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Original article

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)

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http://dx.doi.org/10.1016/j.rbre.2017.05.005

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ARTICLE INFO

Article history:
Received 17 August 2015
Accepted 24 May 2017
Available online 22 July 2017

Keywords:
Rheumatoid arthritis
Tuberculosis
Biologics
Brazil
Registry

ABSTRACT

Objectives: To assess the incidence of tuberculosis and to screen for latent tuberculosis infection among Brazilians with rheumatoid arthritis using biologics in clinical practice.
Patients and methods: This cohort study used data from the Brazilian Registry of Biological Therapies in Rheumatic Diseases (Registro Brasileiro de Monitoração de Terapias Biológicas – BiobadaBrasil), from 01/2009 to 05/2013, encompassing 1552 treatments, including 415 with only synthetic disease-modifying anti-rheumatic drugs, 942 synthetic DMARDs combined with anti-tumor necrosis factor (etanercept, infliximab, adalimumab) and 195 synthetic DMARDs combined with other biologics (abatacept, rituximab and tocilizumab). The occurrence of tuberculosis and the drug exposure time were assessed, and screening for tuberculosis was performed. Statistical analysis: Unpaired *t*-test and Fisher's two-tailed test; $p < 0.05$.
Results: The exposure times were 981 patient-years in the controls, 1744 patient-years in the anti-TNF group (adalimumab = 676, infliximab = 547 and etanercept = 521 patient-years) and 336 patient-years in the other biologics group. The incidence rates of tuberculosis were 1.01/1000 patient-years in the controls and 2.87 patient-years among anti-TNF users (adalimumab = 4.43/1000 patient-years; etanercept = 1.92/1000 patient-years and infliximab = 1.82/1000 patient-years). No cases of tuberculosis occurred in the other biologics group. The mean drug exposure time until the occurrence of tuberculosis was 27(11) months for the anti-TNF group.
Conclusions: The incidence of tuberculosis was higher among users of synthetic DMARDs and anti-TNF than among users of synthetic DMARDs and synthetic DMARDs and non-anti-TNF biologics and also occurred later, suggesting infection during treatment and no screening failure.

Incidência de tuberculose em pacientes com artrite reumatoide em uso de bloqueadores do TNF no Brasil: dados do Registro Brasileiro de Monitoração de Terapias Biológicas BiobadaBrasil

Palavras-chave:
Artrite reumatoide
Tuberculose
Biológicos
Brasil
Registro

RESUMEN

Objetivos: Avaliar incidência de tuberculose e triagem para tuberculose latente em brasileiros com artrite reumatoide em uso de agentes biológicos na prática clinica.
Pacientes e métodos: Estudo de coorte com dados do Registro Brasileiro de Monitoração de Terapias Biológicas (BiobadaBrasil), de 01/2009 a 05/2013, abrangeu 1.552 tratamentos, 415 somente com drogas modificadoras do curso da doença (MMCDs) sintéticas, 942 MMCDs sintéticas em associação com anti-TNF (etanercepte, infliximabe, adalimumabe) e 195 MMCDs sintéticas em associação com outros biológicos (abatacepte, rituximabe e tocilizumabe).

Avaliaram-se ocorrência de tuberculose, tempo de exposição às drogas e triagem para tuberculose. Análise estatística: teste t não pareado e teste de Fisher bicaudal; $p < 0,05$.

Resultados: O tempo de exposição dos controles foi de 981 pacientes-ano, do grupo de anti-TNF foi de 1.744 pacientes-ano (adalimumabe = 676, infliximabe = 547 e etanercepte = 521 pacientes-ano) e o de outros biológicos de 336 pacientes-ano. A incidência de tuberculose foi de 1,01/1.000 pacientes-ano nos controles e de 2,87 pacientes-ano nos usuários de anti-TNF (adalimumabe = 4,43/1.000 pacientes-ano; etanercepte = 1,92/1.000 pacientes-ano e infliximabe = 1,82/1.000 pacientes-ano). Não houve casos de tuberculose no grupo de outros biológicos. O tempo médio de exposição até a ocorrência de tuberculose foi de 27(11) meses para o grupo anti-TNF.

