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Original Article

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Negative Screening Does Not Rule Out the Risk of Tuberculosis in Patients with Inflammatory Bowel Disease Undergoing Anti-TNF Treatment: A Descriptive Study on the GETAID Cohort

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Abstract

Aim: to describe the characteristics of incident cases of tuberculosis [TB] despite negative TB screening tests, in patients with inflammatory bowel disease [IBD] undergoing anti-TNF treatment, and to identify the risk factors involved.

Abbreviations: CD: Crohn's disease; GETAID: Groupe d'études et thérapeutiques des affections inflammatoires du tube digestif; IBD: inflammatory bowel disease; IGRA: Interferon Gamma Release Assay; IQR: interquartile range; TB: tuberculosis; UC: ulcerative colitis.

Methods: A retrospective descriptive study was conducted at GETAID centers on all IBD patients undergoing anti-TNF treatment who developed TB even though their initial screening test results were negative. The following data were collected using a standardized anonymous questionnaire: IBD, and TB characteristics and evolution, initial screening methods and results, and time before anti-TNF treatment was restarted.

Results: A total of 44 IBD patients [including 23 men; median age 37 years] were identified at 20 French and Swiss centers at which TB screening was performed [before starting anti-TNF treatment] based on Tuberculin Skin Tests [*n* = 25], Interferon Gamma Release Assays [*n* = 12], or both [*n* = 7]. The median interval from the start of anti-TNF treatment to TB diagnosis was 14.5 months (interquartile range [IQR] 25–75: 4.9–43.3). Pulmonary TB involvement was observed in 25 [57%] patients, and 40 [91%] had at least one extrapulmonary location. One TB patient died as the result of cardiac tamponade. *Mycobacterium tuberculosis* exposure was thought to be a possible cause of TB in 14 cases [32%]: 7 patients [including 6 health care workers] were exposed to occupational risks, and 7 had travelled to endemic countries. Biotherapy was restarted on 27 patients after a median period of 11.2 months [IQR 25–75: 4.4–15.2] after TB diagnosis without any recurrence of the infection.

Conclusion: Tuberculosis can occur in IBD patients undergoing anti-TNF treatment, even if their initial screening results were negative. In the present population, TB was mostly extrapulmonary and disseminated. TB screening tests should be repeated on people exposed to occupational risks and/or travelers to endemic countries. Restarting anti-TNF treatment seems to be safe.

Key Words: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; tuberculosis; screening; anti-TNF

1. Introduction

Anti-TNF therapy is associated with clinical benefits to IBD patients, higher rates of mucosal healing, fewer hospital stays and surgical procedures, and improves patients' quality of life.[1,2] However, anti-TNF agents are known to increase the risk of opportunistic infections, especially tuberculosis [TB].[3]

In 2001, shortly after the use of infliximab was launched, Keane et al.[4] reported 70 cases of TB in patients undergoing anti-TNF therapy. Most of these cases were severe: 12 patients died and 57% developed extrapulmonary TB. Since this study, systematic TB screening based on Tuberculin Skin Tests [TSTs] and chest X-rays has been recommended whenever treatment with anti-TNF therapy is envisaged. Since 2006, The French National Authority for Health has recommended that screening based on Interferon Gamma Release Assays [IGRAs] and chest X-rays should be performed before starting anti-TNF therapy.[5] The guidelines differ from one country to another: TST is recommended in some countries and IGRAs in others. Incident cases of TB were recently reported in Spain and Belgium in 11 IBD patients undergoing anti-TNF therapy, although they had obtained negative initial TB screening results.[6–8] These patients' TB was mostly severe and characterized by a high rate [= taux] of extrapulmonary involvement. In this situation, it is recommended to stop the anti-TNF therapy and start anti-TB treatment. Little is known so far about the risk factors involved in the occurrence of TB in patients under anti-TNF therapy, and few studies have focused so far on the reintroduction of biological agents into the treatment of relapsing IBD patients whose TB has been successfully treated. Some authors have suggested that anti-TNF treatment can be restarted after at least 2 months of anti-TB treatment.[3]

The aims of this study were [i] to describe cases of TB that developed despite negative TB screening tests in IBD patients undergoing anti-TNF therapy, [ii] to identify the patients' characteristics associated with TB, [iii] to study the course of IBD and TB in these patients, and [iv] to analyze the benefits of restarting anti-TNF treatment after TB diagnosis and to determine the patients' tolerance of this treatment.

