Journal of Crohn's and Colitis (2013) 7, 208–212

Available online at www.sciencedirect.com

SciVerse ScienceDirect

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

Aranzazu Jauregui-Amezaga, Fanny Turon, Ingrid Ordás, Marta Gallego, Faust Feu, Elena Ricart, Julián Panés*

Department of Gastroenterology, Hospital Clínic de Barcelona, CIBER-EHD, Barcelona, Spain

Received 26 March 2012; received in revised form 11 May 2012; accepted 12 May 2012

KEYWORDS:
Inflammatory bowel disease;
Crohn's disease;
Ulcerative colitis;
Infliximab;
Adalimumab;
Tuberculosis

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.

* *Corresponding author at*: Deparment of Gastroenterology, Hospital Clínic de Barcelona, Villarroel 170, Barcelona 08036, Spain. Tel.: +34 93 227 54 18.
E-mail address: jpanes@clinic.ub.es (J. Panés).

1873-9946/$ - see front matter
doi:10.1016/j.crohns.2012.05.012

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%).[1] 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).[1] 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).[2] In Spain the reported incidence rate is 16.6 cases per 100.000 population per year.[2]

The introduction of anti-TNF antibody therapy has changed treatment paradigms in the management of patients with inflammatory bowel disease (IBD), being currently the most potent treatment to achieve clinical remission and mucosal healing.[3] The proportion of patients treated with these drugs is steadily increasing since the approval of the first anti-TNF antibody in 1998.[4] It became soon apparent after marketing that the use of anti-TNF drugs is associated with reactivation of TB.[5] Although the mechanism is not fully understood, it has been linked to the failure of granuloma formation.[6–8] TB incidence studies in patients receiving infliximab (IFX) mostly included mixed populations. In the study of Keane et al in 2001, 70 cases of TB were reported among 147,000 patients who had received IFX, including 45,000 with rheumatoid arthritis and 76,000 with Crohn's disease, representing a significant increase over background rates.[5] These incidence rates were confirmed in population-based studies in Spain.[9] TB was diagnosed a median of 12 weeks after initiation of treatment with IFX and most cases occurred within the first 6 months. The pattern of TB was atypical, 56% of cases having extrapulmonary TB and 24% of cases disseminated TB.[5] These forms of TB had been previously associated with marked immunosuppression. Introduction of LTBI screening protocols in candidate patients to anti-TNF therapy led to a decrease in TB incidence of 78% bringing it close to the levels of the background population.[10]

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.[9] 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.[11,12]

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.

Table 1 Demographic and clinical characteristics of patients developing TB under anti-TNF therapy.

Pt	Sex	IBD	Duration IBD (mo)	TST at LTBI screening	IS at LTBI screening	Age at TB diagnosis	TST at TB diagnosis	IGRA at TB diagnosis	IS at TB diagnosis	Time of anti-TNF treatment before TB (we)	TB location	Diagnosis tests
1	Male	UC	15	+	No IS	28	Not performed	Not performed	IFX	6	Extrapulmonary (renal)	MB Genetic detection
2	Male	UC	132	-	AZA	38	Not performed	Not performed	IFX+AZA	7	Pulmonary	Microscopy and Lowenstein +
3	Male	UC	60	-	AZA	35	Not performed	+	IFX+AZA	52	Extrapulmonary (not confirmed)	No microbiological detection
4	Female	CD	137	-	No IS	21	Not performed	Not performed	ADA	148	Pulmonary	MB Genetic detection
5	Male	CD	25	-	AZA	43	+	+	IFX+AZA	16	Extrapulmonary (nodal)	Microscopy and Lowenstein +
6	Female	CD	131	-	AZA	38	Not performed	Not performed	IFX+AZA	10	Extrapulmonary (peritoneal)	No microbiological detection High levels of Ada in ascitic fluid
7	Male	CD	60	-	Corticoids	31	Not performed	Not performed	IFX+MTX	50	Pulmonary	Lowenstein +

UC: ulcerative colitis. CD: Crohn's disease. IS: immunosuppression. AZA: azathioprine. IFX: infliximab. ADA: adalimumab. MTX: methotrexate. MB: Mycobcaterium. Ada: adenosine deaminase.

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 tuberculostatic 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. Kansasii*, *M Marinum)*. 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 an 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

JP, IO and ER have been advisors and speakers for Abbott and MSD laboratories, and have received unrestricted grants for research from Abbott and MSD laboratories.

Acknowledgements

The authors are grateful to Dr Jose Antonio Martinez from Infectious Disease Service of Clinic Hospital of Barcelona for his assistance in the management of IBD patients with tuberculosis.

