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***Retrospective Cohort Study***

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

Fortes FML *et al*. Tuberculosis in inflammatory bowel disease

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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

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 (TNFα) to TB development.

RESULTS

Azathioprine, anti-TNFα and the combination of these two drugs were associated with a higher risk of active TB incidence. The TNFα blockers increased the relative risk of developing active TB compared to other treatments. All four multivariable models showed that the use of TNFα 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-TNFα 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-TNFα, was the most frequent.

CONCLUSION

Treatment with anti-TNFα increased the risk of active TB in IBD patients from an endemic area in Latin America. This risk was increased when anti-TNFα 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 (TNFα) 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-TNFα 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.

**INTRODUCTION**

Inflammatory bowel disease (IBD) has a higher incidence and prevalence in developed countries[1]. 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[2]. The prevalence was 12.8/10000 persons in the northeast region of Brazil[3].

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

TB is also a very common infectious disease in Brazil, and it is considered a serious public health problem and life-threatening condition[9,10]. Globally, it is estimated that 10 million people develop TB annually, and this number has remained stable according to the United Nations (UN)[11]. 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[12]. Dendritic cells or inflammatory monocytes transport Mbt to the pulmonary lymph nodes to initiate T cell stimulation of TNFα and interferon gamma secretion, which contribute to granuloma formation[12,13]. 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[14,15]. These granulomas are essential for the control of Mbt, but they also provide an environment for the survival, multiplication, latency and dissemination of Mbt[16].

Several studies investigated the probable association between anti-TNFα 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[8,17]. Mañosa *et al*[18] reported an incidence of 1.2% (4/330) active tuberculosis in IBD patients under anti-TNFα therapy in Spain. Lee *et al*[19] showed an incidence of active tuberculosis of 1.4% (9/661) in patients with CD who were treated with anti-TNFα in Korea. However, studies in Brazil and Latin America on the development of active TB in patients with IBD under treatment are scarce[20].

In this scenario of high active TB incidence, increased IBD cases and improved access to anti-TNFα 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-TNFα 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[1] 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[21], 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-TNFα 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-TNFα and chest radiography consistent with past TB. Patients were considered to have a positive TST if the TST result was ≥ 10 mm alone or ≥ 5 mm with at least one of the risk factors listed above[9,22].

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 rifapentine associated with isoniazid, with a weekly dose for 3 mo[23].

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[9].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 ± 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 (RRcrude) of active TB development in patients treated with anti-TNFα, azathioprine and anti-TNFα plus azathioprine compared to other treatments was obtained with the respective 95%CI. Adjusted RR (RRadj) 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®, 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 ± SD age was 45.8 ± 15.0 years. There was a higher frequency of females (188/301; 62.5%) and patients from urban areas (244/301; 82.7%). 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-TNFα as a monotherapy, 31 (10.3%) patients received anti-TNFα associated with azathioprine, 3 (1.0%) patients received anti-TNFα 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 ± 58.9 mo. The age of patients who developed active TB during treatment was 40.3 ± 14.7 years at the time of the interview. Six (75%) patients were male. The mean ± SD time between the start of anti-TNFα therapy and the diagnosis of active TB was 20.0 ± 18.7 mo. One patient developed active TB three months after the start of anti-TNFα 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 (RRcrude = 8.28; 95%CI: 2.13-32.18, Table 4).

The frequencies of active TB in patients undergoing anti-TNFα therapy and with infliximab and adalimumab were 6.5% (4/61), 7.1% (2/28) and 6.1% (2/33), respectively. The four patients received combination therapy with azathioprine. Therapy with immunosuppressants, specifically azathioprine, anti-TNFα and the combination of these two drugs, were associated with a higher risk of active tuberculosis, with RRcrude 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 TNFα blockers significantly increased the relative risk of developing active TB compared to other treatments. Four multivariable models were evaluated, and the use of TNFα 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-TNFα 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 TNFα blockers and azathioprine-associated use.

