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Tuberculosis in Anti-Tumour Necrosis Factor-treated Inflammatory Bowel Disease Patients After the Implementation of Preventive Measures: Compliance With Recommendations and Safety of Retreatment

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Abstract

Background and Aims: Despite having adopted preventive measures, tuberculosis (TB) may still occur in patients with inflammatory bowel disease (IBD) treated with anti-tumour necrosis factor (anti-TNF). Data on the causes and characteristics of TB cases in this scenario are lacking. Our aim was to describe the characteristics of TB in anti-TNF-treated IBD patients after the publication of the Spanish TB prevention guidelines in IBD patients and to evaluate the safety of restarting anti-TNF after a TB diagnosis.

Methods: In this multicentre, retrospective, descriptive study, TB cases from Spanish hospitals were collected. Continuous variables were reported as mean and standard deviation or median and interquartile range. Categorical variables were described as absolute and relative frequencies and their confidence intervals when necessary.

Results: We collected 50 TB cases in anti-TNF-treated IBD patients, 60% male, median age 37.3 years (interquartile range [IQR] 30.4–47). Median latency between anti-TNF initiation and

first TB symptoms was 155.5 days (IQR 88–301); 34% of TB cases were disseminated and 26% extrapulmonary. In 30 patients (60%), TB cases developed despite compliance with recommended preventive measures; *not performing 2-step TST (tuberculin skin test) was the main failure in compliance with recommendations. In 17 patients (34%) anti-TNF was restarted after a median of 13 months (IQR 7.1–17.3) and there were no cases of TB reactivation.

Conclusions: Tuberculosis could still occur in anti-TNF-treated IBD patients despite compliance with recommended preventive measures. A significant number of cases developed when these recommendations were not followed. Restarting anti-TNF treatment in these patients seems to be safe.

Key Words: Anti-TNF; tuberculosis; inflammatory bowel disease; ulcerative colitis; Crohn's disease; infliximab; adalimumab; retreatment; prevention

1. Introduction

Tumour necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that plays an important pathogenic role in inflammatory bowel disease (IBD) and other immune-mediated diseases.[1] Anti-TNF-α (anti-TNF) agents have been used for more than 15 years for the treatment of IBD, both Crohn's disease (CD)[2] and ulcerative colitis (UC).[3] Anti-TNF agents have a favourable safety profile, although a small percentage of patients experience severe adverse effects, including infectious complications.[4]

Soon after infliximab, the first anti-TNF agent, was commercialized in December 1998, these agents were associated with a 2- to 8-fold increased risk of active tuberculosis (TB) compared with the general population.[5–8] TB has also been diagnosed in patients receiving adalimumab[9] and golimumab.[10] Most of these TB cases were diagnosed in the first 4 months after starting anti-TNF therapy, so most of them are considered to be reactivations of latent TB.[5] In more than 50% of TB cases in anti-TNF-treated patients there is extrapulmonary and disseminated disease. This percentage is similar to those observed in immunocompromised patients, more than 50% of cases having extrapulmonary and disseminated disease.[5] The mechanism explaining this increased TB risk is that TNF is a key cytokine in the formation and maintenance of granuloma, an essential mechanism of host defence against intracellular pathogens, like *Mycobacterium tuberculosis*.[11,12]

Since the first reports, different scientific organizations from all over the world have published guidelines and recommendations about active and latent TB screening before anti-TNF treatment.[13–15] In Spain, the Spanish Working Group on Crohn's disease and Ulcerative Colitis (Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa [GETECCU]) published its first guideline in January 2003,[16] updated in 2006.[17]

These screening strategies have lowered the incidence of TB in this population by 78–83%,[18] but TB cases are still being diagnosed despite strictly compliance with these guidelines.[19–21]

The primary objective of this multicentre retrospective study was to analyse the clinical features of TB in anti-TNF-treated IBD patients from Spain after the publication of the GETECCU recommendations, and particularly to evaluate whether these recommendations were accomplished. Secondary objectives were to analyse the course of IBD after TB treatment and to evaluate the safety of restarting anti-TNF after a TB diagnosis.