2. Patients and Methods

2.1. Selection of patients

A retrospective study was performed at several tertiary French and Swiss hospital centers belonging to the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif [GETAID]. Gastroenterologists belonging to the GETAID group were asked to report any cases of TB diagnosed in IBD patients who obtained negative TB screen test results and were given at least one anti-TNF injection. Patients were retrospectively recruited from June 2001—the starting date of the systematic screening for TB before starting an anti-TNF agent in the European Union—to August 2015. Patients with positive TB screen test results, those who did not undergo these tests and those with indeterminate IGRA test results were not included in the study. Patients were recruited from individual databases and/or standardized hospital inpatient diagnostic datasets.[9] The procedure used was approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé [CCTIRS No. 15568].

2.2. Data collected

A standardized anonymous questionnaire was used to collect data on each patient, which were stored in a database [FileMaker Pro 13®].

2.2.1. Inflammatory bowel disease

The following characteristics were recorded on each patient: age at IBD diagnosis, gender, smoking status, duration of the disease, location and phenotype of Crohn's disease [CD] according to the Montreal classification, location of ulcerative colitis [UC] according to the Montreal classification, previous intestinal resections,

IBD activity, Harvey Bradshaw [HBI] score for CD, and partial Mayo score for UC [Mayo score without endoscopy] [remission was defined as an HBI score of <4 for CD and a partial Mayo score of <2 for UC at the time of TB diagnosis], duration of IBD treatment (including immunosuppressors [thiopurines, methotrexate] and anti-TNF [infliximab, adalimumab]), main indication for prescribing anti-TNF treatment, duration of anti-TNF, and associated immunosuppresor and/or corticosteroid treatment.

2.2.2. Tuberculosis

The following characteristics were recorded for each patient: screening for TB before starting anti-TNF treatment (a thorough history and clinical examination, TST and/or IGRA [Quantiferon®], chest-X ray or chest computed tomography), ongoing treatment at the time of the screen tests, risk factors [occupational risks, travelling to endemic countries], age at TB diagnosis, location of TB, TB treatment, TB outcome, time between starting anti-TB treatment and re-starting anti-TNF.

TB diagnosis was based on the patients' history, clinical examination, radiological signs, and bacteriological and/or pathological findings.

2.3. Statistical analysis

Descriptive statistics were used to analyse patients' baseline characteristics. Medians with interquartile ranges [IQRs] or means with standard deviations were calculated on continuous data, and percentages were computed on discrete data.

The Chi-square test and Fisher's exact test were used to compare early and late TB patients, respectively. Early TB was defined as cases of TB diagnosed less than 12 weeks after anti-TNF was started. This time-point was chosen in view of the study of Keane et al., in which a median interval of 12 weeks was recorded between starting anti-TNF to the onset of TB. A 2-tailed *p*-value of <0.05 was taken to be statistically significant. Statistical analysis was performed with SPSS software [version 18.0, Chicago, IL].

3. Results

3.1. IBD characteristics

Forty-four patients with TB undergoing anti-TNF treatment, who had obtained negative screen test results prior to the treatment (36 [82%] with CD and 8 [18%] with UC), were identified at 20 French and Swiss centers. The main characteristics of the IBD and the ongoing treatment at the time of TB diagnosis are presented in Table 1. Six patients [14%] were on anti-TNF induction therapy [with infliximab, none with adalimumab] when TB was diagnosed, and 38 [86%] were on maintenance therapy [10 with adalimumab and 28 with infliximab]

Table 1. Characteristics of patients with inflammatory bowel disease at the time of tuberculosis diagnosis.