Conclusões: A incidência de tuberculose foi maior nos usuários de MMCDs sintéticas e anti-TNF do que nos usuáris de MMCDs sintéticas e de MMCDs sintéticas e biológicos não anti-TNF, e também mais tardia, sugerindo infecção durante o tratamento, e não falha na triagem.

Introduction

The introduction of tumor necrosis factor blockers (anti-TNF) started the era of biological therapies for rheumatoid arthritis (RA), unquestionably benefiting the share of patients unresponsive to disease-modifying anti-rheumatic drugs (DMARDs),[1] thereby resulting in reduced radiographic progression, fewer joint deformities and improved overall health of individuals.[2,3] In Brazil, the following biological DMARDs were available in the Unified Health System (Sistema Único de Saúde – SUS) until 2012: etanercept (ETN), infliximab (IFX), adalimumab (ADA), abatacept (ABT), rituximab (RTX) and tocilizumab (TCZ). In addition to therapeutic failure, the main reason for treatment discontinuation is the occurrence of adverse events, among which infections are the most worrying based on either the relative frequency or the severity.[4,5] The increased incidence of tuberculosis (TB) among anti-TNF users is a worldwide concern, with strong evidence suggesting a causal relationship.[6–8]

TB is a disease with a high worldwide incidence and prevalence, inclusively in Brazil. The World Health Organization (WHO) estimates that the worldwide incidence of TB was 9.4 million cases (equivalent to 137 cases per 100,000 inhabitants) and that the prevalence was 14 million cases (equivalent to 200 cases per 100,000 inhabitants) in 2009.[9] In Brazil in 2010, the estimated incidence was 37.2 cases per 100,000 inhabitants.[10] Brazil is among the 22 countries prioritized by WHO, encompassing 80% of the global tuberculosis burden, and ranks 19th in number of cases. The risk for TB among patients with RA is two to four times higher than among the general population, ranging according to the study region or country.[11] No study on the incidence of TB among patients with RA in the Brazilian population has been published.

TNF plays a key role in the effective immune response against *Mycobacterium tuberculosis*, increasing the phagocytic capacity of macrophages and contributing to destroying the pathogen, forming granulomas and preventing the systemic spread of the infection.[5] Therefore, using anti-TNF in patients with RA further increases the risk for TB, which is extrapulmonary in 60% of the cases and disseminated in 26%.[11] Among anti-TNF drugs, monoclonal antibodies (IFX and ADA) are associated with a higher risk for developing TB than soluble TNF receptors (ETN).[7,8] According to a systematic literature review, the incidence of TB in patients who used ETN ranged from 9 to 39/100,000 patient-years. Conversely, the incidence of TB among those who used IFX and ADA ranged from 95 to 215/100,000 patient-years.[11] Gardam et al. suggest that functional and structural differences between monoclonal antibodies and soluble receptors may explain that difference.[5] The increased incidence of TB among patients with RA using non-anti-TNF biologics has not been undisputedly described thus far in either pre- or post-marketing clinical studies.[12–14]

All patients receiving biological therapy should be tested for latent tuberculosis infection (LTBI). In Brazil, the screening is performed by chest radiography and intradermal test with the purified protein derivative (PPD) of *M. tuberculosis*. Chemoprophylaxis with isoniazid, 300 mg/day for six months, should be performed when the PPD value is higher than or equal to 5 mm, when changes indicating TB are detected by radiography or when the clinical and epidemiological data suggest contact (or history of contact) with tuberculosis, according to recommendations from the Brazilian Department of Health (Ministério da Saúde do Brasil) and the Brazilian Society of Rheumatology (Sociedade Brasileira de Reumatologia – SBR).[15,16]

Assessing the risk for TB among patients using biologics throughout the country and for each disease separately is crucial. Only one Brazilian study showed an increase in the incidence of TB among individuals using anti-TNF for various rheumatic diseases.[17] No previous study has evaluated how the LTBI screening and treatment would be performed among patients with RA using the drugs.

We aimed to assess the incidence of TB among patients with RA using various classes of biologics. Furthermore, we assessed the incidences of TB among patients using each anti-TNF separately, comparing them with the incidence rates of tuberculosis in patients using synthetic DMARDs and in individuals from the general population.

