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Rate of infection (tuberculosis) in brazilians IBD private patients: follow-up 15 years

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HIGHLIGHTS

- Rate of infection (tuberculosis) in Brazilians IBD private patients: follow-up 15 years.
- Patients treated with immunosuppressants and/or anti-TNFs have a higher risk of developing opportunistic infections, among them the most common is latent tuberculosis or even active tuberculosis.
- Similar risks may be noted in patients with inflammatory bowel diseases (IBDs).
- This study reveals that the longer the exposure to anti-TNFs, the greater the risk for de IBD patients.
- The study demonstrated the importance of monitoring these patients permanently and continuously.

ABSTRACT – Background – Latent tuberculosis (LTB) is a condition where the patient is infected with *Mycobacterium tuberculosis* but does not develop active TB. There's a possibility of tuberculosis (TB) activation following the introduction of anti-TNFs. **Objective –** To assess the risk of biological therapy inducing LTB during inflammatory bowel diseases (IBD) treatment over 15 years in a high-risk area in Brazil. **Methods –** A retrospective study of an IBD patients' database was carried out in a private reference clinic in Brazil. All patients underwent TST testing and chest X-ray prior to treatment, and once a year after starting it. Patients were classified according to the Montreal stratification and risk factors were considered for developing TB. **Results –** Among the analyzed factors, age and gender were risk factors for LTB. DC (B2 and P) and UC (E2) patients showed a higher number of LTB cases with statistical significance, what was also observed for adalimumab and infliximab users, compared to other medications, and time of exposure to them favored it significantly. Other factors such as enclosed working environment have been reported as risk. **Conclusion** – The risk of biological therapy causing LTB is real, so patients with IBD should be continually monitored. This study reveals that the longer the exposure to anti-TNFs, the greater the risk.

Keywords – Biologics; Crohn's disease; ulcerative colitis; epidemiology.

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INTRODUCTION

The World Health Organization estimates that one-third of the world's population is infected with the Koch bacillus. Among infectious diseases, tuberculosis (TB) has been considered as one with the highest mortality rates in the world, especially among people with HIV (AIDS)[1]

Brazil is one of the countries with the highest number of TB cases around the world, although it has the lowest mortality[2]. A recent study by Croda et al. in the Midwest region of Brazil suggests that this increase in the number of cases is directly related to the significant increase in the prison population, amplifying the disease within the non-prison community[3]. Immunization is mandatory against Koch's bacillus (BCG) in that country, but the vaccine acts only preventing severe forms of the disease[4].

Tuberculosis is recognized as the result of a weakened immune system caused by diseases such as diabetes, malnutrition, AIDS, among others and the use of illicit or licit drugs among them the immunosupressants[5].

New drugs used to treat inflammatory diseases, inhibitors of tumor necrosis factor alpha (anti-TNFs), changed the natural history of the disease by healing lesions and improving patients' quality of life, but did not exempt them from the undesirable effects. Over time, several studies have shown that patients treated with immunosuppressants and/ or anti-TNFs have a higher risk of developing opportunistic infections, among them the most common is latent tuberculosis or even active tuberculosis, which may evolve into severe and fatal forms when compared to those not treated by these drugs[2,6].

Latent tuberculosis is a condition in which one has been exposed to *Mycobacterium tuberculosis* - complex but not developed the active disease[7]. In Brazil the majority of the population is exposed to MTB in childhood, a large percentage does not develop the disease but in a lower percentage of population, the bacillus remains latent in the primary complex, and in some conditions, even after decades, tuberculosis disease can develop.

The activation of *M. tuberculosis* following the introduction of anti-TNFs has increased the risk of latent tuberculosis by three to four times higher in patients with rheumatoid arthritis compared with those who do not use biological therapy. Similar risks may be noted in patients with inflammatory bowel diseases (IBDs)[8,9].

