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의학석사 학위논문

항종양괴사인자 치료를 받고 있는 염증성 장질환 환자의 결핵 발생 위험 및 특성

Risk and characteristics of tuberculosis after anti-tumor necrosis factor therapy in patients with inflammatory bowel disease

울 산 대 학 교 대 학 원

의 학 과

이 재 용

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지 도 교 수　　박 상 형

이 논문을 의학 석사 학위 논문으로 제출함

2021 년 2 월

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Abstract

Background/Aim Anti-tumor necrosis factor (TNF) treatment for inflammatory bowel disease (IBD) increases the risk of tuberculosis (TB) infection. We analyzed the clinical characteristics and risks of TB in Korean patients with IBD who received anti-TNF treatment.

Methods IBD patients treated with anti-TNF agents between January 2001 and June 2018 at tertiary referral hospital were included in the study. Overall, 1434 patients of ulcerative colitis (UC) and Crohn's disease (CD) were enrolled. We calculated the incidence of active TB infection after anti-TNF treatment, and compared the clinical characteristics of TB group and non- TB group.

Results 21 patients (1.46%) developed active TB infection and the incidence rate of active TB were 366.73 cases per 100,000 person-years. 198 patients (14.9%) were positive for latent tuberculosis infection (LTBI), of which only 8 (4%) did not complete LTBI treatment. The age at which the Anti-TNF therapy started in the TB development group was significantly higher than in the group that did not develop TB (HR = 1.041, 95% CI : 1.014-1.069, P = 0.002), and as the age group increased,

the incidence rate increased linearly (linearity p-value < 0.001). There was no significant difference between TB development group and non-TB group (HR = 0.896, 95% CI : 0.262-3.066, P = 0.862).

Conclusion In patients with IBD, the incidence of TB increased as the age group of Anti-TNF therapy initiation increased. Active treatment of LTBI might be lower the incidence of TB in IBD patients with anti-TNF therapy.

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

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Introduction

Inflammatory bowel disease is a disorder in which abnormal chronic inflammation in the gastrointestinal tract resulting from immune dysregulation, encompassing ulcerative colitis and Crohn's disease[1, 2]. The number of IBD patients has been on the rise recently in Korea and other Asian countries where IBD was once considered rare[3, 4]. Immune dysregulation of IBD results in overproduction of TNF-α, and monoclonal antibodies targeting this TNF-α can suppress abnormal immune response[5]. As the effect of the anti-tumor necrosis factor (anti-TNF) therapy for induction and maintenance therapy has been proven in IBD patients recently, the frequency of the anti-TNF therapy is increasing worldwide[6-8].

Anti-TNF therapy has proven excellent efficacy in IBD patients, but it increases the risk of infection. TB is one of the infections associated with anti-TNF therapy, which is believed to be a mechanism that fails to suppress the activation of TB by inhibiting the formation of granuloma[9]. Because anti-TNF therapy increase the risk of development of active TB by reactivation of latent TB[10, 11], Guidelines are recommended for diagnosing and treating LTBI before starting anti-TNF therapy[11, 12]. Although the incidence of TB is decreasing, interest in TB is increasing in Korea, which has a higher incidence of TB and LTBI than advanced countries[13-15].

Several studies about development of TB after anti-TNF therapy in IBD patients

were reported. Most of research was conducted through multi-institution cohort study, so making it difficult for each institution to apply consistent standards in diagnosis, treatment and follow-up. It is worthwhile to analyze the risk and characteristics of TB infection in patients who have undergone standardized management of IBD and LTBI before the anti-TNF therapy in Korea. In this study, we identified the incidence, characteristics, and risk factors of TB in IBD patients who started anti-TNF therapy in a single large medical institution.

Methods

<Study design>

This retrospective study was conducted at Asan Medical Center, a 2,700-bed tertiary medical center in Korea. The anti-TNF agents that can be administered in IBD include infliximab, adalimumab, and golimumab. 1811 IBD patients including ulcerative colitis and Crohn's disease, who were prescribed these anti-TNF agents from January 2001 to June 2018 were enrolled. The enrolled patient was selected according to the following exclusion criteria: (1) foreigner, (2) follow up or anti-TNF therapy of <1month, (3) previous history of anti-TNF therapy at other medical center. As a result, a total of 1434 IBD patients were selected who were initiated into the anti-TNF therapy (Figure 1).

The selected patients were divided into 21 patients who developed TB during the anti-TNF therapy and 1,413 patients who did not have TB. Age, sex, type of IBD, age at the diagnosis of IBD, smoking status, result of LTBI screening, history of TB, anti-TNF agent type, age at the start of anti-TNF therapy and concomitant medication use such as steroids and immunomodulators were collected in their medical record. The study was approved by the Institutional Review Boards of Asan Medical Center.

<Screening and management of LTBI>

According to Korean guidelines, screening for LTBI is recommended before the anti-TNF therapy starts[16]. Most of the patients subject to LTBI screening were referred to tuberculosis specialists for work-up and management. They were checked for past medical history of TB infection and presence of any symptoms suggestive of TB. Patients under Screening for LTBI were tested for simple chest X-rays, and were performed for tuberculin skin test (TST) and/or interferon gamma release assay (IGRA). TST was carried out following the Mendel-Mantoux method using purified protein derivative (PPD). Induration with a diameter of 10 mm or more was considered positive 48-72 hours after PPD inoculation on the forearm[17]. IGRA was performed with QuantiFERON®-TB Gold In-Tube (QFT-GIT; Cellestis, Carnegie, VIC, Australia) and/or T-SPOT®.TB (T-SPOT; Oxford Immunotec, Abingdon, UK), and test results were defined according to the manufacturer's instructions. LTBI was defined as (1) abnormal chest X-ray case not previously fully treated for TB or

(2) as a positive result of TST or IGRA[16, 17].

Patients with positive LTBI were subjected to TB prophylaxis and usually started with isoniazid and rifampin for 3 months. If there had been comorbid disease unsuitable to use the combination therapy, or adverse effects had occurred, rifampin for 4 months therapy or isoniazid for 9 months therapy was performed. Patients who completed screening for LTBI were followed-up during anti-TNF agent therapy regardless of LTBI, and chest radiography and symptoms or signs implying TB were checked.