Characteristics	*n* [%]
Age	
-range	18.6–66
-median [years]	37 [IQR 25–75: 25–46]
Sex	
-Men	23 [52%]
-Women	21 [48%]
Type of IBD	
-Crohn's disease	36 [82%]
-Ulcerative colitis	8 [18%]
Remission	
-Harvey Bradshaw <4	18 [50% of CD]
-Mayo score[a] <2	4 [50% of UC]
CD location	
-L1	7 [19%]
-L2	6 [17%]
-L3	23 [64%]
-L4	4 [11%]
CD behavior	
-B1	15 [42%]
-B2	13 [36%]
-B3	7 [19%]
-P[b]	18 [50%]
UC location	
-E1	0
-E2	4 [50%]
-E3	4 [50%]
Ongoing treatment	
-corticosteroids	6 [14%]
-immunosuppressors	
-azathioprine	12 [27%]
-methotrexate	3 [7%]
-anti-TNF	
-infliximab	34 [77%]
-adalimumab	10 [23%]
-triple immunosuppression	4 [9%]

[a]Mayo score without endoscopy; [b]P, anoperineal lesions; UC, ulcerative colitis; CD, Crohn's disease

3.2. Screening and risk factors for TB

TB screening was performed as follows before the anti-TNF treatment was started: 25 [57%] patients underwent TSTs alone [including 6 taking corticosteroids alone, 5 taking azathioprine alone, 1 taking both agents, 3 taking methotrexate alone and 10 who had been given no treatment]; 12 [27%] were tested with IGRAs [Quantiferon®] only [including 5 with corticosteroids monotherapy, 2 with azathioprine monotherapy, 2 with both agents, 1 with methotrexate monotherapy and 2 with no treatment]; and 7 [16%] had both TSTs and IGRAs [including 4 with azathioprine monotherapy, 1 with azathioprine and corticosteroids, and 2 with no treatment]. At the time of these TB screening tests, 11 [25%] were being treated with corticosteroids, 11 [25%] with azathioprine, 4 [9%] with corticosteroids and azathioprine, and 4 [9%] with methotrexate [Table 2]. They all had normal chest X-rays.

The median time between starting anti-TNF and TB screening was 28 days (IQR [25–75]: 10–47).

Data about Bacille Calmette–Guérin [BCG] vaccination were available in 8 cases: all of these patients were vaccinated during the first year of life according to French authorities. Among these 8 patients, 3 were taking TST alone, 3 were taking IGRA alone, and 2 were taking both TST and IGRA. Two patients were undergoing no treatment at the time of the screening, 1 was taking corticosteroids, 2 were taking azathioprine, 2 were taking both corticosteroids and azathioprine, and one was taking methotrexate.

Seven [16%] patients were exposed to occupational risks of TB, including 6 hospital health care professionals. Seven [16%] patients had travelled recently to endemic countries [see Table 2]. All of them had travelled to visit family and relatives for more than 2 weeks.

3.3. TB characteristics

The median interval from the first anti-TNF injection to TB diagnosis was 14.5 months [IQR 25–75: 4.9–43.3] [Table 2]. Six patients [14%] had early TB [within the three first months], and 38 [86%]

Table 2. Tuberculosis characteristics.