Taking it into account the aims of this work were to assess the risk of latent tuberculosis and active tuberculosis in patients with inflammatory bowel diseases who used the anti-TNFs (monotherapy), adalimumab and infliximab. Moreover, verify the influence of risk factors such as hospitalization and socioeconomic conditions, work environment, time of illness, time of medication use, pre-existing illnesses and demonstrate the importance of monitoring these patients permanently and continuously (Crohn's and ulcerative colitis).

METHODS

The prospective database analysis study included patients with inflammatory bowel diseases (Crohn's and ulcerative colitis) who received anti-TNFs (infliximab and adalimumab) from March 2004 until December 2019. The study was approved by the ethics committee of *Universidade Estadual de* São Paulo (UNESP/Botucatu) IRB CAAE 53006516.0.0000.5411.

Inflammatory bowel diseases were categorized according to the Montreal classification. Risk factors such as alcohol use, diabetes, illicit drugs, smoking, and type of work (in open or enclosed environment) were taken into account, being considered a time of six to eight working hours per day.

Screening for tuberculosis

All the patients underwent the tuberculin skin test (TST) and a chest X-ray, regardless the type of therapeutic approach to be employed.

Intradermal TST: 5 units (0.1 mL) was conducted according to international recommendations, with 0.1 mL (2 UT) inoculation of purified protein derivative (PPD) TR23, applied intradermally in the middle third of the previous region of the left forearm, approximately 8 cm bellow the lower flexion, with reading after 72 h.

Patients sensitive to the tuberculin skin test, who could have been affected with the use of corticosteroids and/or immunosuppressants were not included in this study during the screening, being considered only patients/candidates for therapy with anti-TNFs and after these (monotherapy) as below.

Positivity criteria

It was considered positive if the dermal reaction was greater than or equal to 5 mm in patients whose baseline was 0 and read after 72 h.

Screening time

Each year all patients underwent the PPD test. At the time of the test, the patients were not on corticosteroids, immunosuppressives or anti-TNFs. Simultaneously to PPD all patients underwent chest X-ray, and in the case of PPD positivity (TST), the patients underwent a chest tomography. We only included in the study patients who were naive to anti-TNFs and /or those who had not made use of corticoids or immunosuppressives for at least six months.

Criteria for use of Anti-TNFs

Anti-TNFs were employed according to disease severity (extensive or fistulizing inflammatory disease). In case of treatment failure, the application time was shortened. In the absence of response to the previous strategy, another anti-TNF was administered and with no satisfactory response, anti-integrin inhibitors or interleukin-12 and 23 inhibitor monoclonal antibody were used.

Inclusion criteria

Patients with inflammatory diseases (Crohn's and ulcerative colitis) without treatment with immunosuppressants, anti-TNFs or corticosteroids (naives) were included in the data bank during the first consultation with subsequent follow-up treatment with adalimumab or infliximab (isolated therapy) over time. It was also considered as patients the ones without treatment with corticoids and immunosuppressants or those who had not made use of these drugs for more than six months as they had been recently diagnosed.

Patients who had not been revaccinated from BCG.

Exclusion criteria

Combination therapy with immunosuppressants, isolated or corticosteroid immunosuppressants, HIV carriers, history of previous treatment of tuberculosis or latent tuberculosis or tuberculosis disease.

Control group criteria

Exclusive use of immunosuppressant (azathioprine) and slow release mesalamine.

Usage time of anti-TNFs.

The usage time of anti-TNFs was longer than one year.

Statistical analysis

Quantitative variables were presented through averages, standard and median deviations while qualitative variables through absolute frequencies and percentages. To compare the average of latent tuberculosis groups, Student's *t*-tests (with Gaussian distribution) and the non-parametric Mann Whitney test (without Gaussian distances) were used. Proportions were compared using the chi-square test or Fisher's exact test. To obtain predictive factors for latent tuberculosis, the multivariate logistic regression model was used. The significance level used for the tests was 5%.