2. Methods

2.1. Patients

A multicentre, retrospective, observational study promoted by GETECCU was designed. All GETECCU members were invited to participate by a structured questionnaire and participating centres were asked to review TB cases registered in their databases. IBD patients under anti-TNF treatment diagnosed with active TB since January 2003 (date of first publication of the GETECCU guidelines) were included and their clinical charts were retrospectively reviewed.

2.2. Variables

All clinical and demographic variables were collected after clinical chart review: age, sex, smoking, IBD type (Crohn's disease, ulcerative colitis, unclassified colitis) and subtype according to the Montreal classification, anti-TNF drug (infliximab or adalimumab), corticosteroid or immunosuppressive co-treatment, time between anti-TNF initiation and TB diagnosis, TB clinical characteristics and adherence to the GETECCU guidelines. Follow-up variables included were the clinical course of TB (hospitalization, intensive care unit stay, death), the clinical course of IBD (assessed by Harvey–Bradshaw index and/or physician global assessment) and retreatment with anti-TNF.

2.3. Definitions

Latent TB was defined according to the GETECCU guidelines for the prevention of TB in IBD patients starting anti-TNF.[16] These include a thorough review of TB risk factors, a chest X-ray and a two-step tuberculin skin test (TST) performed according to the Mantoux method (TST repeated after 1 week if first test is negative). Patients with risk factors, X-ray findings of remote TB or TST >5 mm were considered to have latent TB and treated with a 9-month regimen of 300 mg/day of isoniazid.

Active TB (TB case definition) was defined according to clinical, radiological and microbiological standards as defined by the Spanish Joint Consensus on diagnostic, treatment and prevention of TB by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR).[22]

Smoking was defined as more than 7 cigarettes per week; ex-smoker was defined as >12 months with no tobacco consumption.

Corticosteroid treatment was defined as >10 mg/day of prednisone or equivalent for >7 days.

2.4. Statistical analysis

Continuous variables were reported as mean and standard deviation when normally distributed and with median and interquartile range when the variables did not follow a normal distribution. Categorical variables were described as absolute number (*n*) and relative frequency (%) and their confidence intervals when necessary. Differences in the median time between the start of anti-TNF and first TB symptom among patients treated with infliximab and adalimumab were analysed using the Wilcoxon rank-sum test. Differences were considered significant if $p < 0.05$.

3. Results

3.1. Clinical and demographic characteristics of IBD patients

We collected 57 TB cases in anti-TNF-treated IBD patients from 22 Spanish hospitals. Seven cases were excluded because TB was diagnosed before January 2003. Of the 50 patients included in the analysis population, 30 (60%) were male, with a median age of 37.3 years (interquartile range [IQR] 30.4–47). Thirty-one cases were found in CD patients (62%); infliximab was the anti-TNF used in 41 patients (82%) and most patients were on a standard dose (only 2 patients received higher doses, one with infliximab and another with adalimumab). Forty patients (80%) received concomitant immunosuppressive treatment, mostly thiopurines, and 44% also received corticosteroids along with immunosuppressants. Clinical and demographic characteristics are summarized in Table 1.

3.2. Clinical characteristics of tuberculosis

Only 40% of TB cases were pulmonary forms. Disseminated disease was diagnosed in 34% of patients and extrapulmonary disease in 26% of cases (Table 2).

The most frequent symptoms at presentation of TB were fever, weight loss, respiratory symptoms, enlarged lymph nodes and fatigue (Table 2). As a result of the elevated percentage of extrapulmonary TB disease, many atypical symptoms were found as presenting symptoms (e.g. ascites, abdominal pain, diarrhoea, lingual ulcer, dysphonia, headache). Unexplained fever was the only presenting symptom in 3 patients; in another 6 patients fever and weight loss were the only symptoms reported.

