Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening

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Abstract

Background: In patients treated with TNF-antagonists, incident cases of tuberculosis (TB) after a negative screening have been reported, leading to the suggestion that improved TB testing is necessary.

Aim: The aim of the current study is to establish the incidence of TB and its characteristics in patients with inflammatory bowel disease (IBD) under TNF antagonists to design improved prevention strategies.

Methods: IBD patients from a single center treated with anti-TNF therapy between January 2000 and September 2011 were identified through a database that prospectively records clinical data, treatments and adverse events.

Results: During the study period 423 patients received anti-TNF therapy. Screening for latent TB infection (LTBI) previous to anti-TNF treatment was positive in 30 patients (6.96%). Seven patients (1.65%) developed TB while under anti-TNF treatment. Six patients (five under immunosuppressant treatment) had a negative LTBI screening. TST was positive in one patient not receiving immunosuppressants, and was treated with isoniazid before starting anti-TNF therapy. In 4 patients TB was diagnosed within the first 16 weeks after starting anti-TNF therapy. Three cases had pulmonary TB and 4 extrapulmonary disease.

Conclusions: In the IBD population under study, incidence of TB infection associated with anti-TNF therapy is higher than that reported in controlled trials and occurs early after treatment initiation. False negative results of LTBI despite appropriate measures may occur, suggesting that more effective screening strategies are needed.

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Introduction

Despite a sustained falling in tuberculosis (TB) incidence rates during the last decade, in 2010 there were 8.8 million incident cases of TB worldwide, representing 178 cases per 100,000 population, with 1.1 million deaths from TB among HIV-negative people and an additional 0.35 million deaths from HIV-associated TB. The majority of cases occurred in Asia (59%) and Africa (26%). Smaller proportions of cases occurred in the Eastern Mediterranean Region (7%), the European Region (5%) and America (3%). It has been estimated that one third of the world population has latent TB infection (LTBI). In Europe, there is a high variability in TB incidence among different countries, the higher rates occurring in Rumania, Lithuania and Bulgaria (108, 62 and 38 cases per 100,000 population per year, respectively) and the lower reported rates in Greece, Germany, Luxembourg and Denmark (5.2, 5.4, 5.5 and 6 cases per 100,000 population per year). In Spain the reported incidence rate is 16.6 cases per 100,000 population per year.

The observation of 7 cases of TB among our cohort of 423 patients treated with anti-TNF antibodies prompted us to review LTBI screening protocols and the demographic and clinical characteristics of the patients to determine risk factors predisposing to this complication.

Patients and methods

All IBD patients treated with anti-TNF therapy from January 2000 until September 2011 were identified through the Registry for IBD patients of Hospital Clinic of Barcelona (ENEIDA database). All clinical data of incident cases of TB were corroborated by on-site chart review.

The ENEIDA project is a prospective registry capturing demographic and clinical data, as well as immunosuppressant and anti-TNF therapies with their associated efficacy and adverse events. The database also records the results of the LTBI screening tests and associated therapies when necessary. During the study period LTBI screening previous to anti-TNF treatment in our centre was based on clinical history, tuberculin skin test (TST) and chest radiograph.

Recommendations of the Spanish Health Authorities and the Spanish Society of Rheumatology regarding the management of TB risk in patients who underwent treatment with anti-TNF drugs were established in 2002. Patients with a history of untreated or partially treated TB or exposure to an active case of TB, a chest radiograph showing residual changes indicative of prior TB infection or reaction of more than 5 mm in diameter on TST or booster should undergo treatment for LTBI. Since 2003 the recommendations of the Spanish Group for the Study of Crohn’s disease and Ulcerative Colitis (GETECCU) were followed, and the diagnosis of LTBI was based on patients’ detailed history, chest radiograph and TST, considered as positive when induration of 10 mm is observed in any patient (or a 5 mm induration is observed in patients under immunosuppressants). If a first TST was negative, a second TST (booster) was performed in all patients.

