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Alimentary Tract

How frequently do tuberculosis screening tests convert in inflammatory bowel disease patients on anti-tumour necrosis factor-alpha? A pilot study

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ABSTRACT

Background: Tuberculosis reactivation can lead to severe complications in patients treated with anti-tumour necrosis factor-alpha.
Aim: To assess the usefulness of repeat tuberculosis screening tests in inflammatory bowel disease patients on stable anti-TNF therapy.
Methods: Cross-sectional study, in patients on prolonged anti-TNF treatment (≥12 months) and basal negative screening for latent tuberculosis. Quantiferon®-TB Gold In-tube test was performed and then, tuberculin skin test was administered.
Results: 74 patients were included, median duration of anti-TNF treatment was 30 months (IQR 19–54); 47 patients on infliximab and 27 on adalimumab; no patient was on glucocorticoids. Previous BCG vaccination was present in 5 cases. After anti-TNF was started, 4 patients suffered from potential tuberculosis exposure and two cases travelled to endemic areas. The cumulative incidence of tuberculin skin test conversion was 2.7% (95% CI 0.3–9.4%, 2/74), and the incidence rate of tuberculin skin test conversion was 0.83% (95% CI 0.1–2.9%) per patient-year of treatment with anti-TNF drugs. All Quantiferon tests but one (a patient with an indeterminate result and a negative tuberculin skin test) were negative.
Conclusions: The incidence rate of conversion of tuberculosis screening tests among patients on anti-TNF treatment seems to be low and these conversions were diagnosed based on a positive tuberculin skin test and were discordant with Quantiferon testing.

1. Introduction

Anti-tumour necrosis factor (TNF) alpha agents have significantly improved the management of patients with inflammatory bowel disease (IBD). Although they are generally safe, strict guidelines have to be followed for the prevention and management of adverse effects, especially infections [1]. An increased incidence of tuberculosis (TB) reactivation in patients treated with anti-TNF drugs was described only in the postmarketing surveillance, frequently adopting extrapulmonary or disseminated forms [2]. This led to the implementation of policies to diagnose latent TB prior to the initiation of therapy [3–7]. They generally include a thorough history, a chest X-ray and a specific TB test, either a tuberculin intradermal test with purified protein derivative (PPD), with or without booster re-exposure, or an interferon gamma release assay (IGRA), according to local recommendations. All these procedures have resulted in a significantly decreased number of cases diagnosed with TB after anti-TNF therapy [8], but these protocols have not been able to completely eradicate this problem. Active TB has been described even after a negative screening for latent TB.

The number of TB cases reported in patients treated with anti-TNF drugs is proportional to the local incidence of the infection. In a series of 500 IBD patients treated at the Mayo Clinic, no case of TB was diagnosed [9], whereas in Spain, Gómez-Reino et al. reported an estimated incidence of infliximab-associated TB in rheumatoid arthritis patients of 1893 cases per 100,000 patients in the year

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2000, before official guidelines were established for TB prevention in patients treated with biological agents [10].

The adequacy of PPD retesting during anti-TNF therapy has been proposed for several reasons [11–14]. Initial hypersensitivity skin tests can be falsely negative in a situation of anergy induced by several factors such as immunosuppressive therapy, malnourishment, or the inflammation associated with immune-mediated disease [11,12]. This observation, together with the possibility of a primary TB infection while on anti-TNF, has lead some authors to investigate the usefulness of an annual screening test for latent TB while on maintenance with an anti-TNF agent [14], as is generally done in high-risk populations (exposure to clinical samples with potential mycobacterial contamination, healthcare workers, prison employees, and prisoners). However, the exact rate of conversion of TB screening tests among IBD patients on anti-TNF is not known. On the other hand, anti-TNF therapy does not seem to influence PPD results [13].

The aims of our pilot study were to describe the frequency of PPD conversions among IBD patients on anti-TNF therapy, as well as to evaluate the results of Quantiferon® test in this group of patients and to assess the usefulness of these techniques in the diagnosis of latent TB in patients with IBD while on anti-TNF therapy, such that the risk of an active episode of TB can then be diminished by appropriate chemoprophylaxis.

2. Materials and methods

2.1. Patients

A cross-sectional pilot study was carried-out between January and September 2011 in IBD patients (Crohn's disease and ulcerative colitis) on anti-TNF treatment (infliximab or adalimumab) at standard dosages (infliximab 5 mg/kg IV every 8 weeks, adalimumab 40 mg SC every other week) or intensified dosages for at least 12 months. Patients were recruited at the Gastroenterology Departments of four University Hospitals in the Community of Madrid, Spain. They were seen regularly in these Units and asked to participate only after 12 months of continued therapy with anti-TNF. Diagnoses of IBD were confirmed by routine clinical, radiological, endoscopic and histological criteria [15].