Symptoms of TB developed a median of 155.5 days after the first dose of anti-TNF (IQR 88–301); in 41 cases (82%) TB developed within the first year of treatment (32% within the first 4 months) (Table 2). In the remaining 9 patients, symptoms developed more than 1 year after the start of treatment (more than 3 years later in 5 of them). Median interval between initiation of symptoms and TB diagnosis was 25.5 days (IQR 12–39); however, 6 patients (12%) needed more than 90 days to achieve the diagnosis and in 3 of them (2 pulmonary TB and 1 peritoneal TB) more than 6 months was needed to achieve the correct diagnosis. There was no difference in the median time between the start of anti-TNF and first TB symptom among patients treated with infliximab and adalimumab (148 vs 160 days; $p = 0.78$).

Most patients (82%) had a direct mycobacterial diagnosis, either *M. tuberculosis* detection with Ziehl–Neelssen stain (mostly in sputum, but also in biopsies from different locations), specific Lowenstein culture (mostly from sputum, but also from other body fluids such as urine, blood, ascites or cerebrospinal fluid) or polymerase chain reaction (PCR) analysis of *M. tuberculosis*; in 2 patients the diagnosis was achieved only after performing the last test. In the remaining 9 patients (18%), TB diagnosis was made indirectly by typical chest X-ray pattern, finding of caseating granulomas in biopsies, elevation of adenosine deaminase in body fluids or clinical suspicion and response to empirical anti-tuberculous treatment (Table 2).

Most patients needed hospital admission, with a median stay of 16.5 days (IQR 12–30). Two patients needed intensive care admission and 1 of them died. The patient who died was a 74-year-old woman with UC, treated with infliximab, who developed disseminated TB and died from multi-organ failure.

All patients were treated with isoniazid-based regimens, most of them for 6–12 months. Thirteen patients (26%) developed adverse effects, mainly hepatotoxicity or paradoxical response; 7 of them needed a change in the anti-tuberculosis regimen (Table 2).

3.3. Compliance with Spanish guidelines for prevention of TB

Thirty patients (60%) developed TB despite properly following the Spanish recommendations for prevention, including 5 patients who received TB chemoprophylaxis. In 4 patients, the QuantiFERON-TB Gold-In Tube test was also performed, though this is not included in the guidelines: 2 had a negative result, 1 had an indeterminate result and 1 had a positive result; this was a patient who had also

Table 1. Baseline clinical and demographic characteristics of anti-tumour necrosis factor (TNF)-treated inflammatory bowel disease patients with a diagnosis of tuberculosis ($n = 50$).

Patients' characteristics	*n* (%) or median (range)
Sex	
Male	30 (60)
Female	20 (40)
Age, y, median (range)	37.3 (30.4–47)
Smoking	
Yes	15 (30)
No	29 (58)
Ex-smoker	6 (12)
IBD type	
CD	31 (62)
UC	18 (36)
UCIBD	1 (2)
CD Montreal classification ($n = 31$)	
A1 (<17 y)	3 (9.7)
A2 (17–40 y)	24 (77.4)
A3 (>40 y)	4 (12.9)
B1 (non-stricturing/non-penetrating)	16 (51.6)
B2 (stricturing)	3 (9.7)
B3 (penetrating)	12 (38.7)
L1 (ileal)	14 (45.2)
L2 (colonic)	5 (16.1)
L3 (ileocolonic)	12 (38.7)
L4 (superior digestive tract)	
Yes	4 (12.9)
No	27 (87.1)
Perianal	
Yes	16 (51.6)
No	15 (48.4)
UC Montreal classification ($n = 18$)	
E1 (distal)	0
E2 (left-sided)	8 (44.4)
E3 (extensive)	10 (55.6)
S1 (mild)	0
S2 (moderate)	11 (61.1)
S3 (severe)	7 (38.9)
Extra-intestinal manifestations*	
Yes	12 (24)
No	38 (76)
Anti-TNF drug	
Infliximab	41 (82)
Adalimumab	9 (18)
Co-treatment	
Corticosteroids	26 (52)
Thiopurines	40 (80)
Methotrexate	2 (4)
Anti-TNF + IS + CS	22 (44)

*Eight patients had articular manifestations; 4 were cutaneous manifestations and 1 patient (in a patient who had also arthropathy) had uveitis.

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; UCIBD, unclassified IBD; IS, immunosuppressants; CS, corticosteroids.

