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ORIGINAL RESEARCH

Use of biologic agents and risk of tuberculosis in Brazil, a tuberculosis high-burden country

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Abstract

Background: Brazil is a country with a high burden of tuberculosis (TB). The immunomodulatory effect of biological therapies is associated with an increased risk of infection. This study evaluated the frequency of TB infection in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), and psoriatic arthritis (PsA) after the use of biologic agents in a single center of rheumatology.

Methods: In this observational study, 161 consecutive adult patients with RA, JIA, AS, and PsA using biological therapy were followed up during 55 months to evaluate the occurrence of TB infection throughout treatment. All patients were screened for latent TB infection (LTBI), and TB disease was excluded before introduction of biological therapy. Patients with LTBI received prophylaxis with isoniazid before the start of biological treatment.

Results: Of 161 patients on biologics, 31 (19.25%) had positive tuberculin skin test (TST) and received LTBI treatment. Eleven (6.8%) cases of TB were detected in patients on biologics, six (54.5%) had AS, one had PsA (9.09%), two had RA (18.18%), and two had JIA (18.18%). Regarding the use of different biologics, six (54.5%) patients received adalimumab, three (27.2%) infliximab, one (9.09%) etanercept, and one (9.09%) tocilizumab.

Conclusion: In this study, the frequency of TB infection among 161 patients on biologics, during 55 months of follow-up, was 6.8%. Compared with the national registry of patients receiving biologics (BiobadaBrasil — January 01, 2009 to May 31, 2013), a higher incidence of TB (6.8 *versus* 0.44%) was found in this sample of patients receiving biological therapy. This study highlights that in a country with high TB burden, the possibility of TB infection in a patient receiving biological therapy should always be considered, even after prophylaxis with isoniazid.

Keywords: biological therapy, immunomodulation, latent, tuberculosis, tumor necrosis factor inhibitors.

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Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. Usually, a small proportion of people infected with *M. tuberculosis* develop TB disease, but the probability of developing active TB is considerably higher among people with immunodeficiency. TB commonly presents as the classic pulmonary form but can affect other organs as well (extrapulmonary TB).[1–5]

Not all patients infected with *M. tuberculosis* become symptomatic. Therefore, from a clinical point of view, two different conditions, latent TB infection (LTBI) and TB disease, are considered. If not treated properly, TB infection can be fatal.[4–6]

TB remains a major global health problem and is one of the main causes of death worldwide. It is a leading cause of death from a single infectious agent, ranking above human immunodeficiency virus/acquired immunodeficiency syndrome. In 2016, an estimated 10.4 million people developed TB worldwide (equivalent to 133 cases per 100,000 inhabitants), and 1.3 million died from the disease.[1–3]

TB is more common among men (65%) than women and affects mostly adults (90%) in the economically productive age groups, which explains the high burden that the disease represents not only for patients but for society as a whole.[3–7]

The introduction of biologic agents has dramatically changed the management of rheumatic diseases.[7–9] However, the

immunomodulatory effect of biologics, especially tumor necrosis factor inhibitors (anti-TNFs), is associated with an increased risk of granulomatous infections, including an higher risk of TB infection or reactivation.[8,10,11]

Physicians had been aware of this risk since 2001, when a first report on TB cases after using infliximab was published by Keane and colleagues.[7] TNF plays a crucial role in the immune response against *M. tuberculosis* enhancing the phagocytic capacity of macrophages and preventing the systemic spread of the infection.[7,8]

The recognition of a higher risk of TB disease in patients on anti-TNFs has led to numerous studies, but there is still a lack of data about the incidence of TB among patients with rheumatic diseases in Brazil.[10–17] Therefore, the aim of the present study was to evaluate the association between use of biologic agents and the frequency of TB in a single rheumatology center in Brazil, a TB high-burden country (HBC).

Methods

A descriptive observational study was conducted on a sample of 515 adult rheumatic patients treated at an outpatient clinic (Santa Casa de São Paulo, São Paulo, Brazil), from January 2013 to August 2017.

Patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), and psoriatic arthritis (PsA), who were diagnosed according to American College of Rheumatology (ACR) criteria[9] and on biological therapy (n=161), were included.

Patients were receiving the usual treatment with non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, and steroids at the moment the biological therapy was introduced according to clinical criteria.

Patients were screened for LTBI prior to the introduction of anti-TNF treatment according to the Ministry of Health recommendations.[5] Screening tests included tuberculin skin test (TST), chest X-ray assessment, and history of exposure to TB. TST was performed according to Mantoux method using 0.1 mL of purified protein derivative, injected intradermally into the volar surface of the forearm. Results were evaluated as the transverse diameter in millimeters of induration at 48–72 h. A result was considered positive when the reading was ≥5 mm.[5] The screening was performed using TST only, because interferon-gamma release assay test is not paid by the health public system in Brazil. Signs of previous TB, such as fibrotic lesions, were searched in a chest radiograph, and atypical signs were reassessed by computerized chest tomography. Exposure to TB was defined as present or past contact with known TB cases.