Patients and methods

A cohort study was conducted in patients with RA who were registered in the Brazilian Registry of Biological Therapies

in Rheumatic Diseases (Registro Brasileiro de Monitoração de Terapias Biológicas – BiobadaBrasil),[18] established by the Brazilian Society of Rheumatology (Sociedade Brasileira de Reumatologia – SBR) toward monitoring the use of all biological medications indefinitely licensed for use in rheumatology in the country. The study period extended from January 01, 2009 to May 31, 2013 by online registration, including patient demographic and clinical data and information on the treatments and adverse events from 35 hospital centers from all Brazilian regions. In addition to regular medical visits, patients were followed-up *via* semiannual telephone contact and annual, on-site reviews of medical records.

Inclusion criteria: RA diagnosis (according to the 1987 American College of Rheumatology classification criteria)[19] and inclusion in the BiobadaBrasil from January 01, 2009 to May 31, 2013.

Exclusion criteria: diagnosis other than RA or having RA and using only antimalarials.

We divided the participants into three study groups: Anti-TNF group, represented by patients with RA using synthetic DMARDs and anti-TNF (IFX, ETN or ADA); Other biologics group, represented by patients with RA using synthetic DMARDs and a non-anti-TNF biologic (ABT, RTX or TCZ); and Control group, represented by patients with RA using synthetic DMARDs (methotrexate, leflunomide, sulfasalazine and chloroquine). The patients in this group had never been treated with biologics. No patient migrated from the control to the biologics group. Each anti-TNF was also evaluated separately.

The study variables were the number of treatment courses with each drug, regardless of the number of patients because several patients received more than one biologic during the study period; sex; age; disease time; TB occurrence; drug exposure time; performing screening for TB (PPD skin test and chest radiography) and performing chemoprophylaxis when suspecting LTBI. Patients with PPD $\geq$ 5 mm or those with chest radiographic changes compatible with TB were considered patients with suspected LTBI, regardless of the PPD value.

Statistical analysis was performed with the unpaired *t*-test and Fisher's two-tailed test. Results were considered statistically significant if $p < 0.05$.

The study was approved by the Research Ethics Committee (Comitê de Ética em Pesquisa – CEP) of the University Hospital of the Medical School of Ribeirão Preto (Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto – HCFMRP) under process HCRP number 7694/2009. All patients signed the informed consent form to participate in the present study.

Results

A total of 1256 patients were evaluated in a total of 1552 treatments, including 415 in the Control group, 942 in the Anti-TNF group and 195 in the Other biologics group. The drug exposure times were 981 patient-years for the Control group, 1744 patient-years for the Anti-TNF group and 336 patient-years for the Other biologics group. Among the Anti-TNF group, the highest number of treatments (366, 39%) and the longest drug exposure time (676 patient-years) occurred with ADA, followed by IFX (293, 31%; 547 patient-years) and ETN ($n = 283$, 30%; 521 patient-years). No significant difference occurred between the three groups regarding sex, age and disease time ($p = 0.6$).

One case of TB occurred in the Control group and five cases in the Anti-TNF group, with 1.01/1000 patient-years and 2.86/1000 patient-years incidence rates, respectively. ADA had 4.43 cases/1000 patient-years incidence, followed by ETN (1.92 cases/1000 patient-years) and IFX (1.82 cases/1000 patient-years). No cases of TB were detected in the Other biologics group. Regarding the control group, the relative risk (RR) of developing tuberculosis associated with the use of anti-TNF was 2.83, which was highest among individuals treated with ADA (RR = 4.43). Table 1 outlines these data and the disease screening and chemoprophylaxis data, showing that PPD positivity and the presence of chest radiographic changes show no significant differences between study groups, similar to the ratio of individuals who received chemoprophylaxis ($p = 0.7$).

The case of TB in the Control group occurred after 18 months of exposure to treatment with DMARDs. In this case, no screening or chemoprophylaxis had been performed. The anti-TNF group showed 27.2 ± 11.0 months of drug exposure time until the occurrence of TB, with 22.7 ± 10.4 for ADA and 31 and 40 months for ETN and IFX, respectively. The standard deviations of ETN and IFX were not calculated because only one case of TB occurred for each drug. All patients had been subjected to standard screening with negative results. Individual data from patients who developed TB are outlined in Table 2.