**DISCUSSION**

According to the WHO[11], 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-TNFα 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*[24] 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-TNFα[25]. A 2015 Korean study[6] assessed the risk of active TB in patients with IBD using anti-TNFα therapy and found a frequency of LTBI of 10.6%. Kim *et al*[26], used chest radiography, IGRA and TST as 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-TNFα 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-TNFα therapy[26]. Another Korean study by Byun *et al*[6] showed a TB rate of 1.1% (6/525) in patients with IBD, with 3.1% (5/160) using anti-TNFα. 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 α developed active TB[25], and a cohort of 765 patients in Portugal reported 25 cases (3.3%) of active TB while receiving anti-TNFα therapy[27]. These studies showed a low prevalence of active TB in patients using anti-TNFα, 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[28]. 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[20]. 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[10].

Our group of patients with active TB who received anti-TNFα therapy showed that the association with azathioprine increased the crude relative risk to 9.03 times greater. Byun *et al*[6] reported that 97.5% of patients with active TB who used anti-TNFα therapy were exposed to azathioprine/6-mercaptopurine. Meta-analysis evaluating the risk of reactivation of TB when anti-TNFα therapy was combined with immunosuppressive agents showed a 13-fold increased risk of TB reactivation[29]. 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[29]. 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[30].

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-TNFα, 2 (50%) patients had pleural TB. The usual presentation of active TB described previously in patients under anti-TNFα therapy is extrapulmonary and disseminated. Abitbol *et al*[31] found that 91% of active TB in patients under anti-TNFα 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[26].The pathophysiology of TB, the host’s defense mechanism and granuloma formation explain why patients using anti-TNFα therapy are more prone to extrapulmonary TB. The use of anti-TNF drugs prevents the formation of granuloma[12,32]. 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-TNFα therapy and the development of active TB is described, which suggests reactivation of LTBI. The range between the onset of anti-TNFα 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-TNFα drugs and the diagnosis of active TB, which also suggests that only a small proportion was due to reactivation of TB[31]. Keane *et al*[33] demonstrated a median interval of 3 mo between the development of active TB after the initiation of anti-TNFα, 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[6].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-TNFα therapy, and the risk increased even more that after 15 mo[34].A study in Turkey evaluated patients with past treatment for LTBI and showed the development of active TB at 37.5 ± 27.0 (range: 18-84) mo after starting anti-TNFα therapy[4]. 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-TNFα 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-TNFα 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-TNFα 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-TNFα 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-TNFα therapy, and it increases when anti-TNFα therapy is combined with azathioprine. Late active TB, which is diagnosed 3 mo after the start of anti-TNFα 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 (TNFα), azathioprine and anti-TNFα 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-TNFα 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-TNFα 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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**REFERENCES**

1 **Gomollón F**, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, Peyrin-Biroulet L, Cullen GJ, Daperno M, Kucharzik T, Rieder F, Almer S, Armuzzi A, Harbord M, Langhorst J, Sans M, Chowers Y, Fiorino G, Juillerat P, Mantzaris GJ, Rizzello F, Vavricka S, Gionchetti P; ECCO. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; **11**: 3-25 [PMID: 27660341 DOI: 10.1093/ecco-jcc/jjw168]

2 **Kotze PG**, Underwood FE, Damião AOMC, Ferraz JGP, Saad-Hossne R, Toro M, Iade B, Bosques-Padilla F, Teixeira FV, Juliao-Banos F, Simian D, Ghosh S, Panaccione R, Ng SC, Kaplan GG. Progression of Inflammatory Bowel Diseases Throughout Latin America and the Caribbean: A Systematic Review. *Clin Gastroenterol Hepatol* 2020; **18**: 304-312 [PMID: 31252191 DOI: 10.1016/j.cgh.2019.06.030]

3 **Parente JM**, Coy CS, Campelo V, Parente MP, Costa LA, da Silva RM, Stephan C, Zeitune JM. Inflammatory bowel disease in an underdeveloped region of Northeastern Brazil. *World J Gastroenterol* 2015; **21**: 1197-1206 [PMID: 25632193 DOI: 10.3748/wjg.v21.i4.1197]

4 **Akyuz F**, Cavus B, Iliaz R, Soyer OM, Ormeci A, Evirgen S, Onder S, Koksalan K, Keskin M, Karaca C, Demir K, Gulluoglu M, Cagatay T, Besisik F, Kaymakoglu S. Inflammatory bowel disease and mycobacteria: how much can we trust isoniazid prophylaxis during antitumor necrosis factor therapy? *Eur J Gastroenterol Hepatol* 2019; **31**: 777-780 [PMID: 30964811 DOI: 10.1097/MEG.0000000000001403]