Results

From a cohort of 1716 IBD patients controlled in our center during the study period, 868 had Crohn’s disease (CD) and 848 had ulcerative colitis (UC). Of these, 423 patients received anti-TNF therapy in the period 2000–2011 (329 CD, 94 UC); 222 (52%) were treated with infliximab (IFX), 69 (16%) with adalimumab (ADA) and 132 (31%) received both anti-TNF antibodies sequentially.

LTBI screening was positive in 30/423 (6.96%), 22 of them with CD (6.6% of all patients with CD tested positive at screening) and 8 had UC (8.5% of all patients with UC tested positive at screening). Criteria for positivity at screening was a positive TST in 26 cases, chest x-ray lesions suggestive of past TB in two cases, and a history of recent contact with bacilliferous patients in 2 cases. All patients with positive screening received prophylactic treatment before starting anti-TNF therapy based on isoniazid for 6 months in 11 cases and isoniazid plus rifampicin for three or 4 months in 19 cases.

During the study period, 7 patients (5 men and 2 women), aged 21 to 50 years, developed TB while being under anti-TNF treatment (4 CD and 3 UC). Demographic and clinical characteristics of these patients are summarised in Table 1. Two patients were immigrants from an area with a high prevalence of TB infection (Morocco), and the rest had no TB risk factors. All patients tested negative for HIV.

Six of the seven patients that developed TB had a negative LTBI screening, and five of these were under immunosuppressant treatment at the time of screening, four were receiving thiopurines and one corticosteroids. TST was positive in one patient not receiving immunosuppressants, and he was treated with isoniazid, starting anti-TNF therapy when 3 months of isoniazid treatment had been completed with very good compliance; TB was diagnosed 6 weeks after the introduction of IFX, when the patient was still under isoniazid.
As for the anti-TNF drug used at the time of the infectious complication, 6 cases were under treatment with IFX and one under ADA therapy. Concomitant medication at the time of TB diagnosis included azathioprine in 4 cases and methotrexate in one additional case.

In 4 patients TB was diagnosed early after starting anti-TNF therapy, within the first 16 weeks. Three cases had pulmonary TB and four had an extrapulmonary location (renal, nodal and peritoneal). In five patients Mycobacterium tuberculosis was documented with sputum smear microscopy, conventional culture methods or mycobacterium genetic detection, one case was diagnosed based on high adenosine deaminase levels in ascitic fluid, and one case was based on a positive ELISPOT in a patient with fever of unknown origin. Quadruple tuberculous therapy was initiated in all cases, which resulted in resolution of symptoms in all of them. Anti-TNF therapy was stopped in all cases at the time of TB diagnosis. After resolution of the infection, the same anti-TNF drug was restarted in three patients without relapse of the infection.

None of the 1406 patients having received treatment with corticosteroids, thiopurines or methotrexate in our institution developed active TB during the study period. Furthermore, all 7 patients developing TB under TNF treatment had been previously treated with corticosteroids and thiopurines or methotrexate without developing active TB.

Discussion

The current study shows that TB incidence in a Spanish cohort of IBD patients under anti-TNF treatment is 1.65% despite LTBI screening based on clinical data, TST and chest radiograph before the introduction of anti-TNF therapy. The majority of cases appeared within the first 4 months after starting therapy.

The incidence of TB in our series of IBD patients receiving anti-TNF therapy is high and similar to reports from Spanish population studies in Rheumatology before introduction of LTBI screening, with incidences of 1.8% in 2000 and 1.1% on 2001.9 By contrast, incidence rates observed in randomised clinical trials in IBD patients undergoing proper LTBI screening was considerably lower. In the ACCENT I and ACCENT II trials, none of the 524 patients receiving active induction and maintenance treatment with IFX developed TB, and in the ACT I and ACT II trials one case of TB was diagnosed among the 484 patients with ulcerative colitis receiving induction and maintenance with IFX.13–15 Similarly, in Crohn’s disease patients treated with adalimumab, no case of TB was observed among the 225 patients receiving active treatment in the CLASSIC I induction trial and 2 cases were diagnosed among 517 patients with active maintenance treatment in the CHARM study.16,17 Finally, no case of TB appeared in the certolizumab PRECISE I and PRECISE II induction and maintenance studies.18

