Mycobacterial diseases developed during anti-tumour necrosis factor-α therapy

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ABSTRACT Nontuberculous mycobacterial (NTM) disease and tuberculosis (TB) develop during anti-tumour necrosis factor (TNF)-α therapy. We compared clinical characteristics and outcomes between the two diseases.

A total of 1165 patients were screened for TB and treated with TNF-α antagonists from July 2004 to July 2013 for the following conditions: inflammatory bowel disease (n=422), rheumatoid arthritis (n=320), and ankylosing spondylitis (n=389).

TB and NTM disease were diagnosed at baseline screening in four and three patients, respectively, and developed during anti-TNF-α therapy in 19 and six patients, respectively. The incidence rate of TB and NTM disease was 747.7 per 100 000 and 238.2 per 100 000 person-years, respectively. Patients with NTM disease were older, with a greater proportion of females. All cases of NTM disease involved the lung, with rheumatoid arthritis (83.3%) being the most frequent underlying disease. The most common radiological feature was consolidation in NTM disease, and honeycombing was present in two rheumatoid arthritis patients with NTM disease. The most common pathogen was *Mycobacterium intracellulare* (n=3) followed by *Mycobacterium avium* (n=2). Both the NTM and TB group showed favourable outcomes.

The clinical characteristics differed between NTM disease and TB that developed on anti-TNF-α agents, but clinical outcomes were favourable in both diseases.

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Introduction

Tumour necrosis factor (TNF)-α antagonists provide clinical benefits and are recommended for patients who suffer from rheumatological disease or inflammatory bowel disease (IBD) [1–3]. However, this therapy can increase the risk of infectious complications. TNF-α is an important cytokine involved in the cytotoxic effect of macrophages against intracellular pathogens, granuloma formation, apoptosis and prevention of dissemination of infection to other sites [4]. The granulomatous inflammatory response caused by intracellular pathogens is compromised by the use of these agents, and patients receiving TNF-α antagonists are at an increased risk for granulomatous infectious diseases. Reactivation of tuberculosis (TB) is the most frequently encountered infectious complication during TNF-α antagonist therapy [5–7]. Development of TB in patients treated with TNF-α inhibitors has already been reported in South Korea [8–10].

Nontuberculous mycobacterial (NTM) disease has emerged as another mycobacterial infection in patients receiving TNF-α inhibitors, with several reported cases of NTM disease in patients receiving anti-TNF-α therapy [11–14]. One survey suggested that cases of NTM disease associated with TNF-α inhibitors are twice as frequent as cases of TB associated with anti-TNF-α in the USA [11]. However, compared with TB, little is known about the clinical characteristics of NTM disease in patients receiving TNF-α antagonists. Considering the increasing trend of NTM lung disease and the currently frequent use of TNF-α antagonists, clinical data on NTM lung disease in patients receiving TNF-α antagonists are needed.

The aim of this study was to evaluate the clinical, microbiological and radiological features, and treatment outcomes in NTM disease patients receiving TNF-α antagonists compared with those in TB patients.

Methods

Study design and patients

This study was performed retrospectively on a 2700-bed university-affiliated hospital in Seoul, South Korea, which is an intermediate TB burden country. A total of 1165 patients were screened for mycobacterial infection and treated with TNF-α antagonists between July 2004 and July 2013, with the cause for treatment being IBD (n=422, 36.2%), rheumatoid arthritis (n=320, 27.5%), ankylosing spondylitis (n=389, 33.4%) or other conditions (n=34, 2.9%). A diagnosis of TB was given if *Mycobacterium tuberculosis* was isolated from any clinical specimen or if PCR for *M. tuberculosis* was positive (bacteriologically confirmed TB) [15]. Patients with a high clinical suspicion of active TB and negative mycobacterial culture findings but who had good therapeutic response to anti-TB treatment were also considered as TB patients (clinical TB). NTM disease cases were defined by the 2007 diagnostic criteria proposed by the American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) [16]. Clinical data were collected from medical records, including baseline characteristics, microbiological data (acid-fast bacilli (AFB) smear and culture) and treatment outcomes. The development of mycobacterial diseases was observed until default, transfer out of the hospital, death, or 3 months following completion of anti-TNF-α treatment [14]. Favourable outcomes were defined as treatment completion without relapse or culture conversion to negative status in patients receiving treatment. Data were censored at October 31, 2013. Our study was approved by the Institutional Review Board of Asan Medical Center (number 2013-0995), and the requirement for informed consent was waived due to the retrospective nature of the analysis.