<Statistical analysis>

The hazard ratio and 95% confidence interval (CI) were calculated using Cox proportional hazards models to evaluate the risk factor of development of TB. The incidence rate (IR) of TB among patients with IBD was calculated as the number of TB patients per 100,000 person-year of the population. The 95% CI of IR was based on exact confidence interval for Poisson probabilities of the corresponding patients and P-value for linearity of IR was calculated, based on log-binomial model. TB-free survival probability was constructed using the Kaplan–Meier method. P value < 0.05 was considered statistically significant. Statistical analyses were performed with the R program version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

<Baseline characteristics of study patients>

A total of 1434 IBD patients who started anti-TNF therapy were included in the study (Table 1). The mean age of starting anti-TNF therapy was 31.35 ± 13.59 years, and the mean follow-up period was 48.54 months. 940 (65.6%) patients were male, and patients of Crohn's disease were 1102 (76.8%). There were 991 (69.1%) non-smokers. Subjects received three types of anti-TNF agents: infliximab, adalimumab, and golimumab. There were 1259 patients (87.8%) who used one agent, and most of them used infliximab. There were 166 patients (11.6%) who used two drugs and 3 patients (0.2%) who used three drugs.

939 patients were performed TST and 1328 patients were tested for IGRA. There were 966 patients who underwent both IGRA and TST. 1,333 patients (93.0%) completed LTBI screening, of which 198 patients were positive for LTBI, accounting for 14.9%. Among them, 190 patients (96.0%) did not need to perform TB prophylaxis or completed prophylaxis, and 8 patients (4.0%) did not complete TB prophylaxis.

<Clinical characteristics of patients with developed active TB during anti-TNF therapy>

Twenty-one IBD patients were diagnosed with TB during anti-TNF therapy. The proportion of active TB development was 1.46% and the incidence rate was 366.73 cases/100,000 person-year. The baseline characteristics of patients developed with TB are described in Table 2. There were 6 patients with ulcerative colitis and 15 patients with Crohn's disease. There were 12 males and 9 females, and median duration from the start of anti-TNF therapy to the diagnosis of active TB infection was 14 months (range: 1 ~ 95). One patient had been diagnosed and treated with TB in the past. 17 patients developed TB while using infliximab. There were 4 patients diagnosed with TB who changed to adalimumab or who received adalimumab from the beginning. The three TB patients had positive result of LTBI screening, and all of them completed TB prophylaxis. There were 18 cases (85.7%) of TB involving lung and 8 cases (38.1%) involving extrapulmonary organs. Twenty patients had completely cured TB, and one patient was undergoing treatment at the end of the study.

<Comparison between the TB development group and the TB non-development group>

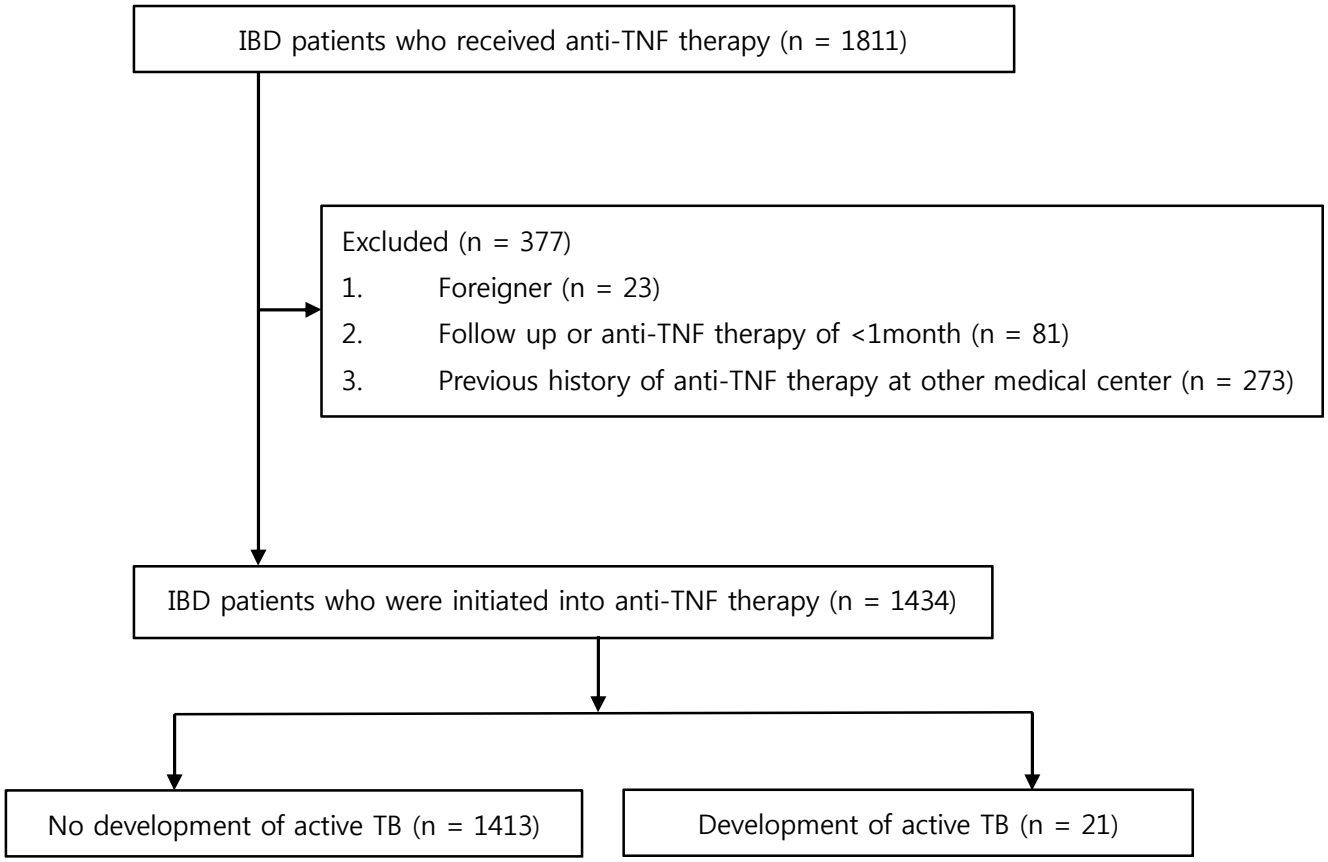
We used the Cox proportional hazard model to identify the risk of development