Discussion

This study is the first conducted in Brazil evaluating patients using biologics in daily clinical practice and the occurrence of TB. Furthermore, although screening for LTBI was performed in most patients, the incidence of TB among RA patients using anti-TNF was higher than among patients who used synthetic DMARDs alone or in combination with other non-anti-TNF biologics. Since the first reports of a higher incidence of TB among anti-TNF users, the mean time to diagnosis of infection is shorter than one year.[5] It should be noted that the occurrence of TB was late in this study, indicating that most patients acquired the infection during use and not due to the presence of latent TB undetected by screening.

Brazil is a developing country, with many problems related to quality of life and public health, consequences of high social inequality and, therefore, high levels of poverty. These facts contribute to an increase in the prevalence of opportunistic infections, such as TB. The prevalence and incidence of the disease in the country are very high when compared with the developed countries.[20] Social problems may be implicated in the large differences in TB rates between developed and undeveloped countries because *M. tuberculosis* is universal. In 2012, 69,000 new cases of TB were reported in Brazil, with an incidence rate of 35.2/100,000 individuals. The highest absolute number of cases occurs in the state of São Paulo, and the state of Rio de Janeiro has the highest incidence rate. Comparing the incidence between capitals, Porto Alegre has the highest incidence rate, followed by Recife, Belém, Rio de Janeiro and Manaus.[10]

Table 1 – Distribution of participants by study group, according to demographic data, related to tuberculosis screening and occurrence.

	Control (*n* = 415)	Anti-TNF (*n* = 942)	ADA (*n* = 366)	IFX (*n* = 293)	ETN (*n* = 283)	Other biologics (*n* = 195)	*p*
Women *(%)*	85.14	86.38	86.51	83.25	88.09	87.3	0.4
Age (years, *x* ± *SD*)	49.7 ± 12.6	49.2 ± 11.1	48.4 ± 11.8	48.6 ± 11.6	50.1 ± 11.5	51.2 ± 9.3	0.3
Disease time (months, *x* ± *SD*)	79.9 ± 99.3	113.4 ± 98.2	112.4 ± 105.4	112.7 ± 85.1	117.1 ± 102.8	121.5 ± 98	0.5
Patient-years (*n*)	981	1744	676	547	521	336	
TB cases	1	5	3	1	1	0	
TB incidence, cases/100,000 patient-years	101	286	443	154	192	0	
Relative risk	–	2.83	4.38	1.52	1.90	–	
Performed PPD tests, *n (%)*	176 (42)	916 (97.2)	357 (97.5)	286 (97.6)	276 (97.5)	161 (82.5)	
Positive PPD tests, *n (%)*	28 (15.9)	108 (11.8)	37 (10.1)	30 (10.2)	41 (14.4)	27 (16.7)	0.6
Chest XR, *n (%)*	241 (58)	920 (97.6)	362 (98.9)	286 (97.6)	273 (96.5)	172 (88.2)	
TB-related XR changes, *n (%)*	11 (4.5)	12 (1.3)	4 (1.0)	1 (0.3)	7 (2.5)	6 (3)	
Chemoprophylaxis, *n (%)*	18	132 (14.0)	43 (11.7)	39 (13.3)	50 (17.6)	34 (17.4)	

ADA, adalimumab; IFX, infliximab; ETN, etanercept; other biologics: abatacept, rituximab and tocilizumab; TB, tuberculosis; PPD, purified protein derivative test for *M. tuberculosis*; XR, radiography.

Table 2 – Clinical and laboratory data from the six patients who developed tuberculosis during treatment with anti-TNF.