Characteristics	*n* [%]
Type of screening	
-TST only	25 [57%]
-IGRA only	12 [27%]
-TST and IGRA	7 [16%]
-Normal chest-X-ray	44 [100%]
-Chest scan	0 [0%]
Ongoing treatment at the time of the screening	30 [68%]
-corticosteroids only	11 [25%]
-azathioprine	11 [25%]
-corticosteroids and azathioprine	4 [9%]
-methotrexate	4 [9%]
Risk factors	
at-risk profession	7 [16%]
- health care workers	6
- other [stallholder]	1
Recent travel in endemic country	7 [16%]
-North Africa	4
-India	1
-Africa	1
-Turkey	1
Time between the first injection of anti-TNF treatment and TB diagnosis	
-<3months	6 [14%]
-3 to 12 months	13 [29%]
-12 to 24 months	7 [16%]
->24 months	18 [41%]
Median time of TB diagnosis [months] [IQR 25–75]	14.5 [4.9–43.3]
TB location	
-pulmonary tuberculosis	
-extra-pulmonary	4 [9%]
-pulmonary and extra-pulmonary	19 [43%]
-disseminated	21 [48%]
-extra-pulmonary location:	19 [43%]
-pleural	11
-lymph nodes	23
-peritoneum	6
-pericardium	4
-spleen	3
-liver	1
-joints	1
-bones	1
-ETN	2
-ileo-colic	1
-kidney	1
-jugular-carotid	1
-ophtalmologic	1

TST, Tuberculin Skin Test; IGRA, Interferon Gamma Release Assay; TB, Tuberculosis, ENT, Eyes, Nose, Throat.

had late TB [more than 3 months after starting anti-TNF treatment]. Among the 6 patients with TB diagnosed within the first 3 months, a short period between anti-TNF starting and TB infection suggests reactivation of latent infection rather than a new infection.

Two-thirds of the patients had fever and 90% had asthenia at the time of TB diagnosis. Among the 25 patients with a pulmonary location, diagnosis was based on acid-fast bacilli or sputum cultures. Twenty-two patients underwent a biopsy to confirm the TB diagnosis. Four patients [9%] had pulmonary tuberculosis with no other location [Table 2]. Twenty-one patients [48%] had both pulmonary and extrapulmonary TB, and 19 patients [43%] had extrapulmonary TB without any pulmonary involvement. Nineteen patients [43%] had disseminated TB [defined as miliary, or at least two distal organs involved]: one of them had peritoneal TB with pleural and lymph-node locations/involvement, for example. Manifestations of extrapulmonary TB are presented in Table 2. In addition, a hemophagocytic lymphohistiocytosis syndrome was observed in 3 patients. One patient had TB with spleen, pleural, pericardic, lymph nodal, and pulmonary involvement. He died of cardiac tamponade 9 days after TB diagnosis. Two patients had miliary TB. One of them was given quadruple TB treatment plus corticosteroids and etoposide for 2 months, and recovered completely within 2 months. The other one was given quadruple TB treatment alone, and recovered completely within 3 weeks.

No differences were observed between the two groups of patients with early and late TB [Table 3].

3.4. Treatment for tuberculosis

All patients stopped the anti-TNF treatment at TB diagnosis and started quadruple therapy with isoniazid, rifampicin, ethambutol, and pyrazinamide, as recommended by the French national consensus guidelines.[10] Quadruple TB treatment was generally well tolerated. Several adverse effects were reported, however: 4 were due to rifampicin [3 vomiting, 1 allergy], 5 to isoniazid [3 cytolytic hepatitis, 2 vomiting], 4 to pyrazinamide [2 cytolytic hepatitis, 1 gout, 1 arthralgia] and none to ethambutol. *Mycobacterium tuberculosis* was resistant to isoniazid in 2 cases and to pyrazinamide in 1. 23 patients were treated for 6 months, 13 patients for 6 to 9 months, and 4 patients for 9 to 12 months.

3.5. TB outcome

Thirty-seven [84%] patients were cured by the end of the anti-tubercular treatment. Five patients [11%] continued to have after-effects such as: night sweats, cough, bronchial dilatation, pleural sequela, and uretral stenosis with hydronephrosis. Night sweats and coughing were taken to be TB sequelae. One patient died of TB pericarditis complicated by a cardiac tamponade. In one case, immune reconstitution inflammatory syndrome was observed 6 months after stopping anti-TNF treatment. The patient was treated with a high dose of corticosteroids, with rapid recovery.

