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ORIGINAL ARTICLE

Incidence of tuberculosis in patients receiving anti-TNF therapy for rheumatic diseases: a systematic review

Natália Sarzi Sartori[1] · Nicole Pamplona Bueno de Andrade[1] · Rafael Mendonça da Silva Chakr[1,2]

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Abstract

Introduction The TNF inhibitors were the first immunobiologicals used to treat rheumatic diseases, but their use is associated with an increased risk of tuberculosis. The primary objective is to estimate the incidence of tuberculosis in patients with rheumatic diseases exposed to anti-TNF therapy. The secondary objectives are to evaluate the incidence of tuberculosis by region and subgroups of diseases, to review the presentation of tuberculosis in these patients, and to assess the time elapsed between onset of anti-TNF therapy and development of active granulomatous disease.

Methods A systematic review of the literature was conducted in MEDLINE, the Cochrane Library, and LILACS. The primary endpoint was described as incidence and secondary outcomes, through subgroup analyses and comparisons of means.

Results We included 52 observational studies. Among the exposed patients, 947 cases of tuberculosis were documented (62.2% pulmonary), with a cumulative incidence of 9.62 cases per 1000 patients exposed. TB incidence across different continents was distributed as follows: South America, 11.75 cases/1000 patients exposed; North America, 4.34 cases/1000 patients exposed; Europe, 6.28 cases/1000 patients exposed; and Asia, 13.47 cases/1000 patients exposed. There were no significant differences in TB incidence among the described diseases. The mean time elapsed from start of anti-TNF therapy until the endpoint was 18.05 months.

Conclusion The incidence of TB in patients with rheumatic diseases exposed TNF inhibitor considering all countries was 9.62 cases per 1000 patients exposed. TB incidence was higher in South America and Asia compared with North America and Europe. Most cases occurred in the first XX months of use, and the pulmonary form predominated.

Key Points
- *Higher incidence of tuberculosis in patients exposed to anti-TNF compared with the general population.*
- *Higher incidence of TB in countries of South America and Asia compared with North America and Europe.*

Keywords Incidence · Infection · Latent · Rheumatic diseases · TNF inhibitors · Tuberculosis · Tuberculosis epidemiology

Introduction

Tumor necrosis factor-alpha (TNF-α) is a cytokine involved in the immune response against intracellular pathogens such as *Mycobacterium tuberculosis*. Through its role in macrophage activation and continuous cell recruitment, it is essential for the maintenance of granuloma structure. The role of this cytokine has gained even more prominence since the advent of immunobiological therapy with TNF inhibitors or anti-TNF agents, for the treatment of rheumatic diseases [1].

Rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PA), and juvenile idiopathic arthritis (JIA) are systemic autoimmune diseases that share chronic joint inflammation as a core feature [2].

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✉ Natália Sarzi Sartori
nataliasartori2007@yahoo.com.br

[1] Department of Rheumatology, Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2350/645, Porto Alegre, Rio Grande do Sul 90035-903, Brazil

[2] Department of Internal Medicine, UFRGS, Porto Alegre, Brazil

Several cytokines are implicated in the pathogenesis of these conditions, including TNF-α, which has a particularly prominent role in development of the systemic inflammatory process and joint damage of rheumatic arthropathies, leading to functional impairment and worsening quality of life [3, 4].

In 2017, an estimated 10 million people developed tuberculosis (TB) worldwide. Of these cases, 87% occurred in the 30 countries designated by the World Health Organization (WHO) as having a high tuberculosis burden, with two-thirds occurring in Asia and Africa. According to WHO, only 6% of cases occurred in the European region, and 3% in the Americas. The incidence of TB varies widely among countries. In 2017, it was estimated at fewer than 10 new cases per 100,000 populations in higher-income countries, versus approximately 150–400 new cases per 100,000 in most of the 30 countries with the highest absolute TB incidence [5].

