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Original Article

Incidence of tuberculosis infection in spondyloarthritis patients treated with biological and conventional disease-modifying anti-rheumatic drugs in an endemic area

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ABSTRACT

Introduction: Registries of spondyloarthritis (SpA) patients' follow-up provided evidence that tumor necrosis factor inhibitors (TNFi) increase the incidence of active tuberculosis infection (TB). However, most of these registries are from low burden TB areas. Few studies evaluated the safety of biologic agents in TB endemic areas. This study compares the TB incidence rate (TB IR) in anti-TNF-naïve and anti-TNF-experienced subjects with SpA in a high TB incidence setting.

Methods: In this retrospective cohort study, medical records from patients attending a SpA clinic during 13 years (2004 to 2016) in a university hospital were reviewed. The TB IR was calculated and expressed as number of events per 10^5 patients/year; the incidence rate ratio (IRR) associated with the use of TNFi was calculated.

Results: A total of 277 patients, 173 anti-TNF-naïve and 104 anti-TNF-experienced subjects, were evaluated; 35.7% (N = 35) of patients who were prescribed an anti-TNF drug were diagnosed with latent tuberculosis infection (LTBI). Total follow-up time (person-years) was 1667.8 for anti-TNF-naïve and 394.9 for anti-TNF-experienced patients. TB IR (95% CI) was 299.8 (37.4-562.2) for anti-TNF naïve and 1012.9 (25.3-2000.5) for anti-TNF experienced subjects. The IRR associated with the use of TNFi was 10.4 (2.3- 47.9).

Conclusions: In this high TB incidence setting, SpA patients exposed to anti-TNF therapy had a higher incidence of TB compared to anti-TNF-naïve subjects, although the TB incidence in the control group was significant.

Keywords: *Spondyloarthritis; tuberculosis; anti-TNF therapy; tumor necrosis factor alpha; tuberculin skin test*

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Tumor necrosis factor inhibitors (TNFi), also called anti-TNF agents, have emerged as an effective treatment in immune-mediated diseases and are associated with clinical benefits in patients with spondyloarthritis (SpA)[1]. However, they may induce progression from latent tuberculosis infection (LTBI) to active tuberculosis (TB)[2]. Cases of TB have been associated with TNFi use in patients with rheumatic diseases[3-6].

The American College of Rheumatology (ACR) recommends LTBI screening for patients who are candidates for anti-TNF therapy, with either tuberculin skin-test (TST) or interferon-gamma release assay (IGRA). It also recommends that patients who live in high TB incidence settings should be tested annually for LTBI[7]. However, TB cases developed despite the screening and treatment for LTBI[3-6,8-10]. Indeed, LTBI diagnosis is difficult in patients already on immunosuppressive medications (disease modifying antirheumatic drugs [DMARDs] and steroids) because of false-negative TST results[11]. In addition, low compliance with LTBI

treatment is another explanation to TB occurrence during anti-TNF therapy[12]. Furthermore, in highly endemic areas, TB cases in patients exposed to TNFi could be a consequence of new infection[3-6].

Previous studies describing TB infection during anti-TNF therapy included mostly patients with rheumatoid arthritis, living in low burden TB areas and outside Latin America[3-6,9]. Then, the objective of the present paper was to study the safety of TNFi in a resource-poor country, evaluating the TB incidence rate in TNFi-naïve and TNFi-experienced subjects with SpA in a high TB incidence setting.

METHODS

A retrospective cohort study was conducted in a public tertiary university hospital located in Porto Alegre, a city in southern Brazil with a high incidence of TB, where 88.8 cases were diagnosed per 100,000 population in 2015[13]. Electronic medical records from patients attending the SpA clinic between July 2004 and December 2016 were reviewed. Age, gender, self-reported ethnicity, time since the SpA diagnosis, past or current use of TNFi, history of TB and/or LTBI, as well as TST and chest radiograph results before the first TNFi were recorded.