of TB in IBD patients treated with anti-TNF therapy (Table 3). The age at which anti-TNF therapy was started was higher in the TB development group than in the non-development group. (39.57 vs 31.22, p-value = 0.002) There were no significant differences between the two groups in sex, IBD type, smoking status, and past TB infection history. In patients who underwent LTBI screening, the positive rates of LTBI did not differ between the two groups. (14.3% vs 13.8%, p-value = 0.862) There was no significant difference in the incidence of TB between the LTBI positive group and the negative group (Figure. p-value = 0.86).

<Incidence rate of TB development according to age>

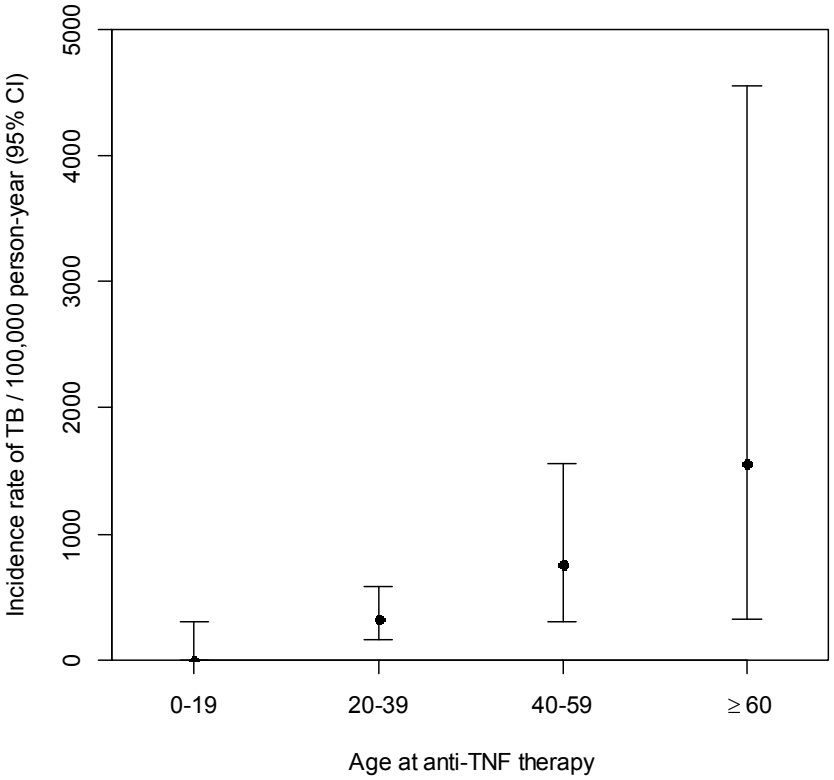
The study subjects were divided into 4 groups by age group (0~19yr, 20~39yr, 40~59yr, 60yr~), and the incidence rate of TB was checked and cross-analysis was performed (Figure 2-4). The incidence rate of TB by age group was 0, 323.4, 756.6, 1557.8 cases / 100,000 person-year, respectively, and the incidence rate increased linearly as the age group increased (linearity p-value <0.001). The incidence of TB in LTBI negative patients (n=1135) was 0, 300, 915.6 2931.6 cases / 100,000 person-year (linearity p-value = 0.011), and the incidence of TB in patients receiving only infliximab (n=939) was 0, 359.6, 798.7, 2061.9 cases / 100,000 person-year (linearity p-value = 0.001).

Figure 1. Study flow diagram



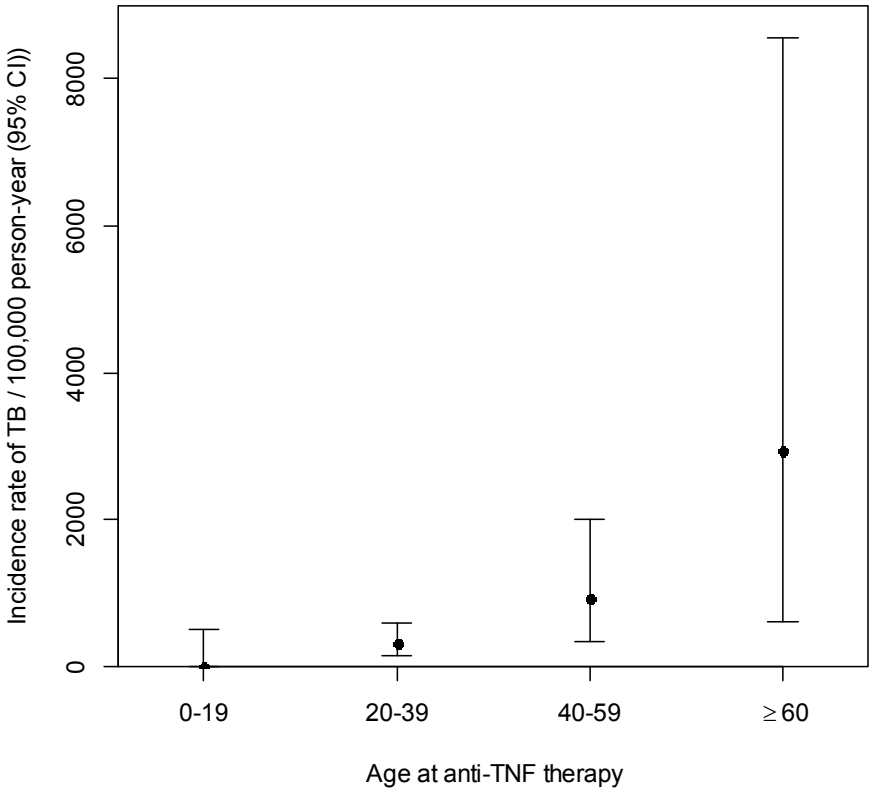
IBD = inflammatory bowel disease, TNF = tumor necrosis factor, TB = tuberculosis