Mycobacteriological tests

All specimens were examined following Ziehl–Neelsen staining and were cultured in both solid Ogawa medium (Korean Institute of Tuberculosis, Osong, Korea) and a liquid mycobacteria growth indicator tube (MGIT) system (Becton Dickinson, Aparks, MD, USA). Cultured isolates were identified as *M. tuberculosis* or NTM disease using the Duplex PCR test (Seegene Inc., Seoul, Korea). NTM species were identified using a PCR-restriction fragment length polymorphism method, based on the *rpoB* gene [17]. Conventional drug susceptibility test (DST) for *M. tuberculosis* was performed using the absolute concentration method with Lowëstein–Jensen media at the Korean Institute of Tuberculosis (Osong, South Korea), a supranational TB reference laboratory. Pyrazinamide susceptibility was determined using the pyrazinamidase test (Korean Institute of Tuberculosis, Osong, South Korea). The DST for NTM was tested using a commercial kit (Sensititre; TREK Diagnostic Systems, Cleveland, OH, USA) and interpreted according to tentative guidelines established by the National Committee for Clinical Laboratory Standards [18].

Statistical analysis

To estimate the incidence of TB and NTM lung disease among patients exposed to TNF-α antagonists, we divided the number of TB or NTM lung disease cases by the total number of patient-years of follow-up. The TB and NTM incidence rate was calculated using only cases of patients who developed the disease while exposed to anti-TNF-α therapy as previously reported [18]. Categorical variables were expressed as n (%), and continuous variables as medians (interquartile range). Categorical data were compared using the

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Chi-squared test or Fisher's exact test, and continuous variables were compared with the Mann–Whitney U-test. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Comparison of baseline characteristics between patients with NTM disease and those with TB disease

Among the 1165 screened patients, three (0.3%) and four patients (0.3%) were found to have NTM and TB disease, respectively, at baseline screening. A total of 25 (six NTM disease and 19 TB) cases of mycobacterial infectious complications occurred during anti-TNF-α therapy. The incidence of NTM disease and TB during anti-TNF-α therapy was 238.2 per 100 000 and 747.7 per 100 000 patients-years, respectively. The characteristics of the 25 patients at the time of NTM/TB diagnosis during anti-TNF-α therapy are shown in table 1. All patients with NTM disease were female, with a higher median age compared with TB patients. While the proportion of ankylosing spondylitis was higher in TB patients, rheumatoid arthritis (n=5, 83.3%) was the most common underlying disease in patients with NTM disease treated with TNF-α antagonists. All patents with NTM disease received a steroid with/without disease-modifying anti-rheumatic drugs concomitantly. The median duration from initiation of anti-TNF-α therapy to development of NTM/TB did not differ between the two groups.

Comparison of clinical, radiological and microbiological characteristics at diagnosis of NTM and of TB disease during anti-TNF-α therapy

A comparison of the clinical and radiological characteristics at diagnosis of TB/NTM disease is shown in table 2. Fever was noted in nine (47.4%) out of the 19 TB patients, but in none of the six NTM patients. All

TABLE 1 Comparison of baseline characteristics between patients with NTM disease and those with TB disease during anti-TNF-α therapy

Characteristics	NTM	TB	p-value#
Subjects n	6	19	
Males	0	10 (52.6)	0.051
Age years	62 (55–71)	40 (29–56)	0.007
Body mass index kg·m^{-2}	20.3 (19.7–22.7)	21.1 (19.2–25.6)	0.733
Ever-smoker	0	4 (21.4)	0.540
History of TB	0	3 (15.8)	0.554
BCG vaccination	2/4 (50)	13/18 (72.2)	0.565
Underlying diseases			
Rheumatoid arthritis	5 (83.3)	3 (15.8)	0.006
Ankylosing spondylitis	0	10 (52.6)	0.051
Inflammatory bowel diseases	1 (16.7)	5 (26.3)	1
Concomitant interstitial lung disease	2 (33.3)	1 (5.3)	0.133
Duration from initiation of anti-TNF-α therapy to development of TB/NTM months	25.4 (4.9–32.6)	12.1 (3.6–30.8)	0.514
TNF antagonists used			
Infliximab	3 (50)	12 (63.2)	0.653
Etanercept	3 (50)	5 (26.3)	0.344
Adalimumab	0	5 (26.3)	0.289
Anti-inflammatory drugs			0.007
Steroid with/without DMARDs	6 (100)	5 (26.3)	
DMARDs only	0	6 (31.6)	
None	0	8 (42.1)	
Positive HIV serology	0/5	0/8	1
Positive TST	0/4	3/18 (16.7)	1
Positive IGRA	0/4	7/16 (43.8)	0.249
LTBI treatment initiation	0	5 (26.3)	0.373
Completion	0	3 (60)	
Interruption	0	2 (40)	