The "on drug" model was used, i.e., TB cases were attributed to anti-TNF therapy if the patient was actively receiving the drug at the time of diagnosis[14,15]. The date of TNFi discontinuation was taken as the first missed dose. The follow-up period was considered as the time between the first visit to the SpA clinic and the most recent follow-up visit or death; follow-up was not censored at the time of TB diagnosis. Patients could restart treatment following an episode of TB, either resuming prior treatment or switching drugs. Subjects in the comparison arm who were prescribed a TNFi contributed person-years to the comparison cohort up to the date this drug was started and subsequent follow-up to the TNFi cohort. Patients initially registered in the anti-TNF arm could not contribute to the comparator arm when the anti-TNF drug was stopped.

TB cases were considered "confirmed cases" if they were culture positive and/or acid fast bacillus smear positive. Patients with a physician-determined diagnosis of TB without these criteria were considered "unconfirmed cases".

Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range; categorical variables were expressed as absolute and relative frequency. The tuberculosis incidence rate (TB IR) was reported as events/10^5 person-years with 95% confidence interval (95% CI). The TB incidence rate ratio (TB-IRR) was calculated using Cox regression, comparing the TNFi-naïve and TNFi-experienced cohorts, with adjustments for age, gender and ethnicity. To compare other characteristics between cohorts, the Pearson's chi-square or Fisher's exact, Mann-Whitney or Student's t tests were used. Significance level was defined as p-value lower than 0.05. The SPSS version 18.0.0 was used[16].

The study was approved by the institutional Ethics Committee at Hospital de Clínicas de Porto Alegre, (GPPG 170231, approval number 2031188), and investigators signed an informed consent for use of patients' data.

RESULTS

A total of 277 patients were evaluated, 173 TNFi-naïve and 104 TNFi-experienced. Those exposed to anti-TNF drugs were diagnosed with SpA in a younger age and were more frequently men than anti-TNF naïve patients (Table 1).

Ankylosing spondylitis (41.5%, N = 111) and psoriatic arthritis (39.0%, N = 108) were the most common diagnoses.

Total follow-up time (in person-years) was 1667.8 for the TNFi-naïve cohort and 394.9 for the TNFi-experienced cohort. The median (IQR, 25-75%) duration of follow-up per patient was 6.1 (1.7-10.6) years for the TNFi-naïve group and 3.8 (2.0-4.9) years for subjects previously exposed to anti-TNF therapy. About 35.0% of subjects (97/277) switched from the TNFi-naïve to the TNFi-experienced group and contributed person-years to both cohorts.

Among the TNFi-experienced cohort, 67.3% (N = 70), 34.1% (N = 36) and 27.9% (N = 29) of patients were exposed to adalimumab, etanercept and infliximab, respectively. The median duration "on drug" (IQR, 25-75%) was 2.8 (1.6-4.4) for adalimumab, 1.7 (0.7-4.1) for etanercept and 2.1 (0.8-4.4) for infliximab. Only one patient was exposed to golimumab and no one was exposed to certolizumab as these drugs were not available in the public health system at the time of study conduction.

From the 104 subjects who were prescribed anti-TNF therapy, 98.1% (N = 101) underwent chest radiography and 95.2% (N = 99) underwent TST before starting the first anti-TNF drug. Among the patients who had both TST and chest radiograph available (94.2%, N = 98/104), 35.7% (N = 35) were diagnosed with LTBI. Among patients with LTBI, 94.3% (N = 33/35) were diagnosed because of TST ≥ 5 mm and 5.7% (2/35) because of abnormal chest radiograph. All patients diagnosed with LTBI underwent 6 months of isoniazid preventive therapy (IPT) and TNFi was started after at least 1 month of IPT.