Figure 2. Incidence rates (case of incidence per 100,000 person-year) of active tuberculosis infection according to age (All patients)



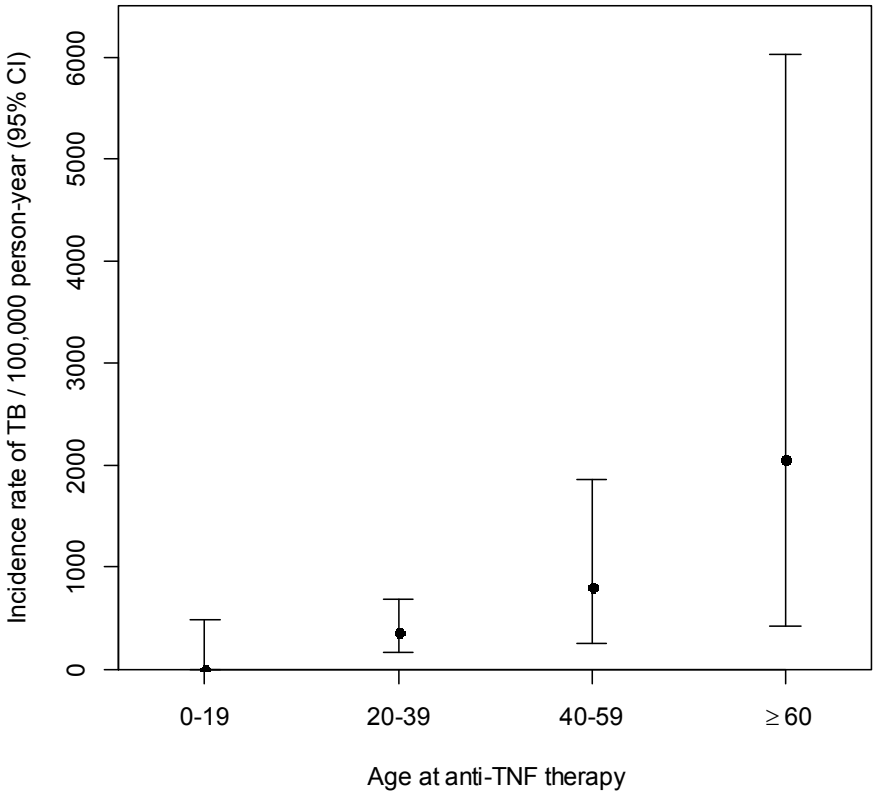
TNF = tumor necrosis factor, TB = tuberculosis

Figure 3. Incidence rates (case of incidence per 100,000 person-year) of active tuberculosis infection according to age (LTBI negative group)



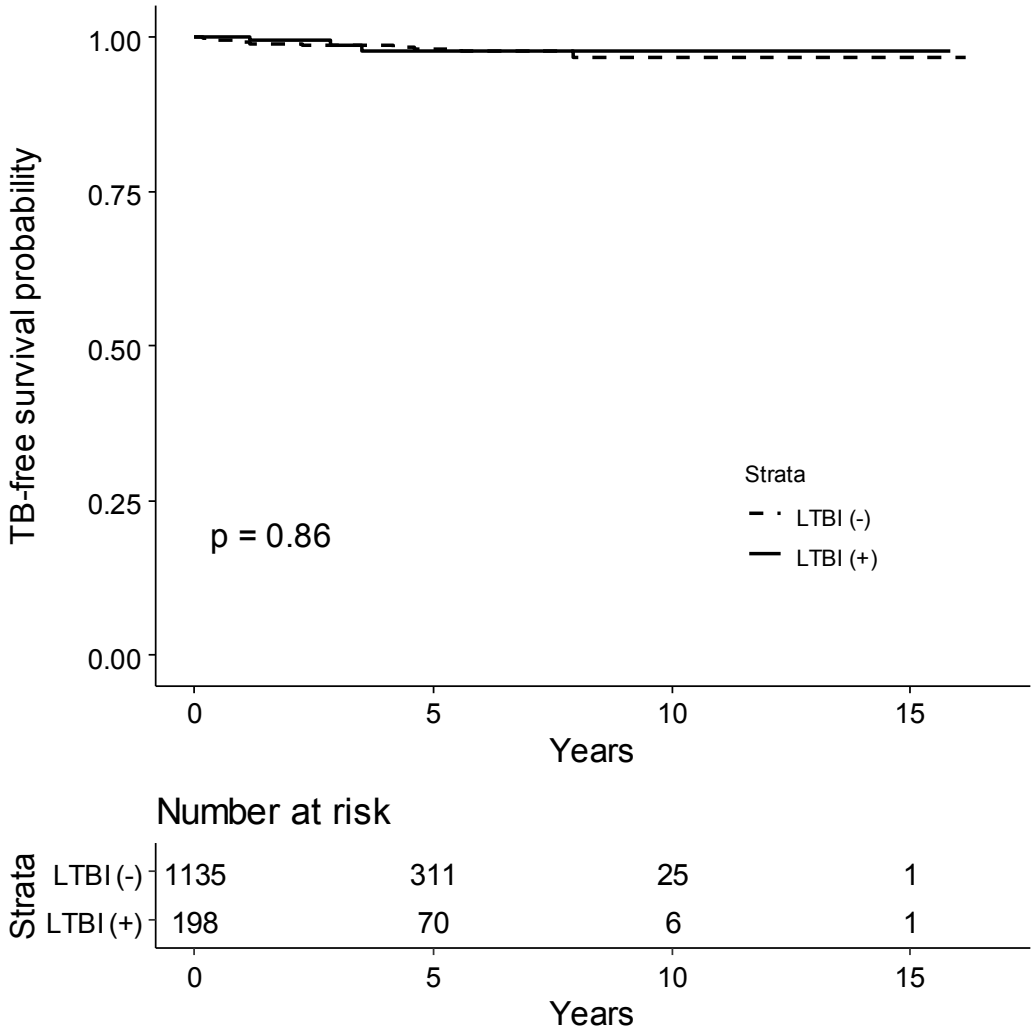
LTBI = latent tuberculosis infection, TNF = tumor necrosis factor, TB = tuberculosis

