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## Retrospective Cohort Study

## Active tuberculosis in inflammatory bowel disease patients under treatment from an endemic area in Latin America

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## Abstract

### BACKGROUND

There has been an increase in cases of inflammatory bowel disease (IBD) in recent years. There is also greater access and availability of immunosuppressive and biological agents, which increase the risk of opportunistic infection despite improving the quality of life and promoting mucosal healing. Tuberculosis (TB) remains a public health problem, and it has a high incidence in several countries. Therefore, knowledge of the risk of developing TB in patients with IBD is important.

### AIM

To evaluate the risk of active TB in patients with IBD under treatment from an endemic area in Latin America.

### METHODS

study design, manuscript revision, supervision of the study and full access to all of the data in the study, responsible for the integrity of the data.

#### Institutional review board

**statement:** The Roberto Santos General Hospital Research Ethics Committee approved this research under the opinion number 1935.651/2017. The patients signed the Informed Consent Term before any procedure.

**Informed consent statement:** All study participants identities were anonymized and details that might disclose their identities were omitted. For this type of study formal consent is not required.

#### Conflict-of-interest statement:

Genoile O Santana: Advisory board–Janssen; Speaker–Abbvie, Ferring, Janssen, Takeda and UCB Pharma; Research–Janssen, Lilly, Pfizer, Roche and Takeda. The other authors declare that they have no conflict of interest.

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A standard questionnaire included demographic variables, clinical aspects of IBD disease, history of active TB during treatment, active TB characteristics and evolution, initial screening and results and time from the start of anti-tumor necrosis factor alpha (TNF $\alpha$ ) to TB development.

## RESULTS

Azathioprine, anti-TNF $\alpha$  and the combination of these two drugs were associated with a higher risk of active TB incidence. The TNF $\alpha$  blockers increased the relative risk of developing active TB compared to other treatments. All four multivariable models showed that the use of TNF $\alpha$  blockers alone or in combination with azathioprine was an important risk factor for the incidence of active TB. After adjustment for sex, age, type of IBD and latent TB, anti-TNF $\alpha$  with azathioprine increased the relative risk to 17.8 times more than conventional treatment. Late TB, which was diagnosed 3 mo after the start of anti-TNF $\alpha$ , was the most frequent.

## CONCLUSION

Treatment with anti-TNF $\alpha$  increased the risk of active TB in IBD patients from an endemic area in Latin America. This risk was increased when anti-TNF $\alpha$  was combined with azathioprine. The time from the beginning of the treatment to the active TB diagnosis suggests a new TB infection.

**Key Words:** Inflammatory bowel disease; Therapy; Tumor necrosis factor alpha; Relative risk; Tuberculosis; Latent tuberculosis

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**Core Tip:** We evaluated the relative risk of developing active tuberculosis in patients receiving treatment for inflammatory bowel disease. A total of 301 patients with inflammatory bowel disease were evaluated, and an interview was conducted using a standard questionnaire and a review of the medical record. We identified the treatment during the diagnosis of active tuberculosis and the screening and past treatment for latent tuberculosis. Immunosuppressive therapy, specifically azathioprine, anti-tumor necrosis factor alpha (TNF $\alpha$ ) and the combination of these two drugs, was associated with an increased risk of active tuberculosis. When adjusted for sex, age, type of inflammatory bowel disease (IBD) and latent tuberculosis, anti-TNF $\alpha$  with azathioprine consistently increased the relative risk to 17.8 times more than conventional treatment. This report is the first study in Latin America to assess the relative risk of developing active tuberculosis in patients with IBD undergoing treatment.