There were 9 cases of TB: 5 in the TNFi-naïve and 4 in the TNFi-experienced cohort (Table 2). Among the 4 patients treated with TNFi who developed TB, 2 had negative screening for LTBI, 1 was diagnosed with LTBI and treated with isoniazid before starting biological

Table 1: Characteristics of the 277 subjects included in the analysis

Characteristics	Anti-TNF-naïve N = 173	Anti-TNF-experienced N = 104	P-value
Age at time of SpA diagnosis, years (mean ± SD)	44.8 ± 14.4	39.2 ± 11.9	< 0.001
Female gender, N (%)	92 (53.2)	41 (39.4)	0.036
Disease duration, years (median [IQR, 25-75%])	10.7 (5.7-19.7)	10.7 (6.7-17.4)	0.615
Self-reported white ethnicity, N (%)	163 (94.2)	96 (92.3)	0.709

IQR: interquartile range; N: number; SD: standard deviation; SpA: spondyloarthritis; TNF: tumor necrosis factor.

therapy, and 1 had no TST available in medical records. Individuals who developed TB during anti-TNF treatment were frequently diagnosed with disseminated infection (75%, N = 3), and all were diagnosed with TB more than 1 year after starting TNFi (Table 2).

Patients with SpA exposed to TNFi had a higher incidence of TB compared to those who had never been exposed to these drugs: the TBIR in cases/10^5 patient/year (95% CI) was 299.8 (37.4-562.2) in the TNFi-naïve cohort versus 1012.9 (25.3-2000.5) in

Table 2. Characteristics of spondyloarthritis patients diagnosed with tuberculosis

Case number	Gender (M = male, F = female)	Self-reported ethnicity	Age at TB diagnosis (in years)	TB confirmed case?	Clinical form of TB	SpA subtype	Current treatment when TB was diagnosed	Delay between the first dose of anti-TNF drug and TB diagnosis (in years)	TST before anti-TNF therapy (in mm)
SUBJECTS EXPOSED TO ANTI-TNF THERAPY									
1	M	White	56	Yes	Disseminated	AS	ADA 40 mg EOW + MTX 20 mg/ week	1.6	8*
2	F	White	44	Yes	Pulmonary	AS	ADA 40 mg EOW	5.0	unknown
3	M	White	61	Yes	Disseminated	PsA	ADA 40 mg EOW + MTX 17.5 mg/ week	4.2	0
4	M	White	72	No	Disseminated	PsA	ADA 40 mg EOW + MTX 15 mg/ week	5.4	0
SUBJECTS NONEXPOSED TO ANTI-TNF THERAPY									
5	F	White	48	No	Pulmonary	AS	NSAID + prednisone 5 mg/day	-	-
6	M	White	67	No	Pulmonary	PsA	MTX 15 mg/week + LEF 20 mg/ day + prednisone 5 mg/day	-	-
7	M	White	68	Yes	Pulmonary	AS	NSAID	-	-
8	M	White	59	No	Adrenal	AS	SSZ 1500 mg/ day	-	-
9	F	White	58	Yes	Pulmonary	PsA	LEF 20 mg/day	-	-

ADA: adalimumab; AS: ankylosing spondylitis; EOW: every other week; LEF: leflunomide; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; PsA: psoriatic arthritis; SpA: spondyloarthritis; SSZ: sulfasalazine; TB: active tuberculosis infection; TNF: tumor necrosis factor; *: patient underwent 6 months of isoniazid preventive therapy.

the TNFi-experienced cohort. The TB IRR (95% CI) associated with the use of anti-TNF therapy was 10.4 (2.3-47.9) and did not change after adjustments for age, gender and ethnicity. It was not possible to compare the TB risk among the various anti-TNF agents as the number of patients on each drug was small.

DISCUSSION

The analysis of SpA patients living in this resource-poor country in Latin America produced three main results: 1) the TNFi-experienced SpA patients had a higher incidence of TB compared to those who had never been exposed to these drugs, 2) the TNFi-naïve patients, i.e., those only taking conventional DMARDs and NSAIDs had a high TB incidence and LTBI screening should also be considered in this population, 3) one-third of SpA patients who underwent screening for LTBI before starting biological therapy were diagnosed with LTBI.

Our results are in accordance with previous research which demonstrated TNFi to increase the incidence rate of TB in SpA patients living in intermediate-burden areas and also in high-burden areas in developed countries[17,18].