3.6. IBD outcome and restarting anti-TNF

Among the 44 patients, anti-TNF treatment was restarted in the case of 23 patients [52%] after a median period of 11.2 months [IQR 25–75: 4.4–15.2] since TB diagnosis, vedolizumab was started in the case of 3 patients, and ustekinumab in the case of 1 patient [Table 4]. Only 2 patients were restarted on anti-TNF treatment <2 months after starting anti-tubercular treatment, 4 after a period of 2–4 months, 1 after a period of 4–6 months, 5 after a period of 6–12 months, 7 after a period of 12–24 months, and 4 after a period of 24 months after starting anti-tubercular treatment. After anti-TNF treatment was restarted, no cases of TB relapse were reported during a median follow-up period/time of 2.8 years (IQR [25–75]: 1.1–5.8).

4. Discussion

This is the largest series of TB cases described so far in IBD patients undergoing anti-TNF treatment since TB screening procedures have been widely adopted. Importantly, all these cases occurred in patients whose previous TB screening tests were negative.

Table 3. Early TB and late TB.

Characteristics	Early TB [*n* = 6]	Late TB [*n* = 38]	*p*
Crohn's disease	5 [83%]	31 [82%]	NS
Ulcerative colitis	1 [17%]	7 [18%]	NS
Ongoing treatment at the time of TB screening			
-none	0 [0%]	14 [37%]	NS
-corticosteroids only	3 [50%]	8 [21%]	NS
-azathioprine	2 [33%]	9 [24%]	NS
-corticosteroids and azathioprine	1 [17%]	3 [8%]	NS
-methotrexate	0 [0%]	4 [10%]	NS
Type of screening			
-TST only	4 [67%]	21 [55%]	NS
-TST and IGRA test	0 [0%]	7 [18%]	NS
-IGRA test only	2 [33%]	10 [26%]	NS
Risk factors			
At-risk profession	1 [17%]	6 [16%]	NS
Recent travel in endemic country	1 [17%]	6 [16%]	NS
Ongoing treatment at the time of TB diagnosis [except anti-TNF]			
-none	2 [33%]	25 [66%]	NS
-corticosteroids only	1 [17%]	1 [3%]	NS
-azathioprine	1 [17%]	8 [21%]	NS
-corticosteroids and azathioprine	2 [33%]	1 [3%]	NS
-methotrexate and corticosteroids	0 [0%]	1 [3%]	NS
-methotrexate	0 [0%]	2 [5%]	NS
TB location			
-pulmonary tuberculosis	0 [0%]	4 [11%]	NS
-extra-pulmonary	3 [50%]	16 [42%]	NS
-pulmonary and extra-pulmonary	3 [50%]	18 [47%]	NS
-disseminated	3 [50%]	16 [42%]	NS

TST, Tuberculin Skin Test; IGRA, Interferon Gamma Release Assay; TB, Tuberculosis; anti-TNF, anti–tumor necrosis factor; NS, not statistically significant.

Table 4. Inflammatory bowel disease treatment management.

Characteristics	*n* [%]
Median time of follow-up [years]	2.8 [IQR 25–75: 1.1–5.8]
Anti-TNF restarted	
No	21 [48%]
Yes	23 [52%]
Time between anti-TNF reintroduction and TB diagnosis	
<2 months	2
2 to 4 months	4
4 to 6 months	1
6 to 12 months	5
12 to 24 months	7
>24 months	4
Median time between anti-TNF reintroduction and TB diagnosis [months] [IQR 25–75]	11.2 [4.4–15.2]
Vedolizumab treatment	3
Ustekinumab treatment	1