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## INTRODUCTION

Inflammatory bowel disease (IBD) has a higher incidence and prevalence in developed countries<sup>[1]</sup>. However, the number of cases is increasing in Latin American countries, including Brazil. A recent systematic review of studies in Latin America and the Caribbean showed an increased incidence in Brazil from 0.68/100000 person-years in 1991-1995 to 5.5/100000 person-years in 2015. The same study showed that the prevalence of Crohn's disease (CD) in Brazil increased from 0.24 per 100000 persons (1986-1990) to 24.1 (2014), and the prevalence of ulcerative colitis (UC) rose from 0.99 to 14.1 during the same period<sup>[2]</sup>. The prevalence was 12.8/10000 persons in the

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Biological therapy emerged with the advent of studies that identified the key presence of pro-inflammatory cytokines in IBD patients<sup>[4,5]</sup>. The appearance and release of drugs blocking tumor necrosis factor alpha (TNF $\alpha$ ) for the treatment of IBD patients changed the course of these diseases and effectively induced clinical remission and mucosal healing<sup>[6]</sup>. Anti-TNF $\alpha$  therapy for the management of immune-mediated inflammatory diseases improved the prognosis and quality of life of these patients. CD patients using anti-TNF $\alpha$  therapy in Brazil increased from 29.6% (2005-2012) to 43.4% (2013/2014)<sup>[2]</sup>. However, an increased risk of infections was also observed as a consequence, including tuberculosis (TB)<sup>[7,8]</sup>.

TB is also a very common infectious disease in Brazil, and it is considered a serious public health problem and life-threatening condition<sup>[9,10]</sup>. Globally, it is estimated that 10 million people develop TB annually, and this number has remained stable according to the United Nations (UN)<sup>[11]</sup>. Brazil reported 73864 new cases of TB in 2019, with an incidence of 35 cases/100000 person-years and ranging between 11.9/100000 person-years and 104.6/100000 person-years. Contact with *Mycobacterium tuberculosis* (Mbt) leads to cure, pathogen latency or active TB. The airway is a gateway for the bacilli, which translocate to the respiratory tract after inhalation, where it finds the macrophage alveoli<sup>[12]</sup>. Dendritic cells or inflammatory monocytes transport Mbt to the pulmonary lymph nodes to initiate T cell stimulation of TNF $\alpha$  and interferon gamma secretion, which contribute to granuloma formation<sup>[12,13]</sup>. Granulomas are characteristic of human TB and are composed of clusters of macrophages and multinucleated giant cells that are surrounded by newly recruited monocyte/macrophage aggregates, neutrophils and lymphocytes<sup>[14,15]</sup>. These granulomas are essential for the control of Mbt, but they also provide an environment for the survival, multiplication, latency and dissemination of Mbt<sup>[16]</sup>.

Several studies investigated the probable association between anti-TNF $\alpha$  therapy and the development of active TB. Previous studies reported several cases of active TB in patients with immune-mediated inflammatory diseases, such as rheumatoid arthritis and ankylosing spondylitis<sup>[8,17]</sup>. Mañosa *et al.*<sup>[18]</sup> reported an incidence of 1.2% (4/330) active tuberculosis in IBD patients under anti-TNF $\alpha$  therapy in Spain. Lee *et al.*<sup>[19]</sup> showed an incidence of active tuberculosis of 1.4% (9/661) in patients with CD who were treated with anti-TNF $\alpha$  in Korea. However, studies in Brazil and Latin America on the development of active TB in patients with IBD under treatment are scarce<sup>[20]</sup>.

In this scenario of high active TB incidence, increased IBD cases and improved access to anti-TNF $\alpha$  therapies, the present study evaluated the risk of active TB and possible associated variables in patients with IBD under treatment in an endemic TB area in Latin America.

## MATERIALS AND METHODS

### Data source and study design

We performed a retrospective cohort study of IBD patients who were followed up at a referral center in Salvador, Bahia, Brazil. The research center is the state's reference center for the treatment of IBD patients and the provision of prescriptions for high-cost drugs. The state health program only released anti-TNF $\alpha$  therapy for CD during the year of the present research. Data from August 2017 to November 2018 were collected. Patients diagnosed with IBD according to the European Crohn's and Colitis Organization (ECCO) consensus criteria<sup>[1]</sup> were included.

A standardized questionnaire was used for each patient under direct interviews and a review of medical charts. The cohort baseline was set as the date of the first immunosuppressive or immunobiological therapy prescription, when the TB screening was first performed. The patients were screened for latent TB before starting immunosuppressive or immunobiological therapy. Medical record reviews and interviews included demographic variables (sex, age), self-declared ethnicity, type of IBD, and clinical aspects of IBD disease (time of diagnosis, age at diagnosis, Montreal classification<sup>[21]</sup>, and ongoing treatment).