5 **Sandborn WJ**, Hanauer SB. Antitumor necrosis factor therapy for inflammatory bowel disease: a review of agents, pharmacology, clinical results, and safety. *Inflamm Bowel Dis* 1999; **5**: 119-133 [PMID: 10338381 DOI: 10.1097/00054725-199905000-00008]

6 **Byun JM**, Lee CK, Rhee SY, Kim HJ, Kim JW, Shim JJ, Jang JY. The risk of tuberculosis in Korean patients with inflammatory bowel disease receiving tumor necrosis factor-α blockers. *J Korean Med Sci* 2015; **30**: 173-179 [PMID: 25653489 DOI: 10.3346/jkms.2015.30.2.173]

7 **Abreu C**, Afonso J, Camila Dias C, Ruas R, Sarmento A, Magro F. Serial Tuberculosis Screening in Inflammatory Bowel Disease Patients Receiving Anti-TNFα Therapy. *J Crohns Colitis* 2017; **11**: 1223-1229 [PMID: 28605520 DOI: 10.1093/ecco-jcc/jjx080]

8 **Kang J**, Jeong DH, Han M, Yang SK, Byeon JS, Ye BD, Park SH, Hwang SW, Shim TS, Jo KW. Incidence of Active Tuberculosis within One Year after Tumor Necrosis Factor Inhibitor Treatment according to Latent Tuberculosis Infection Status in Patients with Inflammatory Bowel Disease. *J Korean Med Sci* 2018; **33**: e292 [PMID: 30450023 DOI: 10.3346/jkms.2018.33.e292]

9  **Ministério da Saúde**, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis, Boletim Epidemiológico de Tuberculose. [cited 21 June 2020]. Available from: https://portalarquivos2.saude.gov.br/images/pdf/2019/marco/22/2019-009.pdf

10 **Ministério da Saúde**. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Boletim Epidemiológico Número Especial -Tuberculose 2020. [cited 21 June 2020]. Available from: https://www.saude.gov.br/images/pdf/2020/marco/24/Boletim-tuberculose-2020-marcas--1-.pdf

11 Global tuberculosis report 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO

12 **Pai M**, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, Ginsberg A, Swaminathan S, Spigelman M, Getahun H, Menzies D, Raviglione M. Tuberculosis. *Nat Rev Dis Primers* 2016; **2**: 16076 [PMID: 27784885 DOI: 10.1038/nrdp.2016.76]

13 **Cabriada JL**, Ruiz-Zorrilla R, Barrio J, Atienza R, Huerta A, Rodríguez-Lago I, Bernal A, Herrero C. Screening for latent tuberculosis infection in patients with inflammatory bowel disease: Can interferon-gamma release assays replace the tuberculin skin test? *Turk J Gastroenterol* 2018; **29**: 292-298 [PMID: 29755013 DOI: 10.5152/tjg.2018.17162]

14 **Parasa VR**, Rahman MJ, Ngyuen Hoang AT, Svensson M, Brighenti S, Lerm M. Modeling Mycobacterium tuberculosis early granuloma formation in experimental human lung tissue. *Dis Model Mech* 2014; **7**: 281-288 [PMID: 24203885 DOI: 10.1242/dmm.013854]

15 **Flynn JL**, Chan J, Lin PL. Macrophages and control of granulomatous inflammation in tuberculosis. *Mucosal Immunol* 2011; **4**: 271-278 [PMID: 21430653 DOI: 10.1038/mi.2011.14]

16 **Palmer MV**. Emerging Understanding of Tuberculosis and the Granuloma by Comparative Analysis in Humans, Cattle, Zebrafish, and Nonhuman Primates. *Vet Pathol* 2018; **55**: 8-10 [PMID: 29254474 DOI: 10.1177/0300985817712795]

17 **Yonekura CL**, Oliveira RDR, Titton DC, Ranza R, Ranzolin A, Hayata AL, Duarte Â, Silveira IG, Carvalho HMDS, Moraes JCB, Abreu MM, Valim V, Bianchi W, Brenol CV, Pereira IA, Costa I, Macieira JC, Miranda JRS, Guedes-Barbosa LS, Bertolo MB, Sauma MFLDC, Silva MBG, Freire M, Scheinberg MA, Toledo RA, Oliveira SKF, Fernandes V, Pinheiro MM, Castro G, Vieira WP, Baaklini CE, Ruffino-Netto A, Pinheiro GDRC, Laurindo IMM, Louzada-Junior P. Incidence of tuberculosis among patients with rheumatoid arthritis using TNF blockers in Brazil: data from the Brazilian Registry of Biological Therapies in Rheumatic Diseases (Registro Brasileiro de Monitoração de Terapias Biológicas - BiobadaBrasil). *Rev Bras Reumatol Engl Ed* 2017; **57 Suppl 2**: 477-483 [PMID: 28739353 DOI: 10.1016/j.rbre.2017.05.005]