The occurrence of TB in these patients may have resulted either from failure of the TB screening tests in patients with latent TB or from a new/recent infection. Since the study by Keane et al. was published in 2001, screening for TB has been mandatory before starting anti-TNF treatment.[4] In France, The French National Authority for Health has recommended since 2006 that IGRA and a chest X-ray should be performed before starting anti-TNF therapy, but TST can also be performed.[5]

In this study, TB screening was based on TST alone in 25 cases [57%], IGRA alone in 12 cases [27%], and both TST and IGRA in 7 cases [16%]. TST has a rather low sensitivity, especially in the case of patients undergoing immunosuppressive therapy, and also shows a lack of specificity for pathogenic *Mycobacterium tuberculosis* complex strains due to cross-reactivity with BCG vaccination and environmental *Mycobacteria*.[11] BCG vaccination is recommended in France for children with a high risk of TB [those born in an endemic country, those living in Paris and the surrounding region or Guyana, those whose parents originate from endemic countries, etc.] and for health care workers.[12] In July 2007, compulsory BCG vaccination was replaced by a strong recommendation to vaccinate children with a high risk of tuberculosis. A national survey was conducted to measure the rate of BCG vaccination coverage in children since this date. The BCG vaccination rate was found to be 89.8% [81.4–94.7] in Paris and the surrounding region and 61.7% [53.8–69.0] in the other regions.[13]

In a study by Belard et al., oral prednisolone was found to greatly reduce the efficiency of TST, whereas immunosuppressive treatment did not have detrimental effects of this kind.[14]

Among the patients included in the present study, 30 [68%] were being treated with immunosuppressors [*n* = 19] and/or corticosteroids [*n* = 15] when they underwent TB screening.

The results of IGRA assays are also negatively impacted by immunosuppressive therapy.[15] In the study by Wolf et al.,[16] patients undergoing immunosuppressive therapy had a higher risk of having indeterminate IGRA test results [16%], with an odds ratio of 2.2 [95% CI: 1.6–2.9] versus patients undergoing no immunosuppressive treatment. Among the seven studies involved in the meta-analysis performed by Shahidi et al. to assess the impact of immunosuppressive therapy on IGRA tests, four were available here for calculating the pooled estimates, which showed that immunosuppressive therapy significantly affects IGRA results [pooled

OR 0.37, 95% CI: 0.16–0.87; $p = 0.02$].[11] In the study by Wong et al.,[15] IBD patients undergoing immunosuppressive treatment had a significantly lower positive IGRA positive rate [$p = 0.002$] than immunosupressant-naïve IBD patients. This difference seemed to be most marked in the case of patients taking azathioprine [$p = 0.006$]. Mariette et al.[17] compared the results of TST and IGRA TB screening tests in a cohort of 392 patients prior to starting anti-TNF therapy: the results of TST and IGRA tests were positive in 35.2% and 9.9% of the patients, respectively [$p < .0001$]. The decision to treat patients for latent TB would have changed the outcome for 113 patients [28.8%, 95% CI: 24.4% to 33.6%] if TST had been replaced by IGRA tests.

These findings suggest that the following procedure should be adopted: [i] for patients who have been vaccinated with BCG, IGRAs may be the best choice, because BCG increases false TST positivity; [ii] screening for latent TB should no doubt be performed before starting immunosuppressive therapy on IBD patients.

The second reason for the results obtained here is the occurrence of new cases of TB. Groups with a risk of TB are persons with HIV [no cases of HIV were included in this study], patients undergoing hemodialysis or organ transplantation, prisoners, health care workers, immigrants from countries at risk, homeless persons, drug users, and elderly persons.[18] In the present study, seven patients were exposed to occupational risks, and seven had travelled to TB-endemic countries.