RESULTS

329 patients were evaluated retrospectively, 212 with Crohn's disease (CD) and 117 with ulcerative colitis (UC). The mean age at CD diagnosis was 36.19 (± 14.33) and for UC, it was 41.61 (± 15.37). The proportion of women in each group consisted of 50% of those with CD and 72.7% with UC ($p < 0.001$). Of the patients evaluated 4% had elementary education, 47.6% had middle education and 48.5% had higher education.

The Montreal Classification was applied for both diseases. CD, stenosing disease (B2) and perianal disease (P) were more likely to develop latent tuberculosis when compared to other behaviors ($P<0.002$) and E2 for ulcerative colitis (left colitis) $P<0.038$ (TABLE 1).

TABLE 1. Absolute frequencies (%) of 'behavior' and 'side' variables by the disease type, according to the latent TBC group.

Disease	Variable	Latent TBC		*P**
		No	Yes	
CD	Behavior			0.002
	B1	119 (74.8)	21 (50.0)	
	B2	20 (12.6)	14 (33.3)	
	B3	13 (8.2)	2 (4.8)	
	P	7 (4.4)	5 (11.9)	
	Side			0.619
	L1	60 (38.0)	15 (35.7)	
	L2	29 (18.4)	11 (26.2)	
	L3	68 (43.0)	16 (38.1)	
	L4	1 (0.6)	0 (0.0)	
UC	Behavior			0.193
	S0	5 (4.8)	0 (0.0)	
	S1	45 (42.9)	1 (12.5)	
	S2	39 (37.1)	6 (75.0)	
	S3	16 (15.2)	1 (12.5)	
	Side			0.038
	E1	50 (47.6)	1 (12.5)	
	E2	41 (39.1)	7 (87.5)	
	E3	14 (13.3)	0 (0.0)	

*Descriptive level of the probability of Fisher's exact test.

In this sample, 56% of patients received anti-TNF, which was more frequent in patients with CD. All patients underwent PPD testing before any medication, and 96% were negative. The 4% who were positive, were excluded from the study.

Only two patients developed active tuberculosis and because it is a small sample, these data were not included in the statistical analysis.

When analyzing the sensitivity of TST (PPD) after the introduction of anti-TNFs over time, the TST had 100% sensitivity and 99.3% specificity. Positive predictive value of 96.2% and negative predictive value of 100.0% and test accuracy 99.4% (TABLE 2).

TABLE 2. Purified protein derivative utility to detect latent TB in individuals receiving anti-TNF.

Latent TB	No	Yes	Total
PPD Result			
<5	263	0	263
>5	2	51	53
Total	265	51	316

PPD: purified protein derivative; TB: tuberculosis.
100% sensitivity, 99.3% specificity, 96.2% positive predictive value and 100.0% negative predictive value and 99.4% accuracy.

Risk factors for latent tuberculosis (patient age, disease duration, gender, hospitalization in the last 12 months, workplace (enclosed), and duration of medication use (anti-TNFs)) were considered. The youngest age group, CD patients, male who worked in enclosed working environment and longer duration of anti-TNF use, were directly related to latent tuberculosis, and statistical significance was found in these data. The time of illness and hospitalization did not influence latent tuberculosis (TABLE 3).

TABLE 3. Descriptive values of the evaluated variables according to the latent TBC group.

Variable	Latent TBC		*P*
	No	Yes	
Age	39.14±15.05	33.61±13.95	0.013[1]
Disease Time			0.183[4]
Average ±sd	12.94 ± 9.06	11.22 ± 8.28	
Median	11.00	9.00	
Male Gender	102 (38.5%)	30 (58.8%)	0.007[2]
Disease			0.002[2]
CD	159 (60.0%)	42 (82.3%)	
UC	106 (40.0%)	9 (17.7%)	
Employed			0.905[3]
No	17 (6.4%)	2 (3.9%)	
Retired	28 (10.6%)	5 (9.8%)	
Student	5 (1.9%)	0 (0.0%)	
Yes	214 (81.1%)	44 (86.3%)	
Hospitalization	66 (24.9%)	18 (35.3%)	0.124[2]
Indoor working Environment	71 (26.8%)	35 (68.6%)	<0.001[2]
Drug Use Time (n=49)			0.007[4]
Average±sd	3.00±1.12	5.15±2.85	
Median	3.00	4.50	

[1] Descriptive level of probability of Student's *t*-test. [2] Descriptive level of probability of the chi-square test. [3] Descriptive level of probability of the Fisher's exact test. [4] Descriptive level of probability of the nonparametric Mann-Whitney test.