Table 2. Clinical characteristics of tuberculosis cases in anti-TNF-treated inflammatory bowel disease patients ($n = 50$).

Characteristics of TB	*n* (%)
TB type	
Pulmonary	20 (40)
Disseminated	17 (34)
Other*	13 (26)
Frequency of symptoms	
Fever	42 (84)
Weight loss	28 (56)
Respiratory symptoms	33 (66)
Enlarged lymph nodes	13 (26)
Days between anti-TNF initiation and first TB symptoms (median and IQR)	155.5 (88–301)
Symptoms ≤4 months	16 (32)
Symptoms ≤12 months	41 (82)
Symptoms >12 months	9 (18)
Days between TB symptoms and TB diagnosis, median (IQR)	25.5 (12–39)
Diagnostic test	
Direct mycobacterium detection	41 (82)
Ziehl–Neelssen stain	23 (46)
Lowenstein culture	29 (58)
PCR of *M. tuberculosis***	4 (8)
Indirect method	9 (18)
Typical radiographic pattern	3 (6)
Elevated ADA in body fluids****	3 (6)
Caseating granulomas in biopsy	1 (2)
Clinical suspicion and response to empirical treatment	2 (4)
Hospital admission	
YES#	42 (84)
NO	8 (16)
Days of admission, months, median (IQR)	16.5 (12–30)
Duration of tuberculostatic regimen	
6	17
9	20
12	10
>12	3
Toxicity of tuberculostatic treatment	13 (26%)
Hepatotoxicity	5 (10%)
Neurotoxicity	2 (4%)
Paradoxical response	4 (8%)
Other*****	2 (4%)

*Peritoneal (3 patients), pleural (2 patients) and pericardial, renal, urinary tract, meningeal, mediastinum, lingual, laryngeal and unknown origin (1 case each).

**In 2 patients this was the only positive bacteriological method; 2 in broncho-alveolar lavage and other in a kidney biopsy.

***Pleural, pericardial, and cerebrospinal.

****Vomiting, cutaneous allergic reaction.

#Two patients needed intensive care unit admission; 1 of them died.

ADA, adenosine deaminase; IQR, interquartile range; TB, tuberculosis; TNF, tumour necrosis factor.

had a positive TST retest after 1 week. However, in 40% of cases ($n = 20$) lack of compliance with recommendations was detected: in 3 patients TST was not performed and in 13 patients it was not repeated after 1 week; in 4 patients chemoprophylaxis was not administered although it was indicated, including 1 patient who received only 1 month of prophylaxis because of toxicity (Table 3).

Globally, 9 patients (18%) fulfilled the definition of latent TB diagnosis: 5 patients had a recent TB contact (2 of them tested first- or second-step TST-positive) and 4 had a positive TST result. Only

Table 3. Compliance with Spanish GETECCU guidelines for tuberculosis prevention in anti-TNF-treated IBD patients (published in January 2003).[16]

	Patients *n* (%)
Compliance with preventive guidelines	
Yes	30 (60%)
No	20 (40%)
First TST not done	3 (6%)
Second TST not done*	13 (26%)
Chest X-ray not done	0
Chemoprophylaxis not administered when indicated	4 (8%)
TB contact	2 (4%)
TST positive	1 (2%)
Incomplete chemoprophylaxis**	1 (2%)

*Second TST after 7 days (if first TST negative).

**Another 5 patients received correct chemoprophylaxis for 6 or 9 months, developing TB anyway.

TB, tuberculosis; TST, tuberculin skin test.

1 patient had a 'positive' chest-X ray with granuloma and apical scarring. In this patient, the second TST and the QuantiFERON test were also positive (Table 4).

3.4. Clinical course of IBD after stopping anti-TNF and adding TB treatment

Anti-TNF was stopped in all patients after TB diagnosis. Forty-eight percent of the patients remained on immunosuppressive therapy (22 on thiopurines, 2 on methotrexate); 8 patients (16%) were maintained on 5-aminosalicylic acid (5-ASA) (7 UC and 1 unclassified inflammatory bowel disease (UIBD)), 8 patients (16%) underwent surgical resection (4 UC, 3 CD) and 1 CD patient received budesonide maintenance treatment. Nine patients (18%; 8 CD, 1 UC) remained without any specific treatment after withdrawal of anti-TNF.