In each patient, TB infection evaluations were performed using the Quantiferon®-TB Gold In-tube test (QFT-GIT) and PPD. Clinical and demographic characteristics and risk factors for TB were also reviewed for each subject.

Prior to the initiation of the anti-TNF drug, all patients had been screened in accordance with local Spanish recommendations, that included a specifically directed anamnesis, PPD skin test, PPD booster in patients on immunosuppressor treatment and chest X-ray [5]. Only patients who tested negative on the baseline one- or two-step PPD were eligible for the study.

2.2. Quantiferon®-TB Gold In-tube test

A blood sample was obtained from each patient and dispensed into the three QFT tubes: Nil (negative control coated with saline), TB-antigen (coated with EAST-6, CFP-10 and TB7.7 antigens) and Mitogen (positive control coated with phytohemagglutinin), according to the manufacturer's instructions (Cellestis Ltd., Australia). Tubes were then incubated at 37 °C for 16–24 h within 16 h after sample collection [16]. Immediately after incubation, samples were centrifuged and the supernatants were stored at −70 °C until interferon-γ analysis by QFT ELISA. QFT-GIT results were calculated using QFT-GIT analysis software (Cellestis Ltd., Australia) and were positive, negative or indeterminate, depending on the interferon-γ production.

2.3. Tuberculin skin test

Two units of purified protein derivative (UCB Pharma, Madrid, Spain) were injected intradermally following the Mantoux method. The transverse diameter of the induration was recorded in millimetres after 72 h. PPD results were interpreted by trained staff according to current guidelines [5]. In patients on anti-TNF treatment, who are at high risk for developing active TB if infected with *Mycobacterium tuberculosis*, PPD conversion was defined as skin induration ≥5 mm [17]. In all cases, the PPD procedure followed blood extraction for QFT-GIT determination.

2.4. Interpretation of diagnostic tests

In patients positive for either QFT-GIT or PPD test, clinical practice protocols were followed by performing a chest X-ray and a repeat epidemiologic history. Complete antituberculous therapy or chemoprophylaxis was then administered according to local recommendations. In patients with an undetermined QFT-GIT, the test was performed again after six to ten weeks [12].

2.5. Statistical analysis

A descriptive statistical analysis was carried out. The main objective was to calculate the cumulative incidence and the incidence rate for PPD conversion in patients with a baseline one- or two-step negative PPD. Frequencies and percentages (with 95% confidence intervals) were determined for categorical variables. For quantitative variables, the Kolmogorov–Smirnov test was used to evaluate normality and data were presented as the arithmetic mean ± standard deviation (SD) or the median and interquartile range (IR), as appropriate. We calculated the 95% confidence interval for the cumulative incidence and incidence rate. A concordance study between Quantiferon® and PPD was impossible due to the lack of positive results of the former. Statistical significance was assumed for p values of less than 0.05.

2.6. Ethical considerations

All participants were asked to sign an informed consent form prior to recruitment. The study was approved by the Research Ethics Committees of all participating centres.

3. Results

Seventy-four patients were included, 62 (84%) with Crohn's disease and 12 (16%) with ulcerative colitis. Mean age was 42 ± 13 years, 55% were women and 45% were smokers. The median time from diagnosis of IBD was 11 years (IQR 5–18). Characteristics of these IBD patients on anti-TNF therapy are shown in Table 1. At the time of the inclusion, the median duration of anti-TNF treatment was 30 months (IQR 19–54), 47 patients were on infliximab, and 27 on adalimumab. An intensified dose was used in 15 (20%) patients and 11 (15%) patients had received another anti-TNF before the current one (9 switches from infliximab to adalimumab, 1 switch from adalimumab to infliximab and 1 switch from etanercept to infliximab in a patient with associated psoriasis). Concomitant medications are shown in Table 1; none of the patients was on glucocorticoids therapy at the time of repeat TB screening.

Prior to initiation of the anti-TNF drug, all patients had been screened for TB. A booster PPD was performed in 51 (68%) patients, in accordance with local recommendations (booster injection is recommended after an initial negative test in patients treated with immunomodulators). There was a history of previous Bacillus Calmette–Guérin (BCG) vaccination in 5 (6.8%) patients, risk of exposure at the workplace in 4 cases (5.4%) and travel to areas of