Figure 4. Incidence rates (case of incidence per 100,000 person-year) of active tuberculosis infection according to age (Infliximab group)



TNF = tumor necrosis factor, TB = tuberculosis

Figure 5. Kaplan-Meier curve for the incidence of active tuberculosis in IBD patients with anti-TNF therapy based on LTBI or not



IBD = inflammatory bowel disease, TNF = tumor necrosis factor, LTBI = latent tuberculosis infection, TB = tuberculosis

Table 1. Baseline characteristics of 1434 patients with Anti-TNF therapy

Characteristics	
Age of IBD diagnosis (year)	25.81 ± 12.45
Age at anti-TNF therapy initiation (year)	31.35 ± 13.59
Follow up (month)	48.54 ± 36.48
Sex (male:female)	940 : 494
IBD type(UC:CD)	332(23.2%) : 1102(76.8%)
History of smoking (no:yes)	991(69.1%) : 443(30.9%)
Anti-TNF agents	
One	1259 (87.8%)
Infliximab	939 (65.5%)
Adalimumab	311 (21.7%)
Golimumab	9 (0.6%)
Two	172 (12.0%)
Infliximab, Adalimumab	166 (11.6%)
Infliximab, Golimumab	2 (0.1%)
Adalimumab, Golimumab	4 (0.3%)
Three	3 (0.2%)
LTBI diagnosis	
Done	1333 (93.0%)
Negative	1135 (85.1%)
Positive	198 (14.9%)
Completion of TB prophylaxis	190 (96%)
Failure to complete TB prophylaxis	8 (4.0%)
Not done, other	101 (7.0%)

TNF = tumor necrosis factor, IBD = inflammatory bowel disease, UC = ulcerative colitis, CD = Crohn's disease, LTBI = latent tuberculosis infection, TB = tuberculosis

Table 2. Characteristics of patients who developed active tuberculosis during anti-TNF therapy

No.	IBD	sex	Age of anti-TNF(yr)	Age of TB(yr)	Interval to TB diagnosis (mo)	Anti-TNF agents	TST	IGRA	Previous TB treatment	LTBI	TB prophylaxis	Smoking	TB site
1	UC	M	67	68	2	IFX	ND	(-)	No	(-)	ND	Ex	Lung
2	UC	M	66	67	10	IFX	(-)	(-)	No	(-)	ND	Ex	Lung + peritoneum
3	UC	F	42	47	55	IFX	(-)	(-)	No	(-)	ND	(-)	Lung
4	UC	M	53	53	2	IFX	ND	(-)	No	(-)	ND	Ex	Lung
5	UC	M	46	47	14	IFX > ADA	ND	(+)	No	(+)	INH+RFP	Ex	Lung + pleura
6	UC	M	60	60	4	IFX	(-)	(-)	No	(-)	ND	(+)	pleura + pericardium
7	CD	F	33	33	3	IFX	(-)	(-)	No	(-)	ND	Ex	Lung
8	CD	M	59	59	3	IFX	(-)	(-)	No	(-)	ND	Ex	Lung
9	CD	M	26	29	34	ADA	(-)	(+)	No	(+)	INH+RFP	(-)	Lung
10	CD	F	26	30	50	IFX > ADA	(-)	(-)	No	(-)	ND	(-)	Lung
11	CD	M	23	25	27	IFX	ND	(-)	No	(-)	ND	(-)	Lung + LN
12	CD	F	32	32	4	IFX	ND	ND	No	Unknown	ND	(-)	Spleen + LN
13	CD	F	22	25	42	IFX	(-)	(+)	No	(+)	RFP	(-)	Lung
14[1]	CD	F	37	42	67	IFX	(-)	(-)	No	(-)	ND	(+)	Lung + pleura
15	CD	M	24	32	95	IFX	(-)	(-)	ITB[2]	(-)	ND	(+)	Lung + pleura
16	CD	M	29	30	5	IFX	(-)	Indeterminate	No	(-)	ND	(-)	Lung
17	CD	F	44	45	14	IFX	(-)	(-)	No	(-)	ND	(-)	Lung
18	CD	M	41	43	17	IFX	(-)	(-)	Lung	(-)	ND	(-)	Lung
19	CD	F	41	43	24	IFX > ADA	(-)	(-)	ITB[2]	(-)	ND	(-)	pleura
20	CD	F	35	36	11	IFX	(-)	(-)	ITB[2]	(-)	ND	(-)	Lung + endobronchus
21	CD	M	25	26	1	IFX	ND	(-)	No	(-)	ND	(+)	Lung

TNF = tumor necrosis factor, IBD = inflammatory bowel disease, UC = ulcerative colitis, CD = Crohn's disease, LTBI = latent tuberculosis infection, TB = tuberculosis, TST = tuberculin skin test, IGRA = interferon gamma release assay, IFX = infliximab, ADA = adalimumab, ND = not done, ITB = intestinal tuberculosis, INH = isoniazid, RFP = rifampin, LN = lymph node

1:This patent was on treatment of tuberculosis at the end of the study. All the patients except this patient were diagnosed with complete cure after tuberculosis treatment

2:These Crohn's patients had experience taking medication for tuberculosis to identify intestinal tuberculosis.