The advent of biologic therapy with TNF inhibitors has greatly advanced the treatment of rheumatic diseases, allowing control of disease activity and reduction of joint damage, especially in patients who are unresponsive to conventional therapy, resulting in better clinical outcomes [6, 7]. However, there is a well-established increase in risk of active tuberculosis in individuals exposed to anti-TNF agents when compared with the general population [8–10]. The risk of TB in individuals exposed to anti-TNF therapy when compared with the general population is approximately 8–12 times greater in countries with a low incidence of TB, and up to 24–40 times greater in countries with a high incidence of TB [8, 11–13].

Previous systematic reviews and meta-analyses corroborate this increased risk of TB in users of anti-TNF therapy; however, most were restricted to randomized clinical trials, and often to a single, specific rheumatic condition [14, 15]. The present systematic review, limited to observational studies providing real-life data, aims to evaluate the actual incidence of TB in patients with rheumatic diseases exposed to anti-TNF agents. As secondary objectives, we seek to ascertain the incidence of TB across different rheumatic conditions for which anti-TNF therapy is prescribed and across subgroups of continents, as well as assess the most common forms of TB manifesting in this population and the time elapsed between first exposure to anti-TNF therapy and development of opportunistic TB infection.

Material and methods

This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study protocol was registered in the PROSPERO (International Prospective Register of Systematic Reviews) platform, with accession number CRD42018083323.

Inclusion and exclusion criteria

We searched for observational studies which evaluated the incidence of TB in patients with rheumatic diseases exposed to anti-TNF agents. There was no date or language limitation. Studies were selected according to inclusion criteria defined in a preexisting protocol.

Participants: patients with any related rheumatic disease (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis) and exposure to one of the five anti-TNF agents (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol).

Exposure: exposure to an anti-TNF agent, with or without prior or concomitant standard treatment.

Outcomes: incidence of TB in users of anti-TNF agents, form of TB, time elapsed between exposure to anti-TNF agent, and development of granulomatous disease.

Comparator: patients receiving standard treatment.

Study design: observational studies.

The exclusion criteria were studies which did not report TB incidence, absence of included exposed patients, duplicate records, randomized controlled trials, meta-analyses, and case reports.

Search strategy

A systematic review of the PubMed, EMBASE, Cochrane Library, and LILACS databases was conducted. There were no limitations on start date, language, or region of publication. The database search was based on the following Medical Subject Headings (MeSH) and combinations thereof: tuberculosis, latent tuberculosis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, infliximab, etanercept, adalimumab, golimumab, certolizumab pegol. By way of example, the PubMed/MEDLINE search strategy is described in the supplement.

Study selection and data collection

Two independent reviewers selected articles by analysis of titles and abstracts. Potentially eligible records were retrieved for full-text review. Disagreements were resolved by consensus with a third reviewer.

Data extraction was performed independently by two reviewers, and again, any discrepancies were resolved by discussion. The quality of the eligible studies was evaluated by the Newcastle–Ottawa Scale, with a maximum score of 9 stars across different categories (selection, comparability, and exposure or outcome). The extracted data included the authors' names, year of publication, study setting, number of patients exposed to anti-TNF agents, number of patients who developed TB, and number of patients included with each of the predefined conditions of interest, as well as time elapsed from anti-TNF

exposure to TB development, mean age, gender, form of TB developed, treatment for latent TB, and TB screening test results.

Statistical analysis

All statistical analysis was carried out in the Review Manager 5.3 software environment. The primary endpoint was evaluated and expressed as the incidence (cases per 1000 exposed patients). A subgroup analysis was performed to compare incidence rates. Continuous variables were presented as means.

Considering the results of study quality assessment, the incidence of the main outcome was calculated only for those studies with lower risk of bias. Studies assigned a score of 6 stars or more were deemed to have a lower risk of bias.

Results

Search results

The search strategy described above identified 478 articles for systematic review: 130 records in PubMed, 170 in EMBASE and the Cochrane Library, and 8 in LILACS. After review of titles and abstracts, 270 articles were selected. The remaining 208 addressed topics irrelevant to this study and were thus excluded. Full-text reading then excluded a further 218 articles, including duplicate records. The reasons for exclusion are described in the flow diagram of study selection (Fig. 1).