18 **Mañosa M**, Domènech E, Cabré E. Current incidence of active tuberculosis in IBD patients treated with anti-TNF agents: still room for improvement. *J Crohns Colitis* 2013; **7**: e499-e500 [PMID: 23689076 DOI: 10.1016/j.crohns.2013.04.021]

19 **Lee CK**, Wong SHV, Lui G, Tang W, Tam LS, Ip M, Hung E, Chen M, Wu JC, Ng SC. A Prospective Study to Monitor for Tuberculosis During Anti-tumour Necrosis Factor Therapy in Patients With Inflammatory Bowel Disease and Immune-mediated Inflammatory Diseases. *J Crohns Colitis* 2018; **12**: 954-962 [PMID: 29757355 DOI: 10.1093/ecco-jcc/jjy057]

20 **Cury DB,** Moss AC, Oliveira RA. Sa1140 Rate of de novo TB Infection in an IBD Population Treated With Adalimumab in Brazil. *Gastroenterology* 2015; **148**: 238 [DOI: 10.1016/s0016-5085(15)30780-0]

21 **Satsangi J**, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; **55**: 749-753 [PMID: 16698746 DOI: 10.1136/gut.2005.082909]

22 **Aberra FN**. Comparison of interferon-gamma release assay versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease. *Gastroenterology* 2009; **136**: 1453-5; discussion 1455 [PMID: 19233329 DOI: 10.1053/j.gastro.2009.02.036]

23 **Ministério da Saúde.** Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos em Saúde. Relatório de recomendação. Rifapentina + isoniazida para o tratamento da Infecção Latente pelo Mycobacterium Tuberculosis (ILTB). [cited 21 June 2020] Available from: http://conitec.gov.br/images/Consultas/Relatorios/2020/Relatorio\_Rifapentina\_Isoniazida\_ILTB\_CP\_14\_2020\_.pdf

24 **Taxonera C**, Ponferrada Á, Bermejo F, Riestra S, Saro C, Martín-Arranz MD, Cabriada JL, Barreiro-de Acosta M, de Castro ML, López-Serrano P, Barrio J, Suarez C, Iglesias E, Argüelles-Arias F, Ferrer I, Marín-Jiménez I, Hernández-Camba A, Bastida G, Van Domselaar M, Martínez-Montiel P, Olivares D, Alba C, Gisbert JP; SEGURTB study group from GETECCU. Early Tuberculin Skin Test for the Diagnosis of Latent Tuberculosis Infection in Patients with Inflammatory Bowel Disease. *J Crohns Colitis* 2017; **11**: 792-800 [PMID: 28333182 DOI: 10.1093/ecco-jcc/jjx022]

25 **Jauregui-Amezaga A**, Turon F, Ordás I, Gallego M, Feu F, Ricart E, Panés J. Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. *J Crohns Colitis* 2013; **7**: 208-212 [PMID: 22677117 DOI: 10.1016/j.crohns.2012.05.012]

26 **Kim ES**, Song GA, Cho KB, Park KS, Kim KO, Jang BI, Kim EY, Jeon SW, Lee HS, Yang CH, Lee YK, Lee DW, Kim SK, Kim TO, Lee J, Kim HW, Jee SR, Park SJ, Kim HJ. Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents. *World J Gastroenterol* 2015; **21**: 3308-3316 [PMID: 25805938 DOI: 10.3748/wjg.v21.i11.3308]

27 **Abreu C**, Magro F, Santos-Antunes J, Pilão A, Rodrigues-Pinto E, Bernardes J, Bernardo A, Magina S, Vilas-Boas F, Lopes S, Macedo G, Sarmento A. Tuberculosis in anti-TNF-α treated patients remains a problem in countries with an intermediate incidence: analysis of 25 patients matched with a control population. *J Crohns Colitis* 2013; **7**: e486-e492 [PMID: 23583099 DOI: 10.1016/j.crohns.2013.03.004]