Table 3. Risks of active tuberculosis infection during anti-TNF therapy derived from Cox proportional hazard Model

	TB+ group (n=21)	TB- group (n=1413)	Hazard ratio (95% CI)	p-value
Age at anti-TNF (year)	39.57	31.22	1.041 (1.014-1.069)	0.002
Age of IBD diagnosis (year)	32.81	25.70	1.039 (1.012-1.067)	0.005
Female	9 (42.9)	485 (34.3)	1.286 (0.541-3.055)	0.570
IBD type			0.660 (0.254-1.714)	0.393
UC	6 (28.6)	323 (23.1)		
CD	15 (71.4)	1087 (76.9)		
History of smoking	10 (47.6)	433 (30.6)	2.094 (0.889-4.932)	0.091
Previous TB history	1 (4.7)	48 (3.4)	1.297 (0.174-9.665)	0.800
LTBI	3 (14.3)	195 (13.8)	0.896 (0.262-3.066)	0.862

TNF = tumor necrosis factor, IBD = inflammatory bowel disease, UC = ulcerative colitis, CD = Crohn's disease, LTBI = latent tuberculosis infection, TB = tuberculosis

Discussion

In Korea, the incidence of IBD is gradually increasing in all age groups, including elderly citizens[18], and the age of IBD patients receiving treatment is increasing as time passes. Because of this trend, there is a growing interest in medication administration and its associated morbidity in old age. As age increases, the production of T-cell and T cell medicated response was decreased, than suppressed formation of granulomas by mononuclear phagocytes activated by Mycobacterium tuberculosis infection, which may increase the risk of active TB infection[19, 20]. In addition, the prevalence of nutritional deficiencies and other age-related diseases increases, which can influence comorbidity of TB[20, 21]. In fact, in a case-control study in which anti-TNF agents (infliximab, adalimumab, etanercept) were administered for the treatment of rheumatic diseases, there was a study that showed a significant age difference between the two groups in the development of TB[22]. We have identified a significant age difference between the TB-development group and the non-development group in IBD patients (39.57 vs 31.22, p-value = 0.002), and furthermore, interesting results that show a linear increase in the incidence rate of TB infection as the age group starting anti-TNF therapy increases (Figure 2).

In Korea, the higher the age group, the higher the prevalence of positive LTBI [23], so the higher the age group starting anti-TNF therapy in IBD patients, the higher

the incidence rate of TB development may be thought to be related to the prevalence of positive LTBI according to the age group. In fact, the age of patients with positive LTBI among the study subjects was significantly higher than that of the LTBI negative patients (39.13 vs 30.76, p-value = 0.001). In this regard, we checked the incidence rate of TB development by age group in patients with negative LTBI (n=1135), and confirmed that the incidence rate of TB development in LTBI negative group also increased as the age group increased (Figure 3). In other words, age itself can be seen as a risk factor for development of TB in IBD patients taking anti-TNF therapy. In the group of infliximab alone, which was the highest proportion among the various anti-TNF therapy, we found that the incidence rate increased linearly as the age group increased (Figure 4). However, in the case of patients receiving other single or multiple anti-TNF agents, there are few cases associated with the low incidence of TB development, so it is necessary to carefully interpret the prevalence of TB for each anti-TNF agent. In addition, since this study is a statistical result in countries with intermediate TB burden[16, 24], it is necessary to be cautious about applying these results in regions with different incidence.

According to our study, the incidence rate of TB development in IBD patients treated with anti-TNF therapy was 366.73 cases/100,000 person-year, and the prevalence was 1.46%. In another multicenter, retrospective study in Korea, 16 cases of TB diagnosis were reported among 376 IBD patients who underwent anti-TNF therapy (incidence rate : 1997.4 / 100,000 person-year)[13], and according to a

study that analyzed data from the National Health Insurance (NHI) system in Korea, the incidence rate was 554.1 per 100,000 person-year[25]. The incidence rate of TB development in this study was lower than that found in other studies. We referred most of the anti-TNF therapy-planned IBD patients to tuberculosis specialists for LTBI screening and management, and continued follow up observation. As a result, a high LTBI evaluation was performed (93%), and only 8 out of 198 patients who did not complete TB prophylaxis showed a high LTBI treatment completion rate (96%). On the other hand, among the 30 LTBI positive patients, 16 patients underwent TB prophylaxis[13]. It was recommended to perform TST or IGRA as a screening test for LTBI before anti-TNF therapy, In "2011 Korean guidelines for tuberculosis"[16]. It is thought that the TB-prophylaxis rate was not high because the LTBI evaluation and treatment were not strictly performed, at the early period of the guidelines. Therefore, we believe that the completion of LTBI treatment in many LTBI-positive patients by applying a system for LTBI screening and management will help lower the incidence rate and prevalence of TB development.

Another interesting finding is that the LTBI positive rate did not show a significant difference between the TB development and non-TB development groups (table 3). This result is different from previous studies that reported that LTBI could be a risk factor for the development of TB[13]. Treatment of LTBI prior to administration of immunosuppressants is expected to prevent active TB infection caused by LTBI reactivation[26, 27]. In this study, the study subjects showed a high rate of LTBI

evaluation and a high rate of completion of LTBI treatment, and it appears that the incidence of TB development in LTBI-positive patients was similar to that of LTBI-negative patients (Figure 5). According to a recent study, 1-year incidence of TB in IBD patients receiving anti-TNF therapy was reported regardless of LTBI status[28], and the expected reduction of the risk of TB development in the LTBI management group was reported as 40-60%[29]. The result of this study is in line with previous studies, and means that LTBI is no longer a risk factor for development of TB in patients undergoing anti-TNF therapy if active management for LTBI is premised.

Although active work-up and management for LTBI was performed, the onset of TB was not completely suppressed. Anti-TNF therapy may increase the risk of LTBI reactivation as well as increase susceptibility to primary TB and exogenous reinfection [30, 31]. Treatment of LTBI can prevent the development of TB due to the reactivation of LTBI, but it is difficult to affect the prevention of acquiring a new infection by active TB individual. Therefore, unless the burden of TB is low, TB infection cannot be completely suppressed even with active LTBI management, and the higher the burden of TB, this issue should be considered more seriously. In addition, since the general indication of anti-TNF therapy in IBD patients is when they do not respond to universal treatments such as steroids and/or immunomodulators, many IBD patients take these drugs when anti-TNF therapy is administered. These drugs can suppress an individual's immune response and increasing the chances of getting TB infection. One study found that low WBC

count may be a risk factor for TB development in patients undergoing anti-TNF therapy, and it was noted that immunosuppressive state by drugs when starting anti-TNF therapy may be related to this[13]. Finally, it is the inaccuracy of the tests for LTBI diagnosis. TST and IGRA are more likely to produce false negative results if they take drugs such as steroids or immunomodulators, or if they have immunodeficiency[32, 33]. Some of the 17 TB cases who had been identified as LTBI negative may be thought to had been developed by LTBI reactivation. In order to confirm the effectiveness of the test, we checked the hazard ratio of TB development in the TST and IGRA group and the IGRA only group, and there was no significant difference between the two groups (HR = 1.170, 95% CI : 0.417–3.284). In immunosuppressed patients, we will need to be aware of the inaccuracy of the LTBI screening test and consider ways to increase the accuracy.