References

1. Global Tuberculosis Control. WHO Report 2011. World Health Organization; 2011. [www.who.int/tb].
2. Tuberculosis Surveillance Report 2009. European Centre for Disease Prevention and Control. Regional Office for Europe. World Health Organization; 2009 [www.ecdc.europa.eu].
3. Van Assche G, Vermeire S, Rutgeerts P. Mucosal healing and anti TNFs in IBD. *Curr Drug Targets* 2010;**11**:227–33.
4. Infliximab approval process in Crohn's disease. Deparment of Health and Human Services. Public Health Service. Food and Drug Administration August 24, 1998.
5. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwietertman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;**345**:1098–104.
6. Kindler V, Sappino AP, Grau GE, Piguet PF, Vassalli P. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. *Cell* 1989;**56**:731–40.
7. Flynn JL, Goldstein MM, Chan J, Triebold KJ, Pfeffer K, Lowenstein CJ, et al. Tumor necrosis factor-alpha is required in the protective immune response against *Mycobacterium tuberculosis* in mice. *Immunity* 1995;**2**:561–72.
8. Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol* 2002;**168**:4620–7.
9. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003;**48**:2122–7.
10. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, Montero D, Pascual-Gomez E, Mola EM, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum* 2005;**52**:1766–72.
11. Obrador A, Lopez San Roman A, Munoz P, Fortun J, Gassull MA. Consensus guideline on tuberculosis and treatment of inflammatory bowel disease with infliximab. Spanish Working Group on Crohn Disease and Ulcerative Colitis. *Gastroenterol Hepatol* 2003;**26**:29–33.
12. Lopez-San Roman A, Obrador A, Fortun J, Munoz P, Gassull MA. Recommendations on tuberculosis and treatment of inflammatory bowel disease with infliximab. 2006 update. *Gastroenterol Hepatol* 2006;**29**:81–4.
13. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541–9.

14. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876–85.
15. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;**353**:2462–76.
16. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;**130**:323–33 [quiz 591].
17. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**:52–65.
18. Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen OO, Hanauer SB, McColm J, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007;**357**:239–50.
19. Colombel JF, Loftus Jr EV, Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004;**126**:19–31.
20. Fidder H, Schnitzler F, Ferrante M, Noman M, Katsanos K, Segaert S, et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;**58**:501–8.
21. Lalvani A, Millington KA. Screening for tuberculosis infection prior to initiation of anti-TNF therapy. *Autoimmun Rev* 2008;**8**:147–52.
22. Lalvani A, Pareek M. Interferon gamma release assays: principles and practice. *Enferm Infecc Microbiol Clin* 2010;**28**:245–52.
23. Papay P, Eser A, Winkler S, Frantal S, Primas C, Miehsler W, et al. Factors impacting the results of interferon-gamma release assay and tuberculin skin test in routine screening for latent tuberculosis in patients with inflammatory bowel diseases. *Inflamm Bowel Dis* 2011;**17**:84–90.
24. Schoepfer AM, Flogerzi B, Fallegger S, Schaffer T, Mueller S, Nicod L, et al. Comparison of interferon-gamma release assay versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease. *Am J Gastroenterol* 2008;**103**:2799–806.
25. Ferrara G, Losi M, D'Amico R, Roversi P, Piro R, Meacci M, et al. Use in routine clinical practice of two commercial blood tests for diagnosis of infection with *Mycobacterium tuberculosis*: a prospective study. *Lancet* 2006;**367**:1328–34.
26. Richeldi L, Losi M, D'Amico R, Luppi M, Ferrari A, Mussini C, et al. Performance of tests for latent tuberculosis in different groups of immunocompromised patients. *Chest* 2009;**136**:198–204.
27. Matulis G, Juni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a *Mycobacterium tuberculosis* antigen-specific interferon gamma assay. *Ann Rheum Dis* 2008;**67**:84–90.
28. Qumseya BJ, Ananthakrishnan AN, Skaros S, Bonner M, Issa M, Zadvornova Y, et al. QuantiFERON TB gold testing for tuberculosis screening in an inflammatory bowel disease cohort in the United States. *Inflamm Bowel Dis* 2011;**17**:77–83.
29. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using Interferon Gamma Release Assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *MMWR Recomm Rep* 2010;**59**:1–25.
30. Interferon-gamma release assays testing versus tuberculosis skin testing for tuberculosis: a review of the clinical effectiveness and guidelines. Rapid response report 2011. Canadian Agency for Drugs and Technologies in Health; May 24 2011. [www.cadth.ca].
31. Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;**3**:47–91.
32. Gonzalez-Martin J, Garcia-Garcia JM, Anibarro L, Vidal R, Esteban J, Blanquer R, et al. Consensus document on the diagnosis, treatment and prevention of tuberculosis. *Arch Bronconeumol* 2010;**46**:255–74.