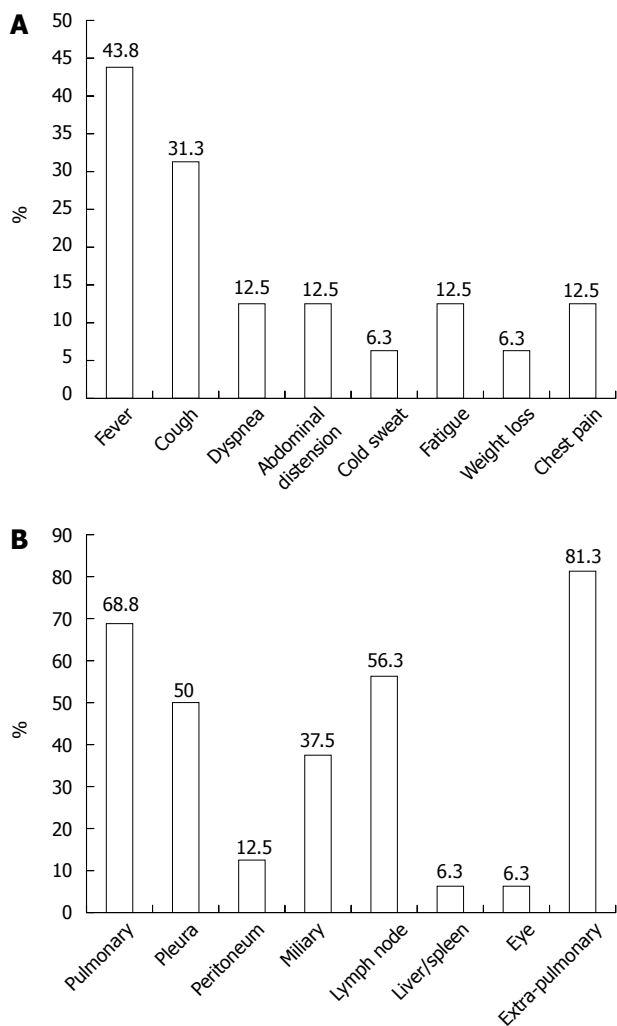


Figure 2 Clinical symptoms (A) and involvement locations (B) of active tuberculosis infection after anti-TNF therapy in patients with inflammatory bowel disease.

factor for active TB infection might indicate the synergistic risk of the substantial level of immunosuppression in anti-TNF users. Anti-TNF blocker plus azathioprine combination therapy has been shown to be the most effective treatment for IBD^[34,35]. A significant proportion (87.5%, 14/16) of patients with active TB infection had concomitant azathioprine treatment at the time of TB diagnosis (Table 3). However, we are not certain that the relative leukopenia at the time of TB diagnosis is entirely a result of immunomodulator therapy alone because leukopenia can be observed in some patients with disseminated TB infection, such as miliary TB^[36]. Mert *et al.*^[36] observed leukopenia in 26% of miliary TB patients, and this was considered to be a poor prognostic sign, although the exact cause was not clear^[37]. Therefore, the results of our study should be interpreted cautiously.

In contrast to TB in immunocompetent individuals, where pulmonary infection is the main manifestation, patients who received anti-TNF therapy showed a significantly high percentage of extrapulmonary disease, at 57%-75%, and 25% had disseminated

disease^[7,38]. Similarly, we determined that the rates of extrapulmonary manifestations and miliary TB were considerably high at 81.3% and 37.5%, respectively (Figure 2B). Furthermore, these patients presented a variety of non-specific symptoms, including fever, fatigue, abdominal distension, dyspnea, and chest pain (Figure 2A). These results suggest that the potential diagnosis of active TB infection should be vigilantly evaluated when any patient taking an anti-TNF inhibitor has these constitutional symptoms aside from coughing because the TB manifestations under anti-TNF therapy are remarkably atypical.

Most cases of TB related to anti-TNFs are considered as reactivations of LTBI because it has been reported that TB develops early after the initiation of TNF blockade, usually within 3-4 mo^[9,10]. In the present study, however, the median time from the first anti-TNF dose to TB diagnosis was 28.7 wk, which was longer than previous studies, and a quarter of TB cases occurred 1 year after the initiation of anti-TNF agents. We presumed that some TB cases in our study might represent *de novo* infection from exposure to other TB-infected persons during the course of anti-TNF treatment instead of representing reactivation of LTBI. This finding is in accordance with another Korean study evaluating the TB incidence in AS patients taking anti-TNFs with a long median time of 21.5 mo^[18]. These results highlight the recommendation that information regarding close contact with TB-infected individuals should be rigorously and continuously assessed in patients receiving anti-TNF therapy, particularly in countries with a significant TB burden such as South Korea. Further prospective studies are needed to clarify whether periodically repeated screening tests for LTBI are effective in this population.

This study has several limitations. The retrospective design is the major limitation. Important information regarding contact with active TB patients could not be obtained. The WBC count was not systematically collected for the analysis of risk factors. The WBC counts of non-TB patients were obtained at the last follow-up visit, whereas the WBC counts of the TB patients were obtained at TB diagnosis.

In conclusion, anti-TNF inhibitors imply significant TB risk in IBD patients residing in areas with an intermediate burden of TB infection. The risk of susceptibility to TB under anti-TNF therapy is significantly associated with LTBI and considerable immunosuppression. Rigorous and sustained assessment of TB infection should be performed in IBD patients undergoing anti-TNF therapy. Further studies to establish the strategy of effective TB monitoring in this population are required.

COMMENTS

Background

Anti-TNF agents are able to favorably change the natural course of inflammatory bowel disease (IBD), and these drugs are currently the most effective treatment to achieve sustained clinical remission and mucosal healing.

However, Anti-TNF agents considerably increase the risk of tuberculosis (TB) infection.

Research frontiers

Although the use of anti-TNF agents in Korean patients with IBD has recently increased, there have been no reports on the risk of active TB infection in this population.

Innovations and breakthroughs

In this study, the incidence rate of TB infection was 1997.4 per 100000 person-years in IBD patients exposed to anti-TNF inhibitors and these rates are much higher than the rates found in Western studies. The risk was associated with LTBI confirmed by the screening tests and with leukopenia (WBC < 5000 mm³) during the follow-up period.

Applications

Rigorous and sustained assessment of TB infection should be performed in IBD patients undergoing anti-TNF therapy. Further studies to establish the strategy of effective TB monitoring in patients residing in areas with an intermediate burden of TB infection are required.

Terminology

Latent TB infection was defined as (1) cases of an abnormal chest X-ray without previous complete TB treatment or (2) positive results with tuberculin skin test or interferon gamma release assay.

Peer-review

This article presents important data concerning the safety of anti-TNF therapy in IBD patients who live in countries with a significant burden of TB infection.

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