In another study, the median period from the start of infliximab to the diagnosis of TB was about 12 weeks, and for adalimumab, the median period was 4-6 months[27, 34, 35]. These studies were conducted in countries with low TB burden, and most cases were thought to have developed TB by LTBI reactivation. On the other hand, in our study, LTBI management was able to prevent LTBI reactivation at the early period of therapy. But the risk of TB development through contact with an active TB individual may have increased in Korea which is country with an intermediate burden of TB, because of increased susceptibility to exogenous infection by anti-TNF therapy. We estimate that the period from the start of anti-

TNF therapy to the diagnosis of TB is longer compared to the Western. (median duration : 14 month) The characteristics of TB seen in patients undergoing anti-TNF therapy are similar to that in immunocompromised patients, and the proportion of extrapulmonary TB is relatively high[26, 36]. In our study, the proportion of pulmonary TB was 85.7% (18/21), which was not significantly different from that of immunocompetent subjects[16, 37]. We believe that the occurrence of extra-pulmonary TB caused by LTBI reactivation may have been prevented, and that the proportion of pulmonary TB may have been increased due to TB strains primarily invading the lungs through air transmission in de novo infections. In summary, the features of TB in IBD patients who underwent LTBI management actively prior to anti-TNF therapy were different from that in patients receiving anti-TNF therapy in previous studies. Further study is needed as to why these features are observed.

There are several limitations to this study. First, LTBI evaluation was conducted in accordance with the Korean guideline, so could not consider several factors that could affect the result of test. BCG vaccination is essential in Korea, an important factor that can affect TST results[38], and immunosuppressants and various diseases can also affect result of TST and IGRA[32, 33]. Second, since the time it takes to develop TB is variable, we cannot assert that the age at which anti-TNF therapy is started is absolutely correlated with the age at diagnosis of active TB. Third, this study showed a tendency to prefer infliximab administration as the first anti-TNF agent. For this reason, the effects of the use of other anti-TNF agents or multiple

drugs which accounted for a small proportion on the development of TB and the identification of risk factors were limited. Further research is needed in the future with a larger population

Conclusion

In conclusion, we confirmed a trend in which the incidence rate of TB increases linearly as the age of starting anti-TNF therapy increases in IBD patients. If anti-TNF therapy is administered to older patients, more rigorous monitoring for active TB development may be required. In addition, conducting LTBI screening and management actively could lower the incidence of TB development, and showed a different aspect of TB characteristics from the general TB characteristics that were found in previous study. Plans for monitoring of TB development need to be established, considering these characteristics.

References

1. Podolsky, D.K., Inflammatory bowel disease. New England Journal of Medicine, 1991. 325(13): p. 928-937.

2. Katsanos, K.H. and K.A. Papadakis, Inflammatory bowel disease: updates on molecular targets for biologics. Gut and Liver, 2017. 11(4): p. 455.

3. Prideaux, L., et al., Inflammatory bowel disease in Asia: a systematic review. Journal of gastroenterology and hepatology, 2012. 27(8): p. 1266-1280.

4. Yang, S.-K., et al., Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986–2005: a KASID study. Inflammatory bowel diseases, 2008. 14(4): p. 542-549.

5. Ordás, I., et al., Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clinical Pharmacology & Therapeutics, 2012. 91(4): p. 635-646.

6. Lee, K.M., et al., Efficacy, safety, and predictors of response to infliximab therapy for ulcerative colitis: AK orean multicenter retrospective study. Journal of gastroenterology and hepatology, 2013. 28(12): p. 1829-1833.

7. Ye, B.D., et al., Guidelines for the management of Crohn's disease. The

Korean Journal of Gastroenterology, 2012. 59(2): p. 141-179.

8. Thorlund, K., et al., Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis in adult patients naive to anti-TNF therapy: an indirect treatment comparison meta-analysis. Journal of Crohn's and Colitis, 2014. 8(7): p. 571-581.

9. Byun, J.M., et al., Risks for opportunistic tuberculosis infection in a cohort of 873 patients with inflammatory bowel disease receiving a tumor necrosis factor-α inhibitor. Scandinavian journal of gastroenterology, 2015. 50(3): p. 312-320.

10. Shim, T.S., Diagnosis and treatment of latent tuberculosis infection in patients with inflammatory bowel diseases due to initiation of anti-tumor necrosis factor therapy. Intestinal Research, 2014. 12(1): p. 12.

11. Horsburgh Jr, C.R. and E.J. Rubin, Latent tuberculosis infection in the United States. New England Journal of Medicine, 2011. 364(15): p. 1441-1448.

12. Rahier, J.-F., et al., European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. Journal of Crohn's and Colitis, 2009. 3(2): p. 47-91.

13. Kim, E.S., et al., Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents. World Journal of Gastroenterology: WJG, 2015. 21(11): p. 3308.

14. Park, D.I., et al., Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: Management. Journal of gastroenterology and hepatology, 2018. 33(1): p. 30-36.

15. Kim, J.H. and J.-J. Yim, Achievements in and challenges of tuberculosis control in South Korea. Emerging infectious diseases, 2015. 21(11): p. 1913.

16. Korean Guidelines for Tuberculosis. 3rd edition. Korea Centers for Disease Control and Prevention, 2017.

17. Lee, S.H., Diagnosis and treatment of latent tuberculosis infection: the updated 2017 Korean guidelines. Korean Journal of Medicine, 2018. 93(6): p. 509-517.

18. Kwak, M.S., et al., Emerging trends of inflammatory bowel disease in South Korea: a nationwide population-based study. Journal of gastroenterology and hepatology, 2019. 34(6): p. 1018-1026.