28 **Lopes DMA**, Pinheiro VGF, Monteiro HSA. Diagnosis and treatment of latent tuberculosis infection in patients undergoing treatment with immunobiologic agents: a four-year experience in an endemic area. *J Bras Pneumol* 2019; **45**: e20180225 [PMID: 31618298 DOI: 10.1590/1806-3713/e20180225]

29 **Lorenzetti R**, Zullo A, Ridola L, Diamanti AP, Laganà B, Gatta L, Migliore A, Armuzzi A, Hassan C, Bruzzese V. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials. *Ann Med* 2014; **46**: 547-554 [PMID: 25105206 DOI: 10.3109/07853890.2014.941919]

30 **Guirao-Arrabal E**, Santos F, Redel-Montero J, Vaquero JM, Cantisán S, Vidal E, Torre-Giménez Á, Rivero A, Torre-Cisneros J. Risk of tuberculosis after lung transplantation: the value of pretransplant chest computed tomography and the impact of mTOR inhibitors and azathioprine use. *Transpl Infect Dis* 2016; **18**: 512-519 [PMID: 27224905 DOI: 10.1111/tid.12555]

31 **Abitbol Y**, Laharie D, Cosnes J, Allez M, Nancey S, Amiot A, Aubourg A, Fumery M, Altwegg R, Michetti P, Chanteloup E, Seksik P, Baudry C, Flamant M, Bouguen G, Stefanescu C, Bourrier A, Bommelaer G, Dib N, Bigard MA, Viennot S, Hébuterne X, Gornet JM, Marteau P, Bouhnik Y, Abitbol V, Nahon S; GETAID. 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. *J Crohns Colitis* 2016; **10**: 1179-1185 [PMID: 27402916 DOI: 10.1093/ecco-jcc/jjw129]

32 **Debeuckelaere C**, De Munter P, Van Bleyenbergh P, De Wever W, Van Assche G, Rutgeerts P, Vermeire S. Tuberculosis infection following anti-TNF therapy in inflammatory bowel disease, despite negative screening. *J Crohns Colitis* 2014; **8**: 550-557 [PMID: 24295645 DOI: 10.1016/j.crohns.2013.11.008]

33 **Keane J**, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; **345**: 1098-1104 [PMID: 11596589 DOI: 10.1056/nejmoa011110]

34 **Kedia S**, Mouli VP, Kamat N, Sankar J, Ananthakrishnan A, Makharia G, Ahuja V. Risk of Tuberculosis in Patients With Inflammatory Bowel Disease on Infliximab or Adalimumab Is Dependent on the Local Disease Burden of Tuberculosis: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2020; **115**: 340-349 [PMID: 32032073 DOI: 10.14309/ajg.0000000000000527]

**Footnotes**

**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.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author atraquelrocha2@yahoo.com.br. Participants gave informed consent for data sharing.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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

|  |  |
| --- | --- |
| **Charact****eristics (total *n* = 301)** | ***n* (%)** |
| Type of IBD |  |
| Crohn's disease | 115 (38.2) |
| Ulcerative colitis | 186 (61.8) |
| Age (yr)1 | 45.8 (15.0) |
| Duration of the disease (mo)1 | 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 perinal | 25 (22.5) |
| B2 associated with perinal | 6 (5.4) |
| B3 associated with perinal | 14 (12.6) |
| UC location |  |
| Proctitis | 23 (12.7) |
| Left colitis | 79 (43.6) |
| Extensive colitis | 79 (43.6) |

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

**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-TNFα | 31 | 28 (24.3) | 3 (1.6) |
| Methotrexate + Anti-TNFα | 3 | 3 (2.6) |  |
| Anti-TNF α | 30 | 29 (25.2) | 1 (0.5) |
| Corticoid | 2 | 2 (1.7) |  |

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; Anti-TNFα: 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-α 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.

**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-TNFα |  |  |  | 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-TNFα | |  |  | < 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-TNFα: 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-TNFα** | ***P* value** | **Azathioprine** | ***P* value** | **Anti-TNFα + 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-TNFα: Anti-tumor necrosis factor alpha; IBD: Inflammatory bowel disease; RR: Relative risk; TB: Tuberculosis.