LTBI treatment was established when indicated according to national guidelines. LTBI treatment was conducted with isoniazid, 300 mg daily throughout 6 months. The biological treatment started only after the patient received isoniazid for at least 2 months.[5,10,15]

This study reports clinical outcomes of adult rheumatic patients on biological therapy using an observational, non-interventional design. All data were collected as part of routine diagnosis and usual treatment, and patients were diagnosed and treated according to national guidelines and current practices in Brazil.[10–17] Therefore, it was considered not necessary to obtain informed consent or ethical committee approval for this study. Nonetheless, measures were taken to ensure patient anonymity and protection of personal data.

Results

In our observational study, 161 rheumatic patients were included. Of these, approximately two-thirds received a diagnosis of RA, while about 20% of patients had AS. Diagnosis of JIA and PSA was less frequent, accounting for about 3 and 6% of patients, respectively. Nearly 90% of patients with RA were women, while male gender was predominant in patients with AS. The age was according to an outpatient rheumatic population (mean age of 53 years for RA), with certainly younger patients among those with JIA. Duration of disease showed a wide range from 1 to 32 years. Main demographic and clinical characteristics of patients can be seen in Table 1.

Patients were on biologics, and 11 (6.8%) cases of TB were detected after treatment commencement. Of those 161 patients receiving biologic agents, 31 (19.25%) had positive TST. All 31 patients received LTBI prophylaxis, but despite its use,

Table 1. Main demographic and clinical characteristics (n=161).

Condition	Rheumatoid arthritis (RA)	Ankylosing spondylitis (AS)	Juvenile idiopathic arthritis (JIA)	Psoriatic arthritis (PsA)
Number of patients (percentage)	111 69.38%	35 21.88%	5 3.13%	10 6.25%
Gender (male/female)	12/99	31/4	3/2	4/6
Age range, years (mean, median)	29–75 y (53, 54)	23–61 y (40, 38)	20–38 y (31, 33)	43–73 y (52, 49)
Duration of disease, years	1–32 y	1–21 y	1–11 y	2–9 y

Table 2. Rheumatologic patients who developed TB disease after treatment with biologic agents.

Patient	Age (years)	Sex	Diagnosis	Duration of disease	Treatment with DMARDs	PPD	Biologic agent	Time B-TB	TB presentation
1	20	M	JIA	11 years	MTX + PDN	Negative	Adalimumab	8 months	Pulmonary
2	41	M	AS	9 years	SSZ + NSAID	Negative	Adalimumab	9 months	Pulmonary
3	29	F	RA	2 years	MTX + LEF + PDN	Negative	Infliximab	3 months	Peritoneal + intestinal
4	73	M	PsA	7 years	MTX + NSAID	Negative	Adalimumab	18 months	Pulmonary
5	32	M	AS	2 years	SSZ + NSAID	10 mm	Adalimumab	10 months	Peritoneal + intestinal
6	56	M	AS	20 years	NSAID	12 mm	Etanercept	15 months	Pulmonary
7	54	M	AS	12 years	MTX + NSAID	17 mm	Adalimumab	22 months	Pulmonary
8	30	F	AS	3 years	SSZ + NSAID	10 mm	Infliximab	18 months	Pulmonary
9	30	M	AIJ	9 years	MTX + PDN	Negative	Infliximab	9 years	Pulmonary
10	41	M	AS	4 years	NSAID	Negative	Adalimumab	15 months	Intestinal
11	44	F	RA	14 years	LEF + PDN	Negative	Tocilizumab	31 months	Pulmonary

AS, ankylosing spondylitis; DMARDs, disease-modifying antirheumatic drugs; JIA, juvenile idiopathic arthritis; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drugs; PDN, prednisone; PPD, purified protein derivative skin test (Mantoux method); PsA, psoriatic arthritis; RA, rheumatoid arthritis; SSZ, sulfasalazine; Time B-TB: time interval between biologic start and tuberculosis onset.

four of them developed TB and received treatment. Table 2 shows main demographic and clinical data of 11 patients who developed TB disease.

Among the 11 patients who developed TB disease, six (54.5%) had AS, one had PsA (9.09%), two had RA (18.18%), and two had JIA (18.18%). Eight patients were men (72.7%); four (36.3%) patients presented a positive TST reaction and were treated for LTBI.

Eight (72.7%) patients showed a pulmonary form of TB, two (18.1%) presented a peritoneal form, and one (9.09%) had only intestinal compromise. Mean time between start of biological therapy and occurrence of TB was 23.3 months.

Regarding biologic agents administered, six (54.5%) patients received adalimumab, three (27.2%) infliximab, one (9.09%) etanercept, and one (9.09%) tocilizumab.