TNF has been demonstrated to play a major role in the formation of granulomas, during macrophage activation as well as cell recruitment to the site of infection[19-21]. Therefore, inhibition of TNF is the biological basis by which TNFi increased the risk of disease by inducing the progression from LTBI to active TB[2]. In our study, 35.7% of SpA patients were diagnosed with LTBI. This prevalence is slightly smaller than that found in the district of Seine-Saint-Denis, France, where 47.2% of patients with inflammatory rheumatic diseases were TST-positive[22]. Lower prevalence of LTBI was described by other studies conducted in Brazil (13.4% and 27.0%), Peru (29.0%) and India (20.4%)[23-26]. However, these studies included mostly rheumatoid arthritis patients, known to have decreased TST positivity attributable to a defect in cellular immunity[27-30]. In fact, in a case-control study conducted in Turkey, the frequency of TST positivity in patients with rheumatoid arthritis (29.8%) was lower than in patients with ankylosing spondylitis (65.9%)[31]. In another study, LTBI prevalence was higher in patients with ankylosing spondylitis (37.6%) than in those with rheumatoid arthritis (12.8%) and psoriatic arthritis (18.8%)[32].

There were 9 cases of TB in the present study: 5 among TNFi-naïve and 4 among TNFi-experienced individuals. The incidence rate of TB among TNFi-naïve patients 299.8 cases (37.4-562.2)/10^5 patients/year was significant in this TB endemic area. Possible explanations for the occurrence of TB in TNFi-naïve subjects are the use of other immunosuppressive medications such as conventional DMARDs and steroids, which can also increase the risk of TB, although in a lesser extent than anti-TNF agents. Also, these patients live in an endemic area, where continuous and repeated exposure to TB is likely. Although recent research showed that in a low TB risk area biological-naïve SpA are not at an increased TB risk[33], our study demonstrated that in endemic TB areas this group of patients had a high incidence of TB. Thus, LTBI screening should be considered even in TNFi-naïve subjects, especially in those taking corticosteroids and/or conventional DMARDs. The screening for LTBI in Brazil is restricted to patients exposed to anti-TNF alpha and patients receiving ≥ 15mg/day prednisone or equivalent for more than 1 month[34].

Among the 4 TB cases reported in TNFi-experienced subjects, 2 had negative screening for LTBI and 1 underwent IPT before starting the anti-TNF agent. Furthermore, all TNFi-experienced patients who developed TB were diagnosed with this condition more than 1 year after exposure to biological therapy, indicating that they were most likely newly acquired infections.

TB cases during anti-TNF treatment are usually a consequence of new infection or reactivation of LTBI not diagnosed during screening (due to a false-negative TST)[3-6]. This reinforces the need of TST repetition during anti-TNF treatment[7]. In addition, TB cases have been described during anti-TNF therapy even in patients with previous LTBI treatment[10] as IPT cannot prevent the development of TB via new infection, especially in highly endemic areas.

This study has some limitations that we must take into account. First, we analyzed information from a single hospital. However, we believe the results may apply to other settings, especially TB endemic areas. Second, the exposure status and outcomes were ascertained retrospectively based on information found in medical records. Despite the retrospective design, there were few missing values. Third, the calculated TBIR had large confidence intervals because of the small number of TB cases in the sample. In spite of these concerns, knowledge of the incidence of TB during anti-TNF treatment in patients with SpA is important to define the best approach for LTBI screening in those patients from populations at risk.

In conclusion, we found that, in a region with high TB prevalence in a resource-poor country, patients with SpA exposed to TNFi had a higher incidence of TB compared to those who had never been exposed to these drugs. Additionally, a high percentage of SpA patients were diagnosed with LTBI. Physicians should be aware of the possibility of TB development during anti-TNF therapy, even after LTBI treatment. Also, our data reinforces the ACR's recommendation that patients who live in endemic settings should be tested annually for LTBI[7].

Conflict of interest

The authors declare no conflict of interest.

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