The Roberto Santos General Hospital Research Ethics Committee approved this research under the opinion number 1935.651/2017. The patients signed the Informed Consent Term before any procedure.

### Criteria for TB diagnosis

Interviews and medical record review collected data on the history of active TB during

treatment (*e.g.*, time of diagnosis, location, diagnostic criteria, duration of treatment with immunosuppressant and/or anti-TNF $\alpha$  before the diagnosis of active TB), results of tuberculin skin test (TST), and past latent TB infection (LTBI). Patients were classified as positive or negative according to the TST scores, and the following risk factors were considered: Use of immunosuppressive drugs, use of anti-TNF $\alpha$  and chest radiography consistent with past TB. Patients were considered to have a positive TST if the TST result was  $\geq 10$  mm alone or  $\geq 5$  mm with at least one of the risk factors listed above<sup>[9,22]</sup>.

The treatment of LTBI during the research followed the guidance of the Brazilian Ministry of Health for isoniazid from 5 to 10 mg/kg/d, with a maximum dose of 300 mg daily for 6 mo. However, the Ministry of Health changed the treatment of latent tuberculosis in March 2020 to rifampentine associated with isoniazid, with a weekly dose for 3 mo<sup>[23]</sup>.

The Brazilian Ministry of Health defines active TB as a person with typical symptoms of active TB, bacterial confirmation (smear and/or rapid molecular test and/or culture) and chest radiography<sup>[9]</sup>. Active TB was included for analysis when the diagnosis of active TB occurred during the interview or IBD treatment.

### Statistical analysis

The results are presented as the means  $\pm$  SD or proportion. The incidence rate was calculated by the ratio of the number of cases of active TB to the total number of cases evaluated. The crude relative risk (RR<sub>crude</sub>) of active TB development in patients treated with anti-TNF $\alpha$ , azathioprine and anti-TNF $\alpha$  plus azathioprine compared to other treatments was obtained with the respective 95%CI. Adjusted RR (RR<sub>adj</sub>) for age, sex, type of IBD and latent TB was calculated using Poisson regression with robust variance (sex-model 1; sex and IBD type-model 2; sex, IBD type, latent TB-model 3; and sex, age, IBD type, latent TB-model 4). Statistical analyses were performed using SPSS software (version 21.0, Chicago, IL) and Stata<sup>®</sup>, version 13.3. A *P* value < 0.05 was considered statistically significant.

## RESULTS

A total of 301 patients were evaluated, including 186 (61.8%) patients with UC and 115 (38.2%) patients with CD. The mean  $\pm$  SD age was 45.8  $\pm$  15.0 years. There was a higher frequency of females (188/301; 62.5%) and patients from urban areas (244/301; 81.1%). The self-declared skin color was mixed race more frequently, with 145 (52.5%), followed by blacks with 109 (36.2%). Demographic and clinical characteristics are summarized in Table 1.

Overall, 131 (43.5%) patients were on immunosuppressive/biological therapy. Twenty-seven (9.0%) patients received anti-TNF $\alpha$  as a monotherapy, 31 (10.3%) patients received anti-TNF $\alpha$  associated with azathioprine, 3 (1.0%) patients received anti-TNF $\alpha$  treatment associated with methotrexate, and 70 (23.3%) patients only used azathioprine (Table 2).

TST was performed in 184 patients, and chest radiography was performed in 142 patients to screen for LTBI. Twenty (10.9%) patients were diagnosed and treated for LTBI. Eight (5.6%) patients had X-rays suggestive of TB sequelae. The TST was greater than or equal to 10 mm in 20 (10.9%) patients.

Eight (2.6%) patients developed active TB during treatment, four (50%) of the patients with UC and four (50%) of the patients with CD. The IBD duration in patients who developed active TB was 111.2  $\pm$  58.9 mo. The age of patients who developed active TB during treatment was 40.3  $\pm$  14.7 years at the time of the interview. Six (75%) patients were male. The mean  $\pm$  SD time between the start of anti-TNF $\alpha$  therapy and the diagnosis of active TB was 20.0  $\pm$  18.7 mo. One patient developed active TB three months after the start of anti-TNF $\alpha$  therapy, and the other three patients developed TB after more than 3 mo. Two patients received treatment with mesalazine, one patient received mesalazine associated with azathioprine, and one patient received azathioprine only.