The results obtained in this study confirm that extrapulmonary TB occurs more frequently than pulmonary TB in patients undergoing anti-TNF treatment. As initially observed in the study by Keane et al.,[4] where 40 patients out of 70 had extrapulmonary TB, 40 [91%] of the present patients had at least, extrapulmonary TB and 19 [43%] had disseminated TB [see Table 2]. In 2012, Jauregui-Amezaga et al.[6] reported the occurrence of 7 cases of TB in a cohort of 423 patients undergoing anti-TNF treatment who had initially obtained negative TB screening results; in 4 of them, TB was present in extrapulmonary locations. In the study by Abreu et al., 15 of the 25 patients who contracted TB while undergoing anti-TNF treatment [60%] had extrapulmonary TB, amounting to a significantly higher rate than in a control group [$n = 18$, 25%] of out-patients with TB but no significant comorbidities [IBD or neoplastic conditions] or immunosuppressive treatment.[19]

The physiopathology of disseminated TB can help to explain these results. During the process of TB infection, alveolar macrophages are contaminated by *Mycobacterium tuberculosis*,[20] inducing TNFα synthesis by macrophages and the formation of granuloma, preventing the dissemination of the disease. When a patient is undergoing anti-TNF treatment, the process of granuloma formation is impaired, which favours the dissemination and reactivation of TB.[8]

It may be necessary to restart anti-TNF treatment in some patients with relapsing IBD. This was recommended in the latest ECCO guidelines, starting no earlier than 2 months after the beginning of treatment with anti-TB agents.[3] In the present study, 23 patients [52%] had restarted taking anti-TNF treatment, vedolizumab was started in the case of 3 patients, and ustekinumab in that of 1 patient after a median time of ~1 year after starting anti-TB treatment. No recurrence of TB was subsequently observed after a median time of ~3 years. In a recent study by Abreu et al.,[21] the authors also concluded that restarting anti-TNF therapy after treating patients successfully for a recurrence of TB seems to be safe. No recurrence of TB was reported during a median follow-up period of >2.5 years in 8 patients whose anti-TNF therapy was resumed after the diagnosis and treatment of TB.

Few data are available so far about starting treatment with vedolizumab or ustekinumab on patients in whom TB has occurred while they were undergoing anti-TNF treatment. In the present study, 3 patients started with vedolizumab and one with ustekinumab. This strategy may have been chosen because of the mechanism of action of vedolizumab, which is gut-specific. However, one case of TB has been described in the Gemini 1 and 2 trials.[22,23] Finally, one case of TB reactivation has been described in a patient treated with ustekinumab for psoriasis.[24]

This study on a large cohort of patients followed at several expert IBD centers belonging to the GETAID group has several strengths. It yielded new safety data regarding the restart of anti-TNF in patients treated for TB incurred while they were undergoing anti-TNF treatment. However, the study has some limitations because of its retrospective nature, which may have resulted in a loss of patients from follow-up and missing data—especially clinical and microbiological studies concerning tuberculosis disease—as well as some selection bias. Due to the retrospective and multicentric design of the study, the estimation of the frequency with which TB occurs following negative screening was not possible.

In conclusion, this study on a large series of patients confirms that TB can occur in IBD patients even though they have obtained negative TB screen test results. The patients in whom this occurred mostly had extrapulmonary TB. The results obtained here suggest that screening for latent TB should be performed before any immunosuppressive therapy is initiated. In the case of IBD patients treated with anti-TNF who are liable to be exposed to TB in the course of their work or when travelling to endemic countries, IGRA screening could be subsequently repeated 8–10 weeks later. However, this suggestion needs to be confirmed by further studies. Once the TB has been successfully treated, restarting anti-TNF treatment seems to be safe in the case of patients with similar characteristics to those of the present cohort.

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Conflict of Interest

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Author Contributions

[1] Study concept and design; [2] data collection; [3] analysis and interpretation of data; [4] drafting of the manuscript; [5] critical revision of the manuscript for important intellectual content; [6] statistical analysis; [7] technical or material support; [8] study supervision.

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