After excluding patients who underwent surgery (4 CD and 4 UC) and patients with missing data (3 UC, 1 CD), we collected data on 38 patients (26 CD, 11 UC, 1 unclassified IBD) regarding clinical activity immediately before anti-TNF withdrawal and anti-tuberculous therapy initiation and 6 and 12 months later. We found no statistically significant changes in IBD activity at 6 or 12 months.

3.5. Course of TB after anti-TNF retreatment

In 17 patients (34%) anti-TNF was restarted after a median of 13 months (IQR 7.1–17.27); in 5 patients anti-TNF was reintroduced while on TB treatment (at 2.5, 3, 4, 5 and 7 months after initiation of anti-tuberculous treatment) and in the remaining 12 patients anti-TNF retreatment was initiated after the anti-tuberculosis regimen was completed. There were no complications in TB course or cases of TB reactivation after anti-TNF retreatment (median of follow-up 34 months, IQR 23–64.5).

4. Discussion

We conducted an observational retrospective study recording 50 TB cases in anti-TNF-treated IBD patients from 22 hospitals in Spain; as far as we know this represents the largest case series reported on this issue. As we excluded TB cases diagnosed before the publication of the Spanish GETECCU recommendations for TB prevention in this group of patients,[16] our results prove that TB cases are still

Table 4. Characteristics and treatment of anti-tumour necrosis factor-treated IBD patients with a diagnosis of latent tuberculosis.

Patient number	Sex/age (y)	TB contact	First TST	Second TST	Chest X ray	QuantiFERON	Latent TB treatment (duration)
1	M 28	Pos	Neg	Neg	Neg	ND	ND
2	F 35	Pos	Pos	ND	Neg	ND	6 months
3	F 50	Pos	Neg	ND	Neg	ND	ND
4	F 48	Pos	Neg	Neg	Neg	ND	9 months
5	M 53	Pos	Neg	Pos	Pos	Pos	6 months
6	M 42	Neg	Pos	ND	Neg	ND	ND
7	M 56	Neg	Pos	ND	Neg	ND	6 months
8	M 29	Neg	Pos	ND	Neg	ND	6 months
9	F 70	Neg	Pos	ND	Neg	ND	Incomplete

IBD, inflammatory bowel disease; TB, tuberculosis; TST, tuberculin skin test; Pos, positive; Neg, negative; ND, not done.

happening despite the publication and dissemination of these recommendations. Eleven of these cases have been previously reported separately.[23,24] Other authors have shown that the publication and dissemination of different international and national guidelines and recommendations for TB prophylaxis in anti-TNF-treated patients have lowered the incidence of TB by 80–90%, but have not completely eliminated the risk.[18,25,26] The incidence of TB in Spain has diminished during the last decade; Spain has moved down from an intermediate-incidence country (20 cases/100 000 inhabitants in 2003) to a low-incidence country (13.4/100 000 in 2013), though in some regions and cities the incidence is still over 20 cases/100 000/year.[27,28]

Clinical characteristics of TB in our study mirror those of TB found in immunocompromised patients, 60% of them developing disseminated or extrapulmonary disease, as found in other series.[5,6,29,30] In the general population, only 18% of TB cases represent extrapulmonary forms and only 2% of patients show disseminated disease. As a result, many patients present atypical symptoms and consequently a high grade of clinical suspicion is required to avoid a delay in diagnosis. Special attention must be paid to patients with unexplained fever, with or without weight loss. In our cohort, 12% of patients required more than 3 months to achieve the correct diagnosis. In most patients in our study, TB was diagnosed within the first 12 months after anti-TNF initiation, 33% in the first 3 months, suggesting that these cases are reactivations of latent TB, as also shown by other authors.[5,31] On the other hand, in 9 patients (18%) TB was diagnosed 1 year later (in 5 patients after 3 years), probably reflecting true reinfections. Regarding time to onset of TB, we found no differences between infliximab- and adalimumab-treated patients, as other authors have pointed out.[32,30] It is worth noting that 80% of patients in the present study had received concomitant immunosuppressive therapy and 44% of them had even received triple immunosuppression also with corticosteroids. Immunosuppressive therapies have shown an increased risk of TB when administered as monotherapy,[33] and a recent systematic review has demonstrated a 13-fold increased risk of TB in patients on combined therapy compared with anti-TNF monotherapy.[34] Thus, more intensive TB screening (i.e. both the TST and the interferon-γ release assay [IGRA]) and a surveillance programme should be advised in these patients.