Extrapulmonary TB was diagnosed in two patients (25%). Five patients (62.5%) developed active TB, despite the negative screening for LTBI. Three (37.5%) patients underwent treatment for LTBI (Table 3).

Latent tuberculosis was a risk factor for active tuberculosis (RR<sub>crude</sub> = 8.28; 95%CI: 2.13-32.18, Table 4).

The frequencies of active TB in patients undergoing anti-TNF $\alpha$  therapy and with infliximab and adalimumab were 6.5% (4/61), 7.1% (2/28) and 6.1% (2/33),

**Table 1 Clinical and demographic characteristics of 301 inflammatory bowel disease patients from a referral center**

Characteristics (total n = 301)	n (%)
Type of IBD	
Crohn's disease	115 (38.2)
Ulcerative colitis	186 (61.8)
Age (yr) <sup>1</sup>	45.8 (15.0)
Duration of the disease (mo) <sup>1</sup>	104.9 (80.3)
CD Montreal - age at diagnosis	
A1 (< 16 yr)	5 (4.35)
A2 (17 to 40 yr)	81 (70.43)
A3 (> 40 yr)	29 (25.22)
CD Montreal - disease location	
L1 (terminal ileum)	21 (18.4)
L2 (colon)	49 (43.0)
L3 (ileum colic)	44 (38.6)
L4 associated with L1	4 (3.6)
L4 associated with L2	4 (3.6)
L4 associated with L3	6 (5.4)
CD Montreal-disease behavior	
B1 (inflammatory)	59 (53.2)
B2 (stricture)	25 (22.5)
B3 (penetrating)	27 (24.3)
B1 associated with perianal	25 (22.5)
B2 associated with perianal	6 (5.4)
B3 associated with perianal	14 (12.6)
UC location	
Proctitis	23 (12.7)
Left colitis	79 (43.6)
Extensive colitis	79 (43.6)

<sup>1</sup>data expressed as a mean ± SD. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis.

respectively. The four patients received combination therapy with azathioprine. Therapy with immunosuppressants, specifically azathioprine, anti-TNF $\alpha$  and the combination of these two drugs, were associated with a higher risk of active tuberculosis, with RR<sub>crude</sub> values of 5.85 (1.20-28.48); 3.93 (1.01-15.29) and 9.03 (2.38-34.28), respectively (Table 4).

Multivariate analysis consistently reinforced that therapy with TNF $\alpha$  blockers significantly increased the relative risk of developing active TB compared to other treatments. Four multivariable models were evaluated, and the use of TNF $\alpha$  blockers alone or in combination with azathioprine was an important risk factor for the incidence of active TB in all models. When adjusted for sex, age, type of IBD and latent TB, anti-TNF $\alpha$  combined with azathioprine consistently increased the relative risk to 17.8 times more than conventional treatment (95%CI: 5.91-53.67;  $P < 0.001$ , Table 5).

Latent TB was an independent risk factor for the incidence of new cases of active tuberculosis with the use of isolated TNF $\alpha$  blockers and azathioprine-associated use.

**Table 2** Ongoing treatment of inflammatory bowel disease patients from a referral center

Medicaments	IBD, n (%)	CD, n (%)	UC, n (%)
Sulfasalazine	63	10 (8.7)	53 (28.5)
Oral Mesalazine	102	7 (6.1)	95 (51.1)
Topic Mesalazine	125		125 (67.2)
Azathioprine	70	42 (36.5)	28 (15.1)
Azathioprine + Anti-TNF $\alpha$	31	28 (24.3)	3 (1.6)
Methotrexate + Anti-TNF $\alpha$	3	3 (2.6)	
Anti-TNF $\alpha$	30	29 (25.2)	1 (0.5)
Corticoid	2	2 (1.7)	

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; Anti-TNF $\alpha$ : Anti-tumor necrosis factor alpha.