Thus, 52 articles were ultimately eligible for complete data extraction (covering publications from 2003 to 2017). We evaluated the quality of these observational studies and found only three with a quality rating of < 5 stars and greater potential for bias. The quality of the included studies was thus deemed satisfactory. Table 1 illustrates the process of methodological evaluation of the quality of included studies.

Considering the 52 observational studies included (Table 2), a total of 98,483 patients were exposed to at least one anti-TNF agent. The mean age of patients on anti-TNF therapy was 42.9 years, and 62% of those exposed were females. Of the exposed patients, 947 developed TB (62.2% with the pulmonary form of the disease and 37.8% with extrapulmonary manifestations). The overall incidence of TB was 9.62 cases [CI 9.01–10.23] per 1000 exposed patients. Considering only studies with a lower risk of bias, a total of 79,172 patients were exposed to anti-TNF agents, 789 of whom developed TB, for an overall incidence of 9.97 [CI 9.27–10.66] cases per 1000 exposed patients (no significant difference vs. all studies included). The mean time elapsed from initiation of anti-TNF therapy to development of TB was 18.05 ± 9.12 months.

When assessing only the adult population exposed to anti-TNF agents, we found a total of 97,896 exposed individuals, 943 of whom developed TB. The overall incidence of TB in adults was 9.62 cases [CI 9.02–10.24] per 1000 exposed patients. Conversely, when considering only the population under 16 years of age, 576 individuals were exposed to anti-TNF therapy, 4 of whom developed TB, yielding an incidence of 6.81 cases [CI 0.16–13.47] per 1000 exposed patients. Again, this rate was not significantly different from that of the adult population exposed to anti-TNF agents.

Subgroup analysis of incidence by specific rheumatic diseases showed no statistically significant difference between the different diagnoses. A total of 73,497 patients with RA were exposed to anti-TNF agents, 677 of whom had a diagnosis of TB, for an incidence of 9.21 cases [CI 8.52–9.90] per 1000 exposed patients. Of the 12,260 patients with SA exposed to anti-TNF therapy, 138 developed TB, for an incidence of 11.25 cases [CI 9.39–10.13] per 1000 exposed patients. Of 886 exposed patients with PA, 10 developed tuberculosis, which corresponds to an incidence of 11.35 cases [CI 4.36–18.35] per 1000 exposed patients. Finally, of the 915 patients with JIA exposed to anti-TNF therapy, 6 developed treatment-emergent TB, for an incidence of 6.56 cases [CI 1.33–11.79] per 1000 exposed patients.

Another subgroup analysis was then carried out, taking into consideration the different locations of each study and their distribution by continents. In South America, a total of 2128 individuals were exposed to anti-TNF therapy, with 25 cases of TB diagnosed among those exposed, for an incidence of 11.75 cases [CI 7.17–16.33] per 1000. In North America, 15,425 individuals were prescribed at least one anti-TNF agent; 67 cases of tuberculosis developed in this population, for an incidence of 4.34 cases [CI 3.31–5.38] per 1000. In Europe, 32,629 patients were exposed to anti-TNF therapy. Of these, 205 developed TB, which corresponds to an incidence of 6.28 cases [CI 5.34–7.14] per 1000. In Asia, 48,257 individuals were exposed to anti-TNF therapy; 650 cases of tuberculosis were diagnosed, for an incidence of 13.47 cases [CI 12.44–14.49] per 1000. These data show a statistically significant difference in incidence of TB between South America and Asia in relation to Europe and North America.

Regarding latent tuberculosis approach, 14 studies included in our review evaluated the treatment of latent tuberculosis and screening prior to initiation of anti-TNF use. Considering these studies, 12,793 tuberculin tests were performed, and 5530 were positive. Treatment for complete latent tuberculosis was performed in 6414 individuals. We also found that 164 patients with PPD reagent did not undergo treatment for latent tuberculosis or had incomplete treatment. Regarding the treatments for latent tuberculosis, these were indicated in patients with tuberculin test alteration or radiographic alterations suggestive of latent disease.