19. Byng-Maddick, R. and M. Noursadeghi, Does tuberculosis threaten our ageing populations? BMC infectious diseases, 2016. 16(1): p. 1-5.

20. Thomas, T.Y. and S. Rajagopalan, Tuberculosis and aging: a global health problem. Clinical infectious diseases, 2001. 33(7): p. 1034-1039.

21. Yoshikawa, T.T., Tuberculosis in aging adults. Journal of the American

Geriatrics Society, 1992. 40(2): p. 178-187.

22. Tubach, F., et al., Risk of tuberculosis is higher with anti–tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective french research axed on tolerance of biotherapies registry. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology, 2009. 60(7): p. 1884-1894.

23. Cho, K.S., Current status of tuberculosis and status of national tuberculosis management in Korea, in Health and Social Welfare Review. 2017. p. 179-212.

24. Yeon, J.H., et al., Prevalence and risk factors of latent tuberculosis among Korean healthcare workers using whole-blood interferon-γ release assay. Scientific reports, 2018. 8(1): p. 1-5.

25. Hong, S., et al., Risk of incident Mycobacterium tuberculosis infection in patients with inflammatory bowel disease: a nationwide population-based study in South Korea. Alimentary pharmacology & therapeutics, 2017. 45(2): p. 253-263.

26. Keane, J., et al., Tuberculosis associated with infliximab, a tumor necrosis factor α–neutralizing agent. New England Journal of Medicine, 2001. 345(15): p. 1098-1104.

27. Keane, J., TNF-blocking agents and tuberculosis: new drugs illuminate an old topic. Rheumatology, 2005. 44(6): p. 714-720.

28. Kang, J., et al., Incidence of Active Tuberculosis within One Year after Tumor Necrosis Factor Inhibitor Treatment according to Latent Tuberculosis Infection Status in Patients with Inflammatory Bowel Disease. Journal of Korean medical science, 2018. 33(47).

29. Erkens, C.G., et al., Monitoring latent tuberculosis infection diagnosis and management in the Netherlands. European Respiratory Journal, 2016. 47(5): p. 1492-1501.

30. van Rie, A., et al., Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. New England Journal of Medicine, 1999. 341(16): p. 1174-1179.

31. Chen, D.-Y., et al., Biphasic emergence of active tuberculosis in rheumatoid arthritis patients receiving TNFα inhibitors: the utility of IFNγ assay. Annals of the rheumatic diseases, 2012. 71(2): p. 231-237.

32. Debeuckelaere, C., et al., Tuberculosis infection following anti-TNF therapy in inflammatory bowel disease, despite negative screening. Journal of Crohn's and Colitis, 2014. 8(6): p. 550-557.

33. Wong, S.H., et al., Effect of immunosuppressive therapy on interferon γ release assay for latent tuberculosis screening in patients with autoimmune diseases: a systematic review and meta-analysis. Thorax, 2016. 71(1): p. 64-72.

34. Wallis, R., et al., Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clinical Infectious Diseases, 2004. 38(9): p. 1261-1265.

35. Wallis, R.S., et al., Granulomatous infections due to tumor necrosis factor blockade: correction. Clinical Infectious Diseases, 2004. 39(8): p. 1254-1255.

36. Abreu, C., et al., Tuberculosis in anti-TNF-α treated patients remains a problem in countries with an intermediate incidence: analysis of 25 patients matched with a control population. Journal of Crohn's and Colitis, 2013. 7(10): p. e486-e492.

37. Rieder, H.L., D.E. Snider Jr, and G.M. Cauthen, Extrapulmonary tuberculosis in the united states1–3. Am. Rev. Respir. Dis, 1990. 141: p. 347-351.

38. Burl, S., et al., The tuberculin skin test (TST) is affected by recent BCG vaccination but not by exposure to non-tuberculosis mycobacteria (NTM) during early life. PloS one, 2010. 5(8): p. e12287.

국문요약

배경/목표: 항종양괴사인자 치료를 받는 염증성 장질환 환자들은 결핵 감염의 위험에 노출된다. 항종양괴사인자 치료를 받는 한국인 염증성 장질환 환자에서 결핵 발생의 임상적 특징과 위험 요소들을 분석하고자 한다.

방법: 이 연구는 2001년 1월부터 2018년 6월까지 한국의 단일 3차기관에서 항종양괴사인자 치료를 받은 염증성 장질환 환자들을 대상으로 진행하였다. 궤양성 대장염 또는 크론병을 진단받은 총 1434명의 염증성 장질환 환자들이 이번 연구에 등록되었다. 항종양괴사인자 치료를 시행한 후 활동성 결핵 감염의 발생률을 계산하고, 결핵이 발병한 군과 결핵이 발병하지 않은 군의 임상적 특징을 비교하였다.

결과: 1434명의 환자들 중 활동성 결핵 감염의 사례는 21건(1.46%)이며, 활동성 결핵의 발병률은 100,000인-년당 366.73건이다. 잠복결핵검사 결과가 양성으로 확인된 환자는 198명(14.9%)이며, 이들 중에서 오직 8명(4%)만이 잠복결핵 치료를 완료하지 못하였다. 결핵이 발병한 군이 결핵이 발병하지 않은 군보다 항종양괴사인자 치료를 시작한 연령이 유의하게 높게 나타났으며(HR = 1.041, 95% CI : 1.013-1.069, P = 0.002), 연령대가 증가할 수록 결핵의 발병률이 증가하였다(linearity p-value < 0.001). 결핵이 발병한 군과 결핵이 발병하지 않은 군간의 잠복결핵의 감염 여부는

유의한 차이를 보이지 않았다(HR = 0.896, 95% CI : 0.262-3.066, P = 0.862).

결론: 염증성 장질환 환자에서 항종양괴사인자 치료를 시작하는 연령이 높을수록 결핵의 발생률이 증가한다. 잠복결핵에 대한 적극적인 치료는 항종양괴사인자 치료를 받는 염증성 장질환 환자의 결핵 발병률을 낮출 수 있을 것이다.