**Table 3** Clinical and demographic characteristics of patients with inflammatory bowel disease who developed tuberculosis from a referral center

Sex/age	IBD type	IBD duration (months)	Previous TB	Treatment during TB	Anti TNF- $\alpha$ time before TB (months)	Chest X-ray screening LTBI	TST screening LTBI	LTBI treatment	Diagnostic TB	TB location
F/23	CD	26	No	IFX + AZA	9	Normal	Negative	No	Smear	Pulmonary
F/30	CD	180	No	IFX + AZA	45	Normal	Negative	No	Biopsy	Pleural
M/45	CD	144	No	ADA + AZA	3	Normal	Negative	No	Biopsy	Pleural
M/31	CD	132	No	ADA + AZA	24	Normal	Negative	No	Sputum culture	Pulmonary
M/32	UC	36	No	MSL		Changed	Negative	Yes	Sputum culture	Pulmonary
M/38	UC	96	No	MSL		Normal	Positive	Yes	Sputum culture	Pulmonary
M/63	UC	180	No	MSL + AZA		Normal	NR	No	Smear	Pulmonary
M/61	UC	96	No	AZA		Changed	Positive	Yes	Sputum culture	Pulmonary

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; TB: Tuberculosis; NR: No registry; LTBI: Latent tuberculosis infection; TST: Tuberculin skin test; IFX: Infliximab; ADA: Adalimumab; AZA: Azathioprine; MSL: Mesalazine.

## DISCUSSION

According to the WHO<sup>[11]</sup>, Brazil is one of the 30 countries with the highest TB burden. Therefore, the risk of active TB is near high levels in Brazil. However, despite being endemic for TB, little is known about the development of active TB in IBD patients under treatment. Our study observed an increased risk of active TB consistent with the use of immunosuppressants, especially after adjusting for age, sex, type of IBD and latent TB. Specifically, the combination therapy with anti-TNF $\alpha$  and azathioprine increased the risk of active TB by nearly 18-fold compared to conventional treatment. To our knowledge, this report is the first study performed in northeastern Brazil, which is an endemic region of TB in Latin America that is characterized by low development indicators, to consistently demonstrate this association.

Our results of the treatment of LTBI were similar to several previous studies. This finding is similar to countries with lower rates of TB, such as Spain, where Taxonera *et al*<sup>[24]</sup> reported that the occurrence of positive TST was 11.5% in IBD patients undergoing screening for LTBI. Another Spanish study found that 30 (7.0%) patients with IBD had LTBI prior to treatment with anti-TNF $\alpha$ <sup>[25]</sup>. A 2015 Korean study<sup>[6]</sup> assessed the risk of active TB in patients with IBD using anti-TNF $\alpha$  therapy and found a frequency of LTBI of 10.6%. Kim *et al*<sup>[26]</sup>, used chest radiography, IGRA and TST as

**Table 4 Univariate analysis assessing the relative risk (95%CI) of inflammatory bowel disease patients under treatment who developed active tuberculosis from a referral center**

Variable	Total, n (%)	Active tuberculosis, n (%)	RR (95%CI)	P value
Sex				0.027
Female	188 (62.5)	2 (1.1)	1.0	
Male	113 (37.5)	6 (5.3)	4.99 (1.02-24.3)	
Age (yr)				0.158
18-40	185 (61.5)	3 (1.6)	1.0	
41-91	116 (38.5)	5 (4.3)	2.66 (0.65-10.91)	
IBD type				0.487
RCU	186 (61.8)	4 (2.2)	1.0	
CD	115 (38.2)	4 (3.5)	1.61 (0.41-6.34)	
Latent TB				< 0.001
No	276 (93.2)	5 (1.8)	1.0	
Yes	20 (6.8)	3 (15.0)	8.28 (2.13-32.18)	
Azathioprine				0.013
No	199 (66.1)	2 (1.0)	1.0	
Yes	102 (33.0)	6 (5.9)	5.85 (1.20-28.48)	
Anti-TNF $\alpha$				0.034
No	240 (79.7)	4 (1.7)	1.0	
Yes	61 (20.3)	4 (6.5)	3.93 (1.01-15.29)	
Aza + Anti-TNF $\alpha$				< 0.001
No	271 (90.0)	4 (1.5)	1.0	
Yes	30 (10.0)	4 (13.3)	9.03 (2.38-34.28)	

RR: Relative risk; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; TB: Tuberculosis; Anti-TNF $\alpha$ : Anti-tumor necrosis factor alpha; Aza: Azathioprine.