Discussion

Anti-TNF therapy has proven efficacy for the control of rheumatic conditions, providing clinical improvement and

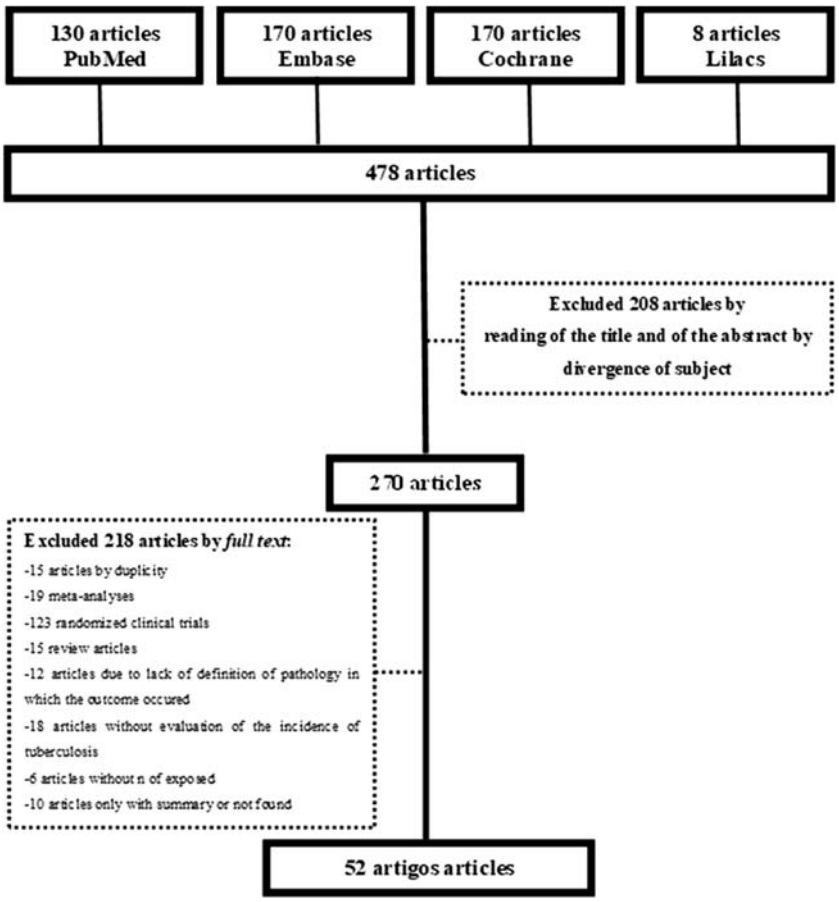

Fig. 1 Selection process of systematic review articles

modifying the natural history of the disease by targeting TNF, a cytokine involved in the pathogenesis of inflammatory arthropathies [6, 66]. Despite the clear benefits of this therapy, it is associated with and increased risk of infections, including serious infections such as TB [15, 67].

This systematic review was designed to assess the risk of developing TB in patients with rheumatic diseases who are receiving anti-TNF therapy. The decision to include only observational studies, rather than controlled trials, was made to ensure reliance on real-life data. We found a high incidence of TB among users of the various anti-TNF agents available, with an overall risk approximately 12 to 25 times greater than that of the general population [11, 13]. There was no significant difference in TB incidence among the different types of rheumatic diseases. [21, 39, 68]

This review also found a higher rate of pulmonary tuberculosis in patients taking anti-TNF agents, a finding previously reported in other studies [42, 45]. The time from onset of TNF inhibitor use to diagnosis of TB in this review was less than 24 months, which corroborates previous data on the development of TB within the first few years of anti-TNF therapy. [8, 16]

This was one of the first reviews to evaluate the incidence of TB among the different regions of the world, considering all five anti-TNF agents available at the time of writing, and in different rheumatic diseases. The incidence of TB in patients exposed to anti-TNF therapy is directly linked to the incidence of TB in the general population. Due to this impact of overall TB incidence, different incidence rates are found between groups of patients on anti-TNF therapy in different regions of the world. The present study found a higher incidence of TB among patients receiving anti-TNF agents for rheumatic diseases in regions such as Asia and South America, both of which have a significantly higher overall incidence of TB than Europe and North America [16, 42, 54, 57, 64, 69, 70].