In 40% of the patients the recommended screening procedures were not fulfilled; in most of them the 2-step TST was not performed, or TB prophylaxis was not administered when required. In a recent cross-sectional survey carried out in 915 high-volume anti-TNF prescribers from the European Union, only 73–80% of gastroenterologists followed TB screening guidelines.[35] Defective screening procedures have also been reported by other authors in up to 80% of TB cases,[8,29,36] increasing the risk of TB 7-fold compared with patients undergoing appropriate screening and prophylaxis recommendations.[31] In these studies, not performing 2-step TST was also the main factor contributing to low compliance with recommendations. This problem of adherence to the guidelines indicates that a greater effort to disseminate national recommendations should be made in order to prevent almost half of TB cases. The repeated supply of reinforcing information by product manufacturers[35] or the inclusion of a TB screening checklist before prescribing anti-TNF[37] may enhance adherence to screening recommendations.

Excluding these 20 patients who had not correctly followed the recommendations, we still report 30 cases of patients who developed TB despite strict compliance with all recommendations. As far as we are aware, this is the largest study reporting this issue in IBD patients. Other authors have previously published case reports[9,21,38,39] and case series[20,26,31,40–42] both in IBD and other immune-mediated diseases. Though the French multidisciplinary RATIO registry collected 69 cases, only 9 patients (13%) had IBD.[2]

There are several possible explanations for the failure of preventive measures. First, though TST has been widely used for over a century for the diagnosis of latent TB, its specificity and sensitivity are low, especially in immunocompromised patients.[43] Some authors have emphasized the limitations of the TST in IBD patients because of their high rates of anergy, specially when treated with corticosteroids or immunosuppressive medication.[44] Using a more stringent cut-off of <5 mm in the TST, the sensitivity of the test would have increased and would have detected more patients with latent TB, as many of the reported cases happened in patients with TST indurations between 5 and 9 mm.[29,45–48] Also, using a two-step TST may increase the sensitivity of the test by 8–14%.[31,49] In recent years the IGRA (as the QuantiFERON-TB Gold In-Tube [QFT-GIT; Cellestis, Carnegie, VIC, Australia] and T-SPOT.TB [T-SPOT; Oxford Immunotec, Abingdon, UK]) has been popularized and is becoming more frequently used for latent TB diagnosis[50,51] because of its higher specificity[52] and sensitivity, especially in immunocompromised hosts.[53–56] Some national guidelines recommend using the IGRA instead of the TST for screening for latent TB before anti-TNF treatment;[57] others recommend using both the TST and the IGRA, whether concomitantly or consecutively.[51,58,61–64] However, although the IGRA has higher specificity and probably better sensitivity for the detection of latent TB,[64,65] it still has some limitations in immunosuppressed patients, with a non-negligible rate of indeterminate results.[53,66,67] In our series, 2 patients had a negative QuantiFERON Gold In-Tube result and another 1 had an indeterminate result; other

authors have also reported TB cases in spite of a negative IGRA result.[47,68,69]