**Table 5 Multivariate analysis of developing active tuberculosis by Poisson regression in patients with inflammatory bowel disease under treatment from a referral center**

Model	Anti-TNF $\alpha$	P value	Azathioprine	P value	Anti-TNF $\alpha$ + azathioprine	P value
	RR (95%CI)		RR (95%CI)		RR (95%CI)	
No adjustment	3.93 (1.01-15.32)	0.048	5.85 (1.20-28.56)	0.029	9.03 (2.37-34.35)	0.001
Sex	3.13 (0.69-14.27)	0.14	5.63 (1.15-27.86)	0.033	7.85 (1.88-32.77)	0.005
Sex, type IBD	6.43 (2.33-17.74)	< 0.001	6.91 (1.50-31.80)	0.013	13.53 (4.50-40.78)	< 0.001
Sex, type IBD, latent TB	10.84 (4.26-27.60)	< 0.001	5.57 (0.86-36.06)	0.071	15.81 (6.07-41.23)	< 0.001
Sex, age, type IBD, latent TB	10.34 (4.28-24.96)	< 0.001	6.27 (1.03-38.05)	0.046	17.81 (5.91-53.67)	< 0.001

Anti-TNF $\alpha$ : Anti-tumor necrosis factor alpha; IBD: Inflammatory bowel disease; RR: Relative risk; TB: Tuberculosis.

screening measures and confirmed LTBI in 30 patients (8.0%). A similar rate of LTBI is observed in countries with intermediate and high TB burden, but the treatment of this condition does not exclude the risk of IBD patients developing active TB. Instead, a history of latent TB increased the risk of active TB during immunosuppressive therapy.

Analyses of only the group using anti-TNF $\alpha$  therapy revealed an increased frequency of 6.6%. Korea has a high prevalence of TB, and one study found a

frequency of 2.0% of active TB in IBD patients using anti-TNF $\alpha$  therapy<sup>[26]</sup>. Another Korean study by Byun *et al*<sup>[6]</sup> showed a TB rate of 1.1% (6/525) in patients with IBD, with 3.1% (5/160) using anti-TNF $\alpha$ . These results show that the prevalence of active TB in Korean IBD patients was lower than the present study. A Spanish group identified that 1.2% (4/329) of IBD patients using anti-TNF  $\alpha$  developed active TB<sup>[25]</sup>, and a cohort of 765 patients in Portugal reported 25 cases (3.3%) of active TB while receiving anti-TNF $\alpha$  therapy<sup>[27]</sup>. These studies showed a low prevalence of active TB in patients using anti-TNF $\alpha$ , which was very likely due to the low prevalence of active TB in the general population.

Research in Fortaleza/Brazil of mostly rheumatological patients and a small group with psoriasis and Crohn's disease diagnosed active TB in 5 (6.3%) of the 79 patients treated with immunobiological agents and in 1 (4.6%) of the 22 patients treated with other immunomodulators/immunosuppressants<sup>[28]</sup>. Another study in Campo Grande/Brazil evaluated active TB cases in patients using Adalimumab and found a prevalence of 3.9% (3/77) in one year of follow-up<sup>[20]</sup>. Salvador had a TB incidence of 49.4 cases/100,000 person-years. Fortaleza had a similar high incidence of 54.9/100000 person-years, and Campo Grande had an intermediate incidence of 23.3/100000 person-years, which may explain the similar rate of active TB in immunosuppressive patients<sup>[10]</sup>.