Regarding the drugs used over the years, patients receiving anti-TNFs (adalimumab or infliximab) were more likely to develop latent tuberculosis when compared to other drugs ($P<0.001$) (TABLE 4). Among the drugs in use, 62.7% received anti-TNFs (44.1% adalimumab, 24.2% infliximab). Patients who were treated with infliximab was 2.9-fold and with adalimumab 4.22-fold more likely to develop latent tuberculosis than those who do not use it (TABLE 4).

TABLE 4. Absolute frequencies (%) of medications used according to latent TBC group.

Medication		Latent TBC		*P*
		No	Yes	
Infliximab	Yes	66 (24.9)	25 (49.0)	<0.001[1]
	No	199 (75.1)	26 (51.0)	
Vedolizumab	Yes	12 (4.5)	5 (9.8)	0.166[2]
	No	253 (95.5)	46 (90.2)	
Ustequinumab	Yes	7 (3.1)	2 (4.9)	0.632[2]
	No	219 (96.9)	39 (95.1)	
Certolizumab	Yes	16 (6.1)	0 (0.0)	0.084[2]
	No	248 (93.9)	51 (100.0)	
Adalimumab	Yes	102 (38.5)	37 (72.6)	<0.001[1]
	No	163 (61.5)	14 (27.5)	
Azathioprine	Yes	79 (29.8)	21 (41.2)	0.110[1]
	No	186 (70.2)	30 (58.8)	
5-Aminosalicylates	Yes	116 (43.8)	25 (49.0)	0.490[1]
	No	149 (56.2)	26 (51.0)	

[1] Descriptive probability level of chi-square test. [2] Descriptive probability level of Fisher's exact test.

Associated with PPD, a chest X-ray was performed, which was normal in all cases. Patients positive for latent tuberculosis (TST >5 mm) underwent a chest tomography with results (100%) correlated with PPD. In cases of positivity, prophylaxis was performed with isoniazid 300 mg for six months and, subsequently, the biological therapy was reintroduced, with favorable evolution. Through those years only three patients developed tuberculosis (disease), being two of them the pulmonary form and one patient with the cutaneous one, the time of tuberculosis was properly treated and there were no major complications when returning to treatment with anti-TNFs. All of them had a history of contact with people who had been diagnosed with tuberculosis.

DISCUSSION

According to data from the World Health Organization (WHO), about 2 to 3 billion people in the world have the tuberculosis bacillus. Latent tuberculosis (FIGURE 1) is asymptomatic and has been responsible for a large number of cases of active tuberculosis; high-risk groups such as inflammatory disease carriers using immunosuppressants and biological therapy have been cited[10]. Brazil is one of

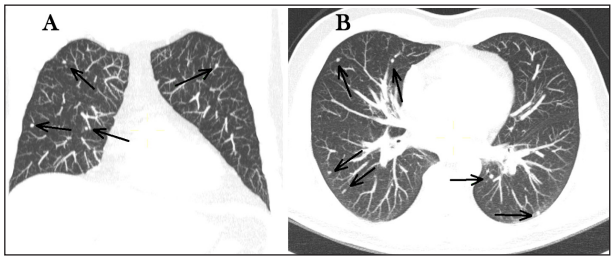

FIGURE 1. Computed tomography of the chest showed images with peripheral pulmonary micronodules in both lungs, a characteristic aspect of latent pulmonary tuberculosis.

the countries with the largest number of tuberculosis cases in the world[2]. Patients with latent tuberculosis have a high risk of progressing to active disease, so it is extremely important not only to recognize cases of active tuberculosis, but those of latent tuberculosis is of fundamental importance to prevent new cases[11]. According to WHO, treatment of latent tuberculosis with isoniazid has substantially reduced the risk of new cases up to 90%[11,12]. With the increasing number of cases of inflammatory bowel disease in the world and also in Brazil, it is expected that the number of cases of tuberculosis infections will assume greater proportions[13].