All studies included in this review have a number of limitations, mainly attributable to their retrospective designs. Hence, data on concomitant use of disease-modifying drugs, corticosteroid therapy, and other comorbidities were incompletely recorded. In addition, many studies did not provide data on screening for and treatment of latent TB, with data often missing or otherwise unavailable. Therefore, a significant limitation of our study was our inability to assess the impact of latent TB treatment prior to exposure to anti-TNF agents. Regarding the different TNF inhibitors, the lack of data on certolizumab pegol and golimumab must be noted.

Considering that this systematic review included publications from different regions and continents, it was expected

Table 1 Process methodological evaluation of the quality of included studies

Evaluation of the quality of observational studies				
Study	Selection	Comparability	Outcome	Total score
Yonekura et al. [16]	****	**	**	8
Lim et al. [17]	***	**	**	7
Garziera et al. [18]	***	**	**	7
Lim et al. [19]	****	**	**	8
Liao et al. [20]	***	**	**	7
Kisacik et al. [21]	****	**	**	8
Watanabe et al. [22]	****	**	*	7
Rotar et al. [23]	***		**	5
Rahman et al. [24]	***		***	6
Mourão et al. [25]	****	*	**	7
Calzada-Hernández et al. [26]	***		**	5
Hsin et al. [27]	****	**	***	9
Jung et al. [28]	***	**	**	7
Borekci et al. [29]	***	**	**	7
Gomes et al. [30]	****	*	**	7
Chiu et al. [31]	****	**	**	8
Chi Chiu et al. [32]	***		**	5
Yoo et al. [33]	***		**	5
Ke et al. [34]	****	**	**	8
Lee et al. [35]	***	*	**	6
Sarychev et al. [36]	**		*	3
Zlnay et al. [37]	***		**	5
He et al. [38]	****		**	6
Kim et al. [39]	****	**	**	8
Jo et al. [40]	***		**	5
Calzada-Hernández et al. [41]	***		**	5
Winthrop et al. [42]	***	**	**	7
Bracaglia et al. [43]	***		***	6
Tomsic et al. [44]	***		**	5
Kim et al. [45]	****	**	***	9
Nobre et al. [46]	***		**	5
Kilic et al. [47]	***		**	5
Titton et al. [48]	****		**	6
Pérez-Sola et al. [49]	***		**	5
Liza et al. [50]	***		**	5
Laas et al. [51]	**		*	3
Cagatay et al. [52]	***		**	5
Dixon et al. [8]	****	**	***	8
Elbek et al. [53]	***		**	5
Favalli et al. [54]	***	**	***	8
Rybar et al. [55]	**		*	3
Garcia-Vidal et al. [56]	***	**	**	7
Gómez-Reino et al. [57]	***	*	***	7
Seong et al. [12]	****	**	**	8
Narayanan et al. [58]	***		***	6
Takeuchi et al. [59]	***		**	5
Sichletidis et al. [60]	***		**	5
Brassard et al. [61]	****	**	**	8
Askling et al. [62]	****	**	**	8
Carmona et al. [10]	****		**	6
Strusberg et al. [63]	***		**	5
Wolfe et al. [64]	****	*	*	6
Gómez-Reino et al. [65]	****	*	**	7

Each asterisk or star corresponds to each article's punctuated topics according to the Newcastle – Ottawa scale

that the overall incidence found might not be reproducible in any particular population exposed to anti-TNF therapy, precisely because of the variation of TB incidence in the general population, hence, our decision to evaluate the incidence

Table 2 Characteristics of the included studies with number of exposed to anti-TNF therapy and number of cases of tuberculosis