Data are presented as n (%), n/N (%) or median (interquartile range), unless otherwise stated. NTM: non-tuberculous mycobacterial; TB: tuberculosis; TNF-α: tumour necrosis factor-α; BCG: bacille Calmette–Guérin; DMARD: disease-modifying anti-rheumatic drug; TST: tuberculin skin test; IGRA: interferon-γ release assay; LTBI: latent TB infection. #: Chi-squared test or Fisher's exact test, as appropriate.

six NTM patients showed pulmonary involvement alone, whereas 77.7% of TB patients showed extrapulmonary manifestations. Consolidation was the most frequent radiological finding for both NTM and TB patients. However, cavitary lesion was observed in only two patients with NTM disease (33.3%) and developed in the lower lobes adjacent to or within honeycombing changes in underlying ILD. Concomitant honeycombing was present in two (33.3%) out of six NTM disease patients, and was present in four (44.4%) out of nine NTM disease patients detected at screening or developed during anti-TNF therapy (all four had a rheumatoid arthritis as an underlying disease). A nodular bronchiectatic type of radiological finding was noted in two (33.3%) out of six NTM patients. There was no significant difference in AFB smear status between NTM and TB patients. MAC was the most common (83.3%) causative organism for NTM disease. All 15 *M. tuberculosis* isolates were susceptible to isoniazid and rifampicin, while all NTM isolates were susceptible to clarithromycin.

Treatment outcomes for six NTM disease and 19 TB patients

The treatment outcomes and status of TNF-α antagonist use after diagnosis of NTM/TB disease are shown in figure 1. Macrolide-based regimens and first-line anti-TB medication were administered in all six NTM and 19 TB patients, respectively. The median duration of treatment was significantly longer in NTM patients than in TB patients (15.2 months *versus* 6.1 months, p=0.015). All six NTM patients achieved negative sputum culture conversion with the final outcomes of treatment completion (n=3), medication maintenance with culture converted status (n=2), and death due to aggravation of the underlying ILD (n=1). Furthermore, 16 (88.9%) out of the 18 TB patients successfully completed treatment without relapse during follow-up, one was still receiving medication at the time of this study and the remaining one was transferred to another hospital.

Anti-TNF-α therapy

After diagnosing NTM/TB disease, anti-TNF-α therapy was discontinued in four of the six NTM disease patients and in 18 of the 19 TB patients (fig. 1). In the four NTM patients in whom anti-TNF-α therapy was discontinued, anti-TNF-α agents were not administered again. The remaining two NTM patients were maintained on anti-TNF-α therapy with concurrent use of anti-NTM treatment. Anti-TNF-α therapy was reinitiated in six patients during anti-TB treatment after a median interruption of 2.9 months. In another three TB patients, anti-TNF-α therapy was initiated after completion of anti-TB treatment. Anti-TNF-α

TABLE 2 Comparison of clinical, radiological and microbiological characteristics between patients with NTM or TB disease during anti-TNF-α therapy

Variables	NTM	TB	p-value[#]
Subjects n	6	19	
Symptoms			
Fever	0	9 (47.4)	0.057
Cough	3 (50)	11 (57.9)	1
Sputum	1 (16.7)	9 (47.4)	0.345
Dyspnoea	1 (16.7)	3 (15.8)	1
None	3 (50)	3 (15.8)	0.125
Location of disease			0.007
Pulmonary only	6 (100)	5 (26.3)	
Extrapulmonary only	0	5 (26.3)	
Pulmonary and extrapulmonary	0	9 (47.4)	
Chest radiological feature			
Cavitary lesion	2 (33.3)	0/14 (0)	0.05
Consolidation	6 (100)	9/14 (64.3)	0.260
Concomitant honeycombing	2 (33.3)	0/14 (0)	0.049
Positive AFB smear	2 (33.3)	5/19 (26.3)	1
Causative organisms			<0.001
Mycobacterium tuberculosis complex	0	15/15	
Mycobacterium avium	2 (33.3)	0	
Mycobacterium intracellulare	3 (50.0)	0	
Mycobacterium abscessus	1 (16.7)	0	

Data are presented as n (%), or n/N (%), unless otherwise stated. NTM: nontuberculous mycobacterial; TB: tuberculosis; TNF-α: tumour necrosis factor-α; AFB: acid-fast bacilli. [#]: Chi-squared test or Fisher's exact test, as appropriate.