The use of anti-TNFs may favor the reactivation of latent tuberculosis. By neutralizing TNF the risk of developing active tuberculosis is about 2 to 3 times higher than when compared to those who do not use these drugs, and the risk could be alarmingly higher in endemic areas such as the region where Campo Grande is located (Centre Western Brazil)[14,15].

This is the first study conducted in Brazil in a private reference health service center for inflammatory bowel diseases located in the Midwest region of Brazil, comparing the different drugs used on their own (monotherapy) over fourteen years, with the main objective of identifying the latent tuberculosis risk in an endemic area[16-18].

Latent tuberculosis is underdiagnosed in Brazil, an extremely worrying fact in a country considered as an endemic area for tuberculosis, where different health programs are established to eliminate the disease[1]. Concerningly, many patients with CD and UC will at some point be subjected to medications that may increase the risk of developing this infection, thereby establishing continuous screening for these patients could be of paramount importance[8,11,18-21]. It is recognized that people with latent tuberculosis

have a high risk of progressing to active tuberculosis, one of the ways to identify these cases is through the screening test TST (tuberculin skin test)[2,12].

The TST was used and a chest X-ray was taken at the same time to screen these patients before the introduction of the drugs - immunosuppressants, anti-TNFs, corticoids and others. TST was negative in 96% of the cases and 4% of positivity were not included in this study. We opted for TST because of its cost and availability simultaneously with chest X-ray, as other tests were not available. Of the 301 patients who were initially negative, 28 of them became positive (PPD >5 mm) after the 72 h reading.

Of the patients who had TST positivity, a chest tomography was applied to confirm latent tuberculosis, and most of the findings were ground-glass imaging or even. Computed tomography was applied because of the impossibility of TST to differentiate bacillus infection from active disease. The tuberculin used in Brazil was (PPD-RT23) and was followed by the application and interpretation criteria according to the WHO, considering latent tuberculosis PPD ≥5[22,23].

In Brazil, immunization (BCG vaccine) is performed at birth, which is mandatory, but it is known to confer only immunity to severe forms of tuberculosis. Thus, all Brazilians are vaccinated, and this influences the TST results since the vaccine is active for ten years after its application[24]. Conversely, this study is composed of adult or young adult patients, being questioned on the first visit the possibility of revaccination, being negative in all cases (TABLE 3)[23,25,26]. In addition, there is the possibility of false positive that have also been described with TST tests, especially in cases when immunosuppressive agents or even corticoids are applied. In this sample, all patients were without medication at the first measure (initial phase of treatment)[27].

Other studies have applied this surveillance test in Brazil to individuals who are candidates for biologic therapy[28,29]. Similar to our data, Brunelli et al. used screening with TST to track patients in Brazil and prevent latent TB, showing the usefulness and applicability of this test in that population. Similar to our study, a chest X-ray showed no utility for this group of patients[8]. We analyzed drug behavior over time through TST, which was performed each year, along with a chest X-ray. We found a higher positivity for CD, which may be related to the higher number of cases for this series. In addition, Cardoso et al. found alterations in radiological findings and, perhaps, this may be justified by the socioeconomic difference of the population in question[29]. We focused on latent tuberculosis and its correlation in several aspects, such as disease classification, gender, age, work environment and others.

By performing Montreal classification for both UC and CD, notably people with severe CD (stenosing or perianal disease) were more likely to develop latent tuberculosis (P<0.002). Similar findings were found for extensive disease in UC (P<0.038). This fact could probably be related to prolonged drug use (TABLES 1 and 3). There are no data in Brazil to date that correlate disease classification with this risk.