Study	Country	Continent	Year	*n* exposed	*n* events
Yonekura et al. [16]	Brazil	South America	2017	942	5
Lim et al. [17]	Taiwan	Asia	2017	835	24
Garziera et al. [18]	Brazil	South America	2017	171	6
Lim et al. [19]	Taiwan	Asia	2016	5349	80
Liao et al. [20]	Taiwan	Asia	2016	5255	188
Kisacik et al. [21]	Turkey	Asia	2016	7230	73
Watanabe et al. [22]	Japan	Asia	2016	7740	22
Rotar et al. [23]	Slovenia	Europe	2016	1693	5
Rahman et al. [24]	Canada	North America	2016	303	0
Mourão et al. [25]	Portugal	Europe	2016	205	1
Calzada-Hernández et al. [26]	Spain	Europe	2015	163	0
Hsin et al. [27]	Taiwan	Asia	2015	111	1
Jung et al. [28]	South Korea	Asia	2015	7375	81
Borekci et al. [29]	Turkey	Asia	2015	1586	12
Gomes et al. [30]	Brazil	South America	2015	265	8
Chiu et al. [31]	Taiwan	Asia	2014	2238	58
Chi Chiu et al. [32]	China	Asia	2014	1345	32
Yoo et al. [33]	China	Asia	2014	709	13
Ke et al. [34]	Taiwan	Asia	2013	829	9
Lee et al. [35]	South America	Asia	2013	371	4
Sarychev et al. [36]	Russia	Europe	2013	14	1
Zlnay et al. [37]	Slovakia	Europe	2013	314	1
He et al. [38]	China	Asia	2013	40	0
Kim et al. [39]	South Korea	Asia	2013	558	14
Jo et al. [40]	South Korea	Asia	2013	40	1
Calzada-Hernández et al. [41]	Spain	Europe	2013	167	0
Winthrop et al. [42]	USA	North America	2012	5499	12
Bracaglia et al. [43]	Italy	Europe	2012	25	0
Tomsic et al. [44]	Slovenia	Europe	2012	969	2
Kim et al. [45]	South Korea	Asia	2011	354	3
Nobre et al. [46]	Brazil	South America	2011	157	3
Kilic et al. [47]	Turkey	Asia	2011	132	2
Titton et al. [48]	Brazil	South America	2011	596	3
Pérez-Sola et al. [49]	Spain	Europe	2011	6389	59
Liza et al. [50]	Malaysia	Asia	2010	57	2
Laas et al. [51]	Slovenia	Europe	2010	153	3
Cagatay et al. [52]	Turkey	Asia	2010	578	6
Dixon et al. [8]	England	Europe	2009	10,712	40
Elbek et al. [53]	Turkey	Asia	2009	240	2
Favalli et al. [54]	Italy	Europe	2008	1064	5
Rybar et al. [55]	Slovakia	Europe	2008	537	2
Garcia-Vidal et al. [56]	Spain	Europe	2008	94	4
Gómez-Reino et al. [57]	Spain	Europe	2007	1665	6
Seong et al. [12]	South Korea	Asia	2007	193	2
Narayanan et al. [58]	India	Asia	2007	52	7
Takeuchi et al. [59]	Japan	Asia	2007	5000	14
Sichletidis et al. [60]	Greece	Europe	2006	610	10
Brassard et al. [61]	Canada	North America	2006	3163	51
Askling et al. [62]	Sweden	Europe	2005	2500	15
Carmona et al. [10]	Spain	Europe	2005	3815	34
Strusberg et al. [63]	Argentina	South America	2005	44	0
Wolfe et al. [64]	USA	North America	2004	6460	4
Gómez-Reino et al. [65]	Spain	Europe	2003	1540	17

of TB in patients on anti-TNF therapy in each region separately as well, to allow better interpretation of data.

Strengths of this review include the evaluation of all articles which reported screening for latent TB, with no date or language restrictions. In addition, the results of this review confirm the previous finding of a higher incidence of TB in users of anti-TNF therapy in relation to the general population, using real-life observational data from clinical practice.

Conclusion

In summary, we found a high incidence of TB in patients receiving anti-TNF therapy for rheumatic diseases worldwide. This incidence was higher in South America and Asia than in North America and Europe. Among the several forms of TB diagnosed, pulmonary tuberculosis predominated. The time from initiation of anti-TNF therapy until development and diagnosis of tuberculosis was roughly 18 months. There was no difference in TB incidence across the different rheumatic diseases for which patients were receiving anti-TNF agents.

Compliance with ethical standards

Disclosure None

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