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therapy was not reinitiated in the remaining eight patients. One patient continued to receive TNF-α antagonists during treatment for TB. There was no aggravation or relapse of NTM/TB disease after reinitiating anti-TNF-α treatment.

Discussion

To the best of our knowledge, this is the first study to evaluate and compare the clinical characteristics and treatment outcomes between NTM and TB diseases developed during anti-TNF-α therapy. The clinical characteristics, causative organisms and treatment response of NTM disease in patients taking anti-TNF-α therapy did not differ to those of immunocompetent NTM patients, whereas TB patients taking anti-TNF-α agents showed atypical manifestations, such as extrapulmonary site predominance. Therefore, this study showed that the clinical characteristics of NTM and TB disease developed during anti-TNF-α therapy are significantly different. However, the treatment response was favourable in both NTM and TB cases if the disease was detected early and treated appropriately.

Clinical data on TB in patients treated with TNF-α antagonists have been extensively reported in several studies [4, 6, 7, 9, 10]. In addition, as clinicians are concerned about the development of TB in patients treated with TNF-α inhibitors, there is a focus on screening and treating latent TB infection (LTBI) before administering TNF-α inhibitors. Although reports of NTM lung disease in patients treated with TNF-α antagonists have been published [5, 12, 19, 20], clinical data on NTM lung disease developed during anti-TNF therapy is lacking. Our results indicate that development of NTM lung disease was during anti-TNF-α therapy. Given an increasing trend of NTM lung disease worldwide [21–23], as well as in South Korea [24, 25], patients treated with TNF-α antagonists are more likely to have NTM lung disease.

Although the number of rheumatoid arthritis patients was lower than that of IBD or ankylosing spondylitis patients in our study, NTM lung disease mainly occurred in patients with rheumatoid arthritis. This may be explained by recent epidemiological studies [23, 26] showing that NTM lung disease is most likely to develop in middle/old aged patients and in immunocompetent subjects. WINTHROP *et al.* [27] revealed that NTM disease was associated rheumatoid arthritis among patients treated with a TNF-α antagonist. Among the six patients with NTM lung disease that developed during anti-TNF-α therapy, one had ulcerative colitis