Observational studies in North America and Northern Europe have also shown low incidence of the infection, with 0/500 cases and 1/614 cases in the two largest series of patients.19,20

Various factors may have contributed to the high and unexpected incidence of TB in our cohort of patients treated with anti-TNF drugs. One is a field effect related to a high LTBI prevalence in the Spanish population, with three fold higher incidence rates than in North European countries.2

Another factor is that anti-TNF therapy has been used in the
majority of cases as third line therapy in patients failing, but still under immunosuppressive treatment. Indeed, 5 of the 7 patients developing TB were receiving immunosuppressants at the time of LTBI screening. This observation, along with the finding that 4 out of the 7 patients developed TB within the first 16 weeks after starting anti-TNF therapy suggests that these may correspond to false negative results of the screening protocol. As for the patient developing renal TB after a positive TST and receiving treatment with isoniazid, the possibility also exists that the mycobacterium was resistant to this drug.

These observations raise the need to revise current LTBI screening protocols and to use more sensitive and specific tests. It has been suggested that new screening tests based on interferon gamma release assays (IGRAs), may have a higher accuracy. 21 IGRAs include an enzyme-linked immunosorbent assay (ELISA-Quantiferon-TB Gold) and an enzyme-linked immunospot assay (ELISpot-TSpOT.TB) that measure IFN-gamma concentration (ELISA) or IFN-gamma-secreting T cells (ELISpot) in response to antigens present in Mycobacterium tuberculosis. IGRAs are more specific than TST as they are not influenced by previous BCG vaccination or other non-tuberculous mycobacteria species (except M. Szulgai, M. Kansassii, M Marinnum). ELISpot and ELISA seem to have comparable efficacy. 21,22

It is difficult to establish the real sensitivity and specificity of the two IGRAs because of the lack of a gold standard for diagnosing LTBI. Indeterminate results are less common with ELISpot than with Quantiferon. 22 Both tests have been compared with TST in immunosuppressed patients in different studies. In patients with immune-mediated inflammatory diseases undergoing immunosuppressive therapy, IGRAs are in general more sensitive than TST but false negative results may also occur. Some studies in IBD patients have linked false negative results of IGRAs to concomitant immunosuppressant therapy, 23–27 although other studies did not observe major differences in the proportion of patients testing positive in relation to concomitant treatments. 28

Over the last years, guidelines have changed the position concerning the diagnosis of latent TB infection. US guidelines recommend replacing TST with IGRAs as the diagnostic test for LTBI in all patients. 29 However, Canadian and European guidelines maintain TST as a primary test, and recommend the use of IGRAs as a confirmatory test. 30,31 This recommendation is based on the poor correlation between IGRAs and TST reported in different studies. By performing both tests the sensitivity for latent TB diagnosis might be improved.

The choice of the screening protocol may have to be adapted to the different risk of TB according to geographic area. In Spain, the latest recommendation of the Infections and Clinic Microbiologic Spanish Society (SEIMC) and the Pneumology and Thoracic Spanish Society (SEPAR) of April 2010 includes the use of TST in combination with IGRAs in the diagnosis of LTBI, because the use of IGRAs alone is not yet established and new studies are still needed. 32

In summary, our results indicate that a majority of cases of TB in patients under TNF antagonists occur within the first months of therapy and in those under immunosuppressants at the time of screening, suggesting that improved screening, but not repeated LTBI testing would be key for reducing this infection. In addition, it is reasonable to consider LTBI screening in all IBD patients before starting any immunosuppressant treatment to reduce the rate of false negative results.

Conflict of interest statement

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