Discussion

Our study found a higher incidence of TB (6.8 *versus* 0.44%) compared with data from BiobadaBrasil — from January 1, 2009 to May 31, 2013, where they found only five TB cases among 1137 patients on biologics.[15]

BiobadaBrasil was set up by the Brazilian Society of Rheumatology aiming to develop a national registry of rheumatologic patients receiving biologics. BiobadaBrasil includes all patients undergoing biological therapy, and a strict record with complete data is associated to the patient clinical follow-up. Infections are a central concern for patients using biological therapies and are a permanent focus in the registry.[12–15]

Unique characteristics of Brazil, such as genetic diversity of the population, particular socio-economic situations through different regions, and endemic diseases, including TB, have impelled the establishment of this national registry of patients on biological therapies for rheumatologic diseases. The main purport of this registry is to develop large epidemiological studies for monitoring patients receiving biologic agents. A recent cohort study conducted by Yonekura and colleagues, on behalf of BiobadaBrasil, found that the incidence of TB was 1.01/1000 patient-years in controls and 2.87 patient-years among anti-TNF users, considering exposure times of 981 patient-years in controls and 1744 patient-years in the anti-TNF group.[15]

A previous study reported by Bonfiglioli in São Paulo, Brazil, evaluated LTBI screening in rheumatic patients living in an endemic area. In this study, 202 RA patients were screened for LTBI by means of TST, chest radiography, and history of TB exposure. Patients were periodically followed for LTBI, and only two cases of active TB were reported after biological therapy initiation.[11]

Brazil belongs to a list of 30 countries designated by the World Health Organization (WHO) as TB HBC.[1–3] In 2016, with more than 208 million inhabitants, Brazil had an indirect estimated prevalence of 51 TB cases per 100,000 inhabitants, equivalent to a total of approximately 110,000 cases. The estimated incidence was 42 cases per 100,000 inhabitants (equivalent to

87,000 cases per year), with a mortality rate of 3.5 per 100,000 population (7300 deaths per year).[2,3]

Gender differences in the risk of TB are commonly reported.[12,18] We found a substantially larger incidence of active TB in male than in female patients (8/11 *versus* 3/11 cases, respectively). In most parts of the world, usually more men than women are diagnosed with TB. According to WHO, in 2015, nearly 6 million adult men contracted TB compared with an estimated 3.5 million adult women. In our study, as typically reported, rheumatic male patients under biological therapy showed a greater risk of contracting TB than women.[6]

Screening for active TB and LTBI is mandatory prior to the start of biological therapy in patients with rheumatic diseases.[17–23] In a study conducted to determine the prevalence of LTBI in patients with RA before biological therapy and the conversion rate during biological treatment, Cuomo and colleagues included 275 patients showing negative baseline TST, with rescreening every year. After a follow-up of 12–120 months, 34 (13.6%) patients showed conversion of at least one screening assay. According to investigators, these results endorse the ACR recommendation for annual screening in patients treated with biologic agents.[21]

Overall, about 5–15% of infected persons who do not receive treatment for LTBI will develop TB disease within the first 5 years after initial infection. Therefore, patients with LTBI need treatment to prevent the development of TB disease.[4,5,19–27]

According to Getahun and colleagues, LTBI is characterized by the presence of immune responses to previously acquired *M. tuberculosis* infection without clinical evidence of active disease.[1] Patients with LTBI have no symptoms, do not feel sick, and may have a normal chest x-ray and a negative sputum smear. However, they may have a positive TST reaction or a positive TB blood test, and may develop active TB if they suffer an immune system deficiency.[1,4,5,16–20]

In our study, 36.3% of the patients, who received LTBI treatment, had TB disease and the biologic agent was started 2 months after the use of isoniazid. The other 63.7% who also developed TB disease had negative TST and normal chest X-ray, and therefore no indication for LTBI treatment.

The III Brazilian Thoracic Association Guidelines on TB, coordinated by M. Conde, stated that the diagnosis of LTBI is based on positive TST results in combination with the exclusion of active TB. With a positive purified protein derivative reaction, the size of the induration on the TST guides the need for treatment of LTBI.[17]

Ferreira and colleagues maintain that treatment of individuals with TB disease and the identification and treatment of LTBI contacts are the two most important strategies for the control of TB.[16] However, there is no gold standard test for diagnosis of LTBI. TST and blood (interferon-gamma release assay) tests are performed to diagnose LTBI. In Brazil, LTBI individuals are usually diagnosed by means of a positive TST associated with the exclusion of TB disease. The advantages of TST include the technical ease of the method and its low cost. However, the sensitivity of TST may be reduced in certain conditions, such as malnutrition, cancer, and immunosuppression, and its specificity can also be affected by false-positive results. For diagnosing TB disease, the most common method worldwide is sputum smear microscopy, and the use of rapid molecular tests is increasing following recent technical advances.[16–21]