Patient	Group	Drug exposure time *(months)*	Sex	Age *(years)*	Disease time *(years)*	PPD	Radiography	Chemoprophylaxis	TB form
1	Control	17	M	54	2	Not performed	Unrelated to TB	Not performed	Pulmonary
2	ADA	10	F	67	5	Negative	Unrelated to TB	Not performed	Disseminated
3	ADA	25	M	39	4	Negative	Unrelated to TB	Not performed	Pulmonary
4	ADA	30	F	48	5	Negative	Unrelated to TB	Not performed	Ganglionar
5	ETN	31	F	52	7	Negative	Unrelated to TB	Not performed	Pulmonary
6	IFX	40	F	65	20	Negative	Unrelated to TB	Not performed	Ganglionar

TB, tuberculosis; PPD, purified protein derivative test for *M. tuberculosis*; ADA, adalimumab; ETN, etanercept; IFX, infliximab.

Similar to other case series, we found that the subgroup given treatment with a monoclonal antibody against TNF had the highest incidence of TB (ADA).[21] The patients treated with IFX had the lowest incidence in the group, and ETN had an intermediate value, in contrast to the findings of other case series.[22,23] None of these patients had received previous anti-TNF treatment. The Other biologics group showed no cases of TB, a result also in agreement with most of the available data thus far, which show the relative safety of those drugs regarding the occurrence of TB.[24,25]

The relative risk for tuberculosis development is increased among RA patients using anti-TNF, reaching a magnitude of 2–4 times higher than that of patients using synthetic DMARDs alone. Furthermore, treatment with anti-TNF is apparently a key risk factor for the extrapulmonary and disseminated forms of TB, as observed in three patients – two with the ganglionar form and one with the disseminated form. The occurrence of extrapulmonary TB is higher among anti-TNF users and, in a country such as Brazil, where the incidence of TB is high among the general population, this group should also be considered a priority in the context of public health surveillance policies for monitoring the occurrence of the disease, especially extrapulmonary forms. Our study showed an incidence of TB very similar to that of other studies conducted in European countries, the USA and Japan.[26–28] Therefore, anti-TNF therapy apparently removes the effect of improved life conditions in protecting against the occurrence of TB, showing that the granuloma destabilization is the crucial step to the high risk of disease development among these individuals.

The incidence of TB among the group of patients using synthetic DMARDs was also higher than among the general Brazilian population (101 *vs.* 37.2 cases/100,000 individual-years). Although the event occurred in only one individual, this datum is in agreement with findings from several countries, showing that the incidence of TB is higher among RA patients, regardless of the use of biologics, most likely partly because of the disease itself and partly because of the treatment with synthetic DMARDs.

Screening for LTBI is essential but has failed to identify patients at high risk of developing the disease.[18,21,29] PPD positivity in the general Brazilian population ranges from 25 to 35%,[10] although, as expected, PPD positivity was lower in our study, ranging from 10.1% to 16.7%, because the patients used immunosuppressants. Regional studies assessing PPD positivity among patients with RA before starting biologics showed similar results to those of our registry, including 14% in Pernambuco,[30] 15% in Ceará[31] and 21% in São Paulo.[32]

The high efficacy of isoniazid treatment in LTBI cases is well known[33]; thus, defining who will receive the drug remains a key discussion point. Treatment for LTBI could have been presumably protective in various patients who did not receive it and were subsequently diagnosed with TB because no patient treated with the drug developed the disease. Screening methods must be improved, especially for non-reactors to PPD. It must be questioned herein whether it would be pertinent to perform tests for a PPD booster effect[34] or even to use an interferon-gamma release assay (IGRA) for improving the tests for latent TB.[29] In our survey, these methods were not mentioned. Some hospital departments in Brazil may perform such tests, but they are not used on a daily basis due to technical difficulties and cost.

Among our patients, all cases of TB occurred after negative initial screening, and TB occurred in one patient within 12 months of treatment, raising the possibility of screening failure. However, in the other four groups of patients with RA, TB occurred after at least 24 months, suggesting contact with the mycobacterium during treatment.

In conclusion, this study is the first conducted in Brazil assessing the occurrence of TB in patients using biologics in daily clinical practice, based on the Brazilian Registry of Biological Therapies in Rheumatic Diseases (Registro Brasileiro de Monitoração de Terapias Biológicas – BiobadaBrasil). The incidence of TB among patients with RA using anti-TNF and the late disease onset should be noted, indicating that most patients acquired the infection during use and not due to the presence of LTBI undetected by screening.

Conflicts of interest

The authors declare no conflicts of interest.

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