Our group of patients with active TB who received anti-TNF $\alpha$  therapy showed that the association with azathioprine increased the crude relative risk to 9.03 times greater. Byun *et al*<sup>[6]</sup> reported that 97.5% of patients with active TB who used anti-TNF $\alpha$  therapy were exposed to azathioprine/6-mercaptopurine. Meta-analysis evaluating the risk of reactivation of TB when anti-TNF $\alpha$  therapy was combined with immunosuppressive agents showed a 13-fold increased risk of TB reactivation<sup>[29]</sup>. As seen in the present study and the meta-analysis cited, the risk for active TB increased with this association, so care must be redoubled. Until now, there has been no uniform program to prevent the development of active TB in IBD patients undergoing combination therapy. Each country adopts national guidelines to care for this risk according to the local prevalence and populational risk of active TB.

As seen in [Table 5](#), azathioprine increased the risk of developing TB almost 6 times. Few studies relating the risk of active TB in patients under treatment with azathioprine are reported. Generally, a description of the risk is an association of anti-TNF with azathioprine<sup>[29]</sup>. A Spanish group evaluated the risk of developing active TB in patients after lung transplantation and showed that azathioprine increased the risk 10.6 times<sup>[30]</sup>.

The assessment made by multivariate analysis showed the presence of a high risk of developing active TB in patients with IBD treated with azathioprine alone. However, such data need to be confirmed by prospectives studies in patients with IBD from countries with low endemicity for TB.

Of the total active TB cases using anti-TNF $\alpha$ , 2 (50%) patients had pleural TB. The usual presentation of active TB described previously in patients under anti-TNF $\alpha$  therapy is extrapulmonary and disseminated. Abitbol *et al*<sup>[31]</sup> found that 91% of active TB in patients under anti-TNF $\alpha$  therapy had at least one extrapulmonary involvement. A Portuguese study reported that 15 (60.0%) of the 25 patients who developed active TB in their study had extrapulmonary TB, nine of which were disseminated<sup>[26]</sup>. The pathophysiology of TB, the host's defense mechanism and granuloma formation explain why patients using anti-TNF $\alpha$  therapy are more prone to extrapulmonary TB. The use of anti-TNF drugs prevents the formation of granuloma<sup>[12,32]</sup>. The low frequency of extrapulmonary/disseminated TB in the present sample was likely due to the probability of acquiring a new infection and not a reactivation.

Generally, a short period of time between the start of anti-TNF $\alpha$  therapy and the development of active TB is described, which suggests reactivation of LTBI. The range between the onset of anti-TNF $\alpha$  therapy until active TB infection was 20.2 (3-45) mo in our study, with 2 patients showing TB after 24 and 45 mo, which is more suggestive of a new infection. A European study showed an average interval of 14.5 mo between the first injection of anti-TNF $\alpha$  drugs and the diagnosis of active TB, which also suggests that only a small proportion was due to reactivation of TB<sup>[31]</sup>. Keane *et al*<sup>[33]</sup> demonstrated a median interval of 3 mo between the development of active TB after the initiation of anti-TNF $\alpha$ , which indicates reactivation. A survey in a Korean country found longer intervals, similar to our results, and showed an average time between the beginning of anti-TNF therapy and active TB diagnosis of 23 (2-76) mo, which suggests a new infection<sup>[6]</sup>. The screening for LTBI is only performed before the start of anti-TNF. However, numerous articles showed a later average time for the onset of active TB. A meta-analysis showed that the average duration for the development of active TB was 7 mo from the start of anti-TNF $\alpha$  therapy, and the risk increased even more

that after 15 mo<sup>[34]</sup>. A study in Turkey evaluated patients with past treatment for LTBI and showed the development of active TB at  $37.5 \pm 27.0$  (range: 18-84) mo after starting anti-TNF $\alpha$  therapy<sup>[4]</sup>. These results raise concerns about how to follow the screening of these patients using biological methods. Perhaps an annual screening of patients who are at risk of developing active TB should be performed in countries with a high TB burden.

Our study has some limitations. It was performed in a single center with a small sample of patients using anti-TNF $\alpha$  therapy. A prospective assessment of these patients would provide better data on risk factors and the development of active TB. Better knowledge about risk factors for active TB, such as smoking history, nutritional status, and occupational or family exposure to tuberculosis, is lacking.