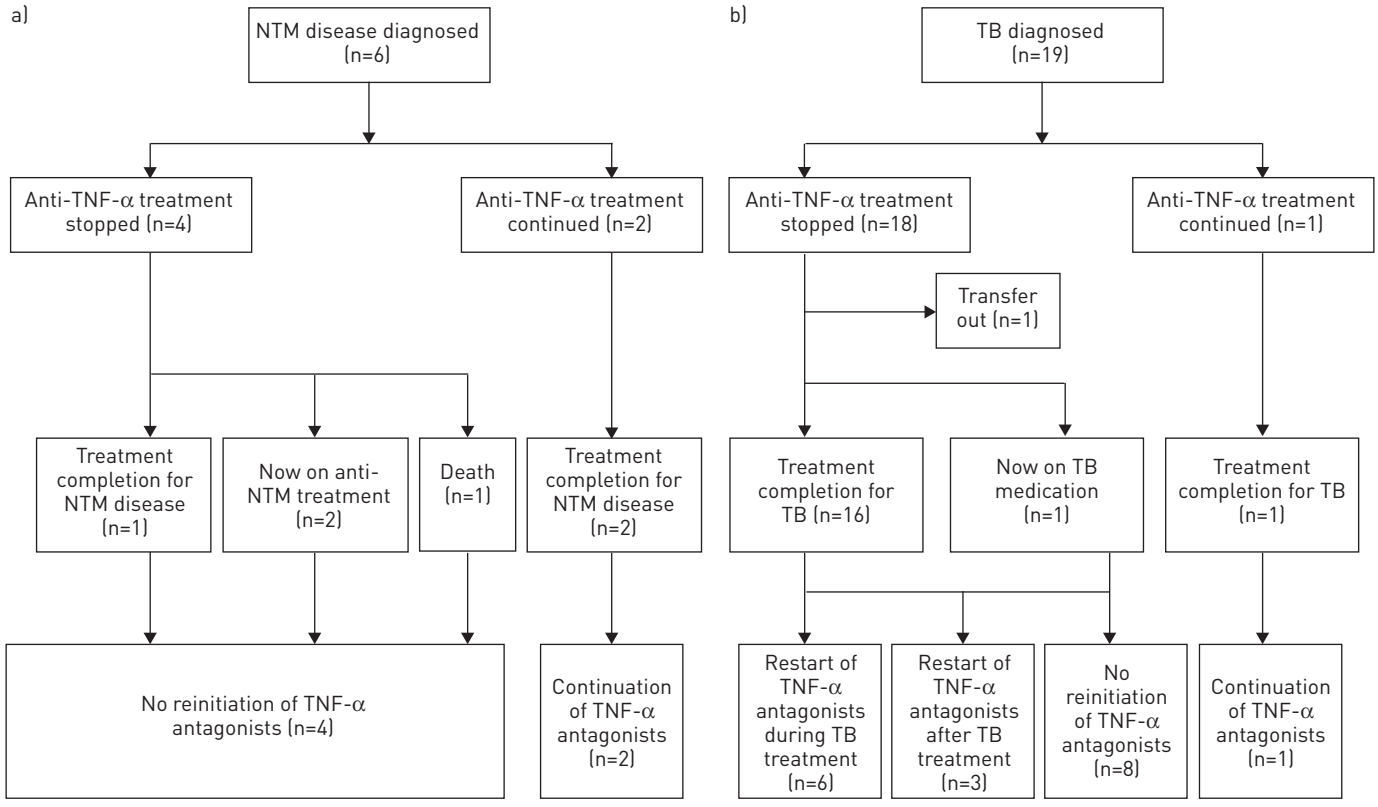

FIGURE 1 Treatment outcomes of nontuberculous mycobacterial (NTM) disease and tuberculosis (TB) patients and status of anti-tumour necrosis factor (TNF)-α therapy during treatment of NTM or TB disease.

and five had rheumatoid arthritis; all six patients were middle-to-old age (age range 42–72 years). Consequently, the development of NTM lung disease should be considered in mid-old age female patients, especially rheumatoid arthritis patients, who are candidates for anti-TNF-α therapy.

The clinical and radiological features were different between patients who developed NTM and those who developed TB during anti-TNF-α therapy in our study. The median age was older and there was a female predominance in NTM patients compared with TB patients. In all patients, the most common symptoms were cough and sputum without fever. All six NTM patients showed pulmonary manifestations, and consolidation with cavitary lesion was the most common radiological feature in NTM patients. By contrast, TB developed in younger patients, with a higher tendency towards men. Half of the TB patients treated with TNF-α inhibitors complained of fever in addition to cough and sputum. There were no cavitary lesions or consolidation noted in half of the TB patients. Extrapulmonary manifestation was higher in patients receiving anti-TNF-α therapy than in the general population, which has also been shown in previous studies [6, 9, 10]. These findings may be explained by systemic spreading of mycobacteria due to inhibition of TNF-α by anti-TNF-α therapy in TB patients [28, 29].

Similar to the findings of previous studies, our results showed favourable clinical outcomes in patients with NTM disease [19, 20]. In addition, the clinical outcomes of NTM patients did not differ significantly compared with those of TB patients. Screening and prophylaxis for LTBI before anti-TNF-α therapy is well established, but prophylaxis for NTM disease is not currently available. The uncertainty regarding the need for prophylaxis in NTM disease patients may be because, in contrast to TB, a latent phase has not been identified in NTM disease. Furthermore, isoniazid prophylaxis may not be helpful in preventing NTM lung disease. Therefore, currently, the most feasible modality is to screen NTM lung disease before anti-TNF-α therapy and then to closely monitor disease progression during anti-TNF-α therapy.

Most guidelines recommend temporary discontinuation of TNF-α antagonists when TB develops during anti-TNF-α therapy [30–34]. Whether TNF-α antagonists should be discontinued in patients who develop NTM lung disease during anti-TNF-α therapy remains a clinical issue. The 2007 ATS/IDSA official statement recommends that patients with active NTM disease should receive anti-TNF-α agents only if they are also receiving adequate therapy for NTM disease [16]. In transplant recipients, the clinical course of NTM lung disease, especially the nodular bronchiectatic type, does not differ from that of immunocompetent hosts [35]. In our study, two patients continued to receive TNF-α inhibitors during treatment of NTM lung disease, suggesting that continuous use of TNF-α antagonists may be possible during treatment of NTM lung disease. However, definite conclusions cannot be drawn in our study due to the small number of cases. Further large studies are needed to confirm these findings.

Our study has several limitations. Firstly, the number of subjects was small, limiting the statistical power of the results. Secondly, this study was conducted retrospectively at a single tertiary referral centre; therefore, selection bias cannot be excluded and our data should be interpreted with caution. Further large cohort studies are needed to confirm our results.

In conclusion, the occurrence of NTM and TB disease during TNF-α inhibitor therapy is not rare, and clinical outcome is favourable if the disease is detected early and treated properly. Physicians should consider both diseases when respiratory problems develop during anti-TNF-α therapy.

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