When analyzing the sample, we observed preponderance in males (P<0.007), young people (P<0.013), indoor working area (P<0.001) who used anti-TNFs for more than one year (TABLE 3) P<0.007. Conversely, the length of illness or previous hospitalization did not influence the greater predisposition to latent tuberculosis (TABLE 3). Unlike the study by Alawneh et al., the correlation of more than one anti-TNF with latent tuberculosis has not been studied, but time of use (>12 months) was an important factor for this undesirable effect[30]. A similar relationship between the exposure of time to anti-TNFs (>12 months) was also described by Kang et al.[15]. In addition, when comparing anti-TNFs with other drugs used, notably infliximab and adalimumab showed a higher risk for latent tuberculosis than when compared to other drugs. Interestingly with each year of medication use, the possibility of latent tuberculosis increases by 3.48 and similar data were found for infliximab. Thus, all patients received isoniazid 300 mg for six months, being followed by an infectologist or even a pulmonologist, following Cochrane's norms[31]. At the end of the treatment, anti-TNFs were reintroduced, with satisfactory evolution in all cases. Other drugs such as vedolizumab and certolizumab demand more time and even a higher number of patients to have information robust enough to make this kind of correlation.

These data are unprecedented in Brazil and show the importance of the request of screening tests for latent tuberculosis over the years and have an increasing observation according to the time of use, since we are facing a high-risk country for this disease, although the disease has low mortality[32-36].

Patients with inflammatory bowel disease should have a preliminary assessment and an ongoing evaluation for opportunistic infections, including latent tuberculosis prior to any therapy, especially anti-TNFs. In Brazil, studies should be performed during a period superior to one year, since the longer the exposure to anti-TNFs, the greater the chance of latent tuberculosis. Primary prophylaxis should be rethought for all patients with Crohn and ulcerative rectocolitis at least before introducing biological therapy in at-risk countries such as Brazil to prevent latent tuberculosis and decrease the incidence of active tuberculosis.

Authors' contribution

Cury DB: the author that conceived the study and collected all data, analyzed and interpreted them and drafted the manuscript. Micheletti AC: drafted the manuscript and the tables. Oliveira RA: performed the statistical treatment of the datas, analyzed and interpreted them. Cury LCB: the responsible for filling out the study database. Gonçalves JJS: guided and led the tracking and treatment of patients, also analyzed and interpreted the datas. All authors commented on drafts of the paper. All authors have approved the final draft of the article.

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RESUMO – Contexto – A tuberculose latente (TBL) é uma condição em que o paciente está infectado com *Mycobacterium tuberculosis*, mas não desenvolve tuberculose (TB) ativa. Existe a possibilidade de ativação da TB após a introdução de anti-TNFs. **Objetivo** – Avaliar o risco da terapia biológica induzindo TBL durante o tratamento de doenças inflamatórias intestinais (DII) ao longo de 15 anos em uma área de alto risco no Brasil. **Métodos** – Foi realizado um estudo retrospectivo de um banco de dados de pacientes com DII em uma clínica privada de referência no Brasil. Todos os pacientes foram submetidos a teste de TST e radiografia de tórax antes do tratamento e uma vez por ano após seu início. Os pacientes foram classificados de acordo com a estratificação de Montreal e foram considerados fatores de risco para o desenvolvimento de TB. **Resultados** – Entre os fatores analisados, a idade e o sexo foram fatores de risco para TBL. Os pacientes com doença de Crohn' (B2 e P) e colite ulcerativa (E2) apresentaram maior número de casos de TBL com significância estatística, o que também foi observado para usuários de adalimumab e infliximab, em comparação com outros medicamentos, e o tempo de exposição a eles favoreceu significativamente. Outros fatores, como ambiente de trabalho fechado, foram relatados como riscos. **Conclusão** – O risco da terapia biológica causar TBL é real, por isso os pacientes com DII devem ser monitorados continuamente. Este estudo revela que quanto maior a exposição aos anti-TNFs, maior o risco.

Palavras-chave – Produtos biológicos; doença de Crohn; colite ulcerativa; epidemiologia.

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