Second, treatment of latent TB is not fully efficacious, mainly because fewer than 80% of patients complete the treatment.[70] In our study, we report 5 patients who developed TB despite receiving chemoprophylaxis (4 patients received a 6-month course and 1 received a 9-month course); in another patient, treatment for latent TB was incomplete because of intolerance. In a retrospective study performed in rheumatology patients, 11 out of 45 patients developed TB, 7 of them despite having received complete latent TB treatment; the remaining 4 cases either refused to take the treatment or stopped it due to hepatotoxicity.[71] Other authors have also reported TB chemoprophylaxis failure,[19,34,39,41,46,47] most of them using 6-month isoniazid courses or incomplete treatments because of adverse effects. Randomized clinical trials and a recent network meta-analysis[72] have shown that completing a 9-month course of isoniazid provides nearly 90% protection against developing TB, while protection falls to around 60% when a 6-month course is used.[73,74] Thus, we suggest that in this group of patients latent TB treatment should be extended for at least 9 months, changing the regimen if isoniazid toxicity occurs. There is also the possibility that some patients were infected with an isoniazid-resistant strain. In recent years, isoniazid–rifamycin short-course regimens for the treatment of latent TB have been recommended.[15] Although this regimen could overcome isoniazid resistance, TB cases in patients treated with these regimen have also been described.[71]

Third, more attention has to be paid to medical history and TB risk factors, including being born or having travelled to endemic areas, recent or past TB contacts, and being an institutionalized patient.[69] In the RATIO registry, patients born in an endemic area had a 10.3-fold higher risk of developing TB.[29] The British Thoracic Society recommendations include clinical risk stratification for choosing patients as candidates for prophylaxis.[15]

Finally, new infection during long-term anti-TNF treatment may still occur. In the present study, 18% of cases were diagnosed later than 1 year after anti-TNF initiation, as reported by other authors.[20,29,71] To minimize this problem, some authors advocate repeating TST or IGRA tests annually for patients in long-term anti-TNF treatment.[68,75,76]

Although different guidelines state that restarting anti-TNF in patients who are diagnosed with TB is safe,[48,77–79] data analysing this issue are scarce.[29,47,80,81] In the RATIO registry,[29] 2/69 cases maintained anti-TNF while antituberculous treatment was administered and another 8 patients restarted anti-TNF after a median of 5.8 months. None of them had a recurrence of TB. In a Korean study, 8 patients were re-administered anti-TNF without reporting TB recurrence.[47] In a Greek report,[82] 3 out of 5 patients with TB were restarted on anti-TNF, all of them after completion of antituberculous treatment, without evidence of TB reactivation. There is only 1 reported case of TB reactivation in this situation; Masiá et al.[83] described a case of TB reactivation 11 months after resumption of anti-TNF in a 19-year-old CD patient. In our study 17 patients were restarted on anti-TNF after TB diagnosis, 5 of them while still receiving antituberculous treatment. To the best of our knowledge, this is the largest series reporting anti-TNF resumption after TB diagnosis. We found no cases of TB recurrence or worsening; therefore, our data support the concept that restarting anti-TNF after antituberculous treatment has been initiated is safe.

The present study has several limitations, mainly because of its retrospective nature and voluntary participation. Also, we did not include in the analysis ethnicity or other comorbidities influencing the risk of TB, such as diabetes or chronic renal failure. On the other hand, this is the largest study reporting TB cases in anti-TNF-treated IBD patients and the largest series studying the resumption of anti-TNF in patients with a TB diagnosis. Also, the study includes only TB cases in IBD patients after the publication of preventive guidelines, making the population included more homogeneous than those in previous studies.

In conclusion, TB remains an important problem in anti-TNF-treated patients despite the adoption of preventive measures, especially in countries with moderate or high prevalence of TB. As almost half of the cases occur because of failure to adhere to the guidelines, greater effort in disseminating national and international recommendations for TB prevention is needed. Also, guidelines should be improved to minimize TB risk in this population, the effectiveness of measures such as increasing TST sensitivity and including IGRA in the evaluation of latent TB and lengthening its treatment remains to be proved. Retreatment with anti-TNF after a TB diagnosis seems to be safe.

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Conflict of Interest

The authors have no conflict of interest to declare regarding this paper.

Author Contributions

D. Carpio designed the study, collected, analysed and interpreted the data and wrote the paper. M. Barreiro-de-Acosta, M. Chaparro, D. Ginard and X. Calvet reviewed the draft and made important contributions to the final manuscript. All authors collected data and reviewed and approved the final version of the manuscript.

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