Lalvani and colleagues affirm that patients with immune-mediated inflammatory disorders, including rheumatic diseases, are prone to false-negative TST results because they are already on immunosuppressive medications[19] False-negative TST results can also be explained by exposure time as a period of 6–8 weeks post exposure to *M. tuberculosis* bacillus is necessary for a positive result.[17–22]

Another topic about the diagnosis of LTBI is the use of chest tomography. In our study, chest tomography was not systematically used. Skoura and colleagues refer that although new imaging methods are being used, conventional radiography remains the initial modality for suspected TB and for mass screening purposes.[23] Computed tomography and magnetic resonance imaging are preferred for the evaluation of specific parts of the body. In primary pulmonary TB, chest radiography is still the basis for the diagnosis of parenchymal disease, while chest tomography is more sensitive in detecting lymphadenopathy. In post-primary pulmonary TB, chest tomography is the main method to reveal early bronchogenic spread. Relating to classification of the infection as active or not, chest tomography may be more sensitive than radiography. Other diagnosis methods used in some clinical trials, such as ^{18}F-fluorodeoxyglucose positron emission tomography scan, reported promising results but need additional confirmation.[19–23]

In recent years, several non-anti-TNF-targeted biologics, such as ustekinumab and secukinumab, have been approved for the treatment of RA, AS, and PsA. According to Cantini and colleagues, data from controlled trials and postmarketing surveillance show that risk of TB reactivation in patients receiving non-anti-TNF-targeted biologics is negligible. Therefore, TB reactivation risk should be assessed periodically in all patients under anti-TNFs, and in case of positive results, the use of non-anti-TNF-targeted biologics may represent a safer option.[22]

TNF is a proinflammatory cytokine produced by lymphocytes and macrophages that have a key role in the host response to infections and in the pathogenesis of different chronic immune-mediated diseases, such as RA, AS, JIA, and PsA. There are several TNF inhibitors available for clinical use, such as infliximab, adalimumab, golimumab, certolizumab pegol, and etanercept. TNF favors the recruitment and the activation of lymphocytes, neutrophils, and platelets, the expression of adhesion molecules on endothelial cells, and induces the neo-angiogenesis in the sites of inflammation. Thus, TNF has a central role in the initial host response to infection. In TB infection, it results in macrophage activation, cell recruitment, granuloma formation, and maintenance of granuloma

integrity. Several studies analyzed the association between TNF inhibitor administration and the risk of TB infection. Reactivation of LTBI and the overall risk of opportunistic infections should be considered before the beginning of TNF inhibitor treatment.[24–27] According to Murdaca and colleagues, infliximab more so than etanercept appears to be responsible for the increased risk of infections.[24,25] Current treatment guidelines recommend the discontinuation of TNF inhibitors when active TB occurred in patients receiving anti-TNF therapy. However, there is no guidance on the safety or the most appropriate time for the reintroduction of TNF inhibitors. The reintroduction of TNF inhibitors should be delayed until completion of anti-TB therapy.[7–9,11,14,19,24,25]

The activity of regulatory lymphocytes is important to preserve the homeostasis of immune system function. In recent years, studies on regulatory lymphocytes demonstrated that CD8+ T suppressor cells may control immune system homeostasis and avoid development of chronic inflammatory diseases.[26,27] The type 2 (non-antigen-specific) CD8+ T suppressor lymphocyte is characterized by the capacity to inhibit both T-cell proliferation and cytotoxic T-lymphocyte activity through secretion of soluble factors. The impairment of type 2 CD8+ cells has been observed in patients with multiple sclerosis, systemic lupus erythematosus, systemic sclerosis, and in patients with HIV or chronic infections. According to Filaci and colleagues, these studies suggest that type 2 CD8+ T suppressor cells may participate in the control of pathologic chronic immune responses and play a role in the pathogenesis of chronic inflammatory diseases.[26,27]

Finally, in our study, 6 out of 11 cases of active TB infection were detected in patients who had received a diagnosis of AS. A recent meta-analysis of randomized controlled trials did not find any significantly increased risk of infection associated with anti-TNF therapy in patients with AS. Due to the limited number of cases, these findings must be interpreted with caution, and AS patients treated with anti-TNF agents should be closely monitored in clinical practice.[28]

Conclusion

In this study, the frequency of TB infection among 161 consecutive patients on biologics, during a follow-up of 55 months, was 6.8%. Despite some limitations, this study reinforces that in a TB HBC, the possibility of TB infection in a patient receiving biological therapy should always be considered even after the LTBI treatment with isoniazid. Compared with national data from BiobadaBrasil, we found a higher incidence of TB (6.8 *versus* 0.44%). Multicenter and long-term studies could provide more data about this important health issue.

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