The frequency of active TB in patients with IBD under treatment varies between countries, and one possible explanation for this difference in results is an effect of the epidemiological characteristics of each locality. Trials with anti-TNF $\alpha$  are rigorous, with strict inclusion criteria, and adverse events, such as active TB, are best studied in real-world situations. Most studies that reported the occurrence of active TB in patients undergoing anti-TNF $\alpha$  treatment were performed in countries with a low or intermediate frequency of tuberculosis. There is a knowledge gap in high endemic countries.

## CONCLUSION

In conclusion, treatment with anti-TNF $\alpha$  significantly increased the risk of active TB in patients with IBD from an endemic area in Latin America, which is a region with a high TB burden. This risk is present when the IBD patient is under immunosuppressive and anti-TNF $\alpha$  therapy, and it increases when anti-TNF $\alpha$  therapy is combined with azathioprine. Late active TB, which is diagnosed 3 mo after the start of anti-TNF $\alpha$  therapy, was the most common, which suggests a new infection. This finding provides an important alert for the need to maintain care and evaluate when to screen for active TB risk in patients under biological therapy.

## ARTICLE HIGHLIGHTS

### **Research background**

Tuberculosis is a highly prevalent disease in Brazil, which is also seeing an increase in the incidence of inflammatory bowel diseases. Biological therapy improves quality of life but increases the risk of tuberculosis. This report is the first study in Latin America to relate the risk of developing tuberculosis in patients with inflammatory bowel disease under treatment.

### **Research motivation**

The motivation was the lack of knowledge about the risk of developing tuberculosis in inflammatory bowel disease patients, especially patients using immunosuppressants and biologicals. The identification of active tuberculosis (TB) risk and how to prevent it is essential to alert physicians to the need for infectious screening and maintenance of care throughout the treatment.

### **Research objectives**

The main objective was to identify the risk of developing active tuberculosis in inflammatory bowel disease patients under treatment. Knowledge of this risk will benefit the care of the patient before starting immunosuppressive and biological therapy and encourage surveillance throughout the treatment.

### **Research methods**

This study was a retrospective cohort study of inflammatory bowel disease (IBD) patients followed at a referral center in Salvador, Bahia, Brazil. A standardized, structured questionnaire was used for each patient in a direct interview, and medical records were reviewed. The cohort baseline was defined as the start of drug therapy directed at inflammatory bowel disease. Patients in this cohort were screened for latent TB using the tuberculin skin test before starting immunosuppressive or immunobiological therapy. The gross relative risk of developing active TB in patients

treated with anti-tumor necrosis factor alpha (TNF $\alpha$ ), azathioprine and anti-TNF $\alpha$  in combination with azathioprine compared to other treatments was obtained with the respective 95%CI. The adjusted relative risk for age, sex, type of IBD and latent TB was calculated using Poisson regression with robust variance (sex-model 1; sex and type of IBD-model 2; sex, type of IBD, latent TB-model 3; and sex, age, type of IBD, latent tuberculosis-model 4).

### Research results

Immunosuppressive therapy, specifically azathioprine, anti-TNF $\alpha$  and the combination of these two drugs, were associated with a higher risk of active tuberculosis, with RRs of 5.85 (95%CI: 1.20-28.48), 3.93 (95%CI: 1.01-15.29) and 9.03 (95%CI: 2.38-34.28), respectively. When adjusted for sex, age, type of IBD and latent TB, anti-TNF $\alpha$  combined with azathioprine consistently increased the relative risk to 17.8 times more than conventional treatment (95%CI: 5.91-53.67;  $P < 0.001$ ). Azathioprine was not affected by other variables, but infliximab presented a higher risk when adjusted for age, gender, latent tuberculosis and the type of inflammatory bowel disease.

### Research conclusions

Azathioprine and anti-TNF agents as monotherapy or in combination increased the risk of developing tuberculosis in inflammatory bowel disease patients. We reinforce that screening for latent tuberculosis should also be performed routinely in patients who start azathioprine.

### Research perspectives

A prospective study that monitors the evolution of IBD patients under treatment should be performed to identify possible variables that reduce the risk of developing active tuberculosis during treatment.

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