



# REVISTA BRASILEIRA DE REUMATOLOGIA

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## Letter to the Editor

# Preliminary guidelines of the Brazilian Society of Rheumatology for evaluation and treatment of tuberculosis latent infection in patients with rheumatoid arthritis, in face of unavailability of the tuberculin skin test



## Orientações preliminares da Sociedade Brasileira de Reumatologia para avaliação e tratamento da tuberculose infecção latente em pacientes com artrite reumatoide na indisponibilidade do teste tuberculínico

### Introduction

The detection and treatment of tuberculosis latent infection (TBLI) in individuals with increased risk of progression to tuberculosis (TB) disease are strategies recommended by the World Health Organization to control this disease. The tuberculin test, which uses PPD (purified protein derivative), is a procedure widely incorporated to the clinical practice for the diagnosis of TBLI. Patients with rheumatoid arthritis are in increased risk for the development of active TB, particularly when treated with biological agents of TNF- $\alpha$  inhibitor class. The 2012 Consensus of The Brazilian Society of Rheumatology (BSR) for treating rheumatoid arthritis recommends the use of screening procedures and, where indicated, the treatment of TBLI in every patient candidate to use some biological agent.

In addition to the evaluation of the epidemiological risk, this screening includes performing chest radiography and a tuberculin test. After the exclusion of TB disease, the treatment of TBLI consists of isoniazid at a dose of 5–10 mg/kg/day (with a maximum of 300 mg/day) for 6 months. This treatment is indicated in patients with tuberculin test  $\geq 5$  mm, positivity for IGRA (interferon- $\gamma$  release assays), radiographic findings consistent with prior TB, or close contact with a TB case. The treatment of TBLI (chemoprophylaxis) should be established at least one month before introducing the biological agent; however, exceptionally and when the symptomatic urgency of the situation demands it, both drugs may be initiated concomitantly.

In September 2014, the Ministry of Health, through the General Coordination of the National Program for Tuberculosis Control, published a note informing on the difficulties to acquire PPD, thanks to its unavailability in the international market, which should result in shortages of the Brazilian health system, still without any prediction for resumption of its distribution (information note n° 8/CGPNCT/DEVEP/SVS/MS, of September 10, 2014). The unavailability of the tuberculin test has already been effectively felt in our health care network. Considering that the current situation require a quick attitude in order to guide clinical practice, the Arthritis Rheumatoid Committee of BSR decided to disclose the following preliminary guidelines, which were developed by expert consensus. The Committee suggests a consultation of selected references, which extend the discussions here developed.<sup>1-12</sup>

*The recommendations for an evaluation and treatment of TBLI in patients with rheumatoid arthritis are different when using TNF- $\alpha$  inhibitors and biological agents with other mechanisms of action?*

There is a difference in the risk of TB reactivation when using TNF- $\alpha$  inhibitors, which represent an increased risk – especially in the case of monoclonal antibodies, in comparison with other not-TNF- $\alpha$ -inhibitor biologicals. However, the 2012 BSR Consensus for the treatment of rheumatoid arthritis, considering the high prevalence of TB in Brazil, and

also considering reports of disease reactivation during the immunosuppressive treatment, recommended TBLI screening when using any biological DMARDs.

Inserts of some of the not-TNF- $\alpha$  inhibitor biologicals, such as tocilizumab and abatacept, also recommend carrying out a TBLI screening prior to the use of the drug. Thus, considering also possible medico-legal implications, at present BSR prefer to keep the same recommendations for evaluation and treatment of TBLI, in the case of use of any biological DMARDs for treatment of rheumatoid arthritis. These recommendations also apply to the use of corticosteroids at a dose equivalent to prednisone  $\geq 15$  mg/day for more than 30 days in individuals older than 65 years.

#### **What should be regarded as a positive epidemiology for tuberculosis?**

Contact with a bacilliferous case of pulmonary or respiratory TB is the key epidemiological factor. The risk of acquiring TBLI by contacting a bacilliferous patient is increased by conditions such as household contact (especially among those who share the same bedroom); longer exposure time; exposure in places with poor ventilation; cavitation revealed in a chest X-ray from the index case; positive direct bacilloscopy, and greater amount of bacilli in the index case sputum. Patients exposed to coexistence situations with a high disease burden, namely, health professionals, prison inmates, residents of nursing homes or hostels, and injectable drug users, are defined as people in greater epidemiological risk.

The risk of developing TB disease is higher in the first two years after infection. Contacts of bacilliferous individuals are at increased risk of developing TB disease, when in situations of extreme age ( $\leq 10$  years or  $> 60$  years), immunosuppression, household exposure, and exposure to patients with positive bacilloscopy or sputum culture. Tuberculin test  $\geq 5$  mm is also a risk factor for developing TB disease in contacts. The main clinical condition associated with progression from TBLI to TB disease is co-infection with HIV, particularly when CD4+ T cells  $\leq 200/\text{mm}^3$ . Other medical conditions meaning risk for progression from TBLI to TB disease are: use of a TNF- $\alpha$  inhibitor, diabetes mellitus, chronic renal failure on dialysis, malignant neoplasms, immunosuppression associated with organ transplantation, malnutrition, changes in chest X-ray – especially fibrotic lesions in upper areas (with or without calcified nodules or pleural thickening) – suggestive of sequel of a previously untreated pulmonary TB.

#### **Patients with rheumatoid arthritis, when in use of biopharmaceuticals and with a positive history of contact with a pulmonary TB case, should be treated for TBLI without a tuberculin test?**

Yes. The recommendation is to proceed with the TBLI treatment without the tuberculin test in contacts of pulmonary TB cases, when using TNF- $\alpha$  inhibitors. TNF- $\alpha$  inhibitor users with a suggestive X-ray of untreated pulmonary TB sequel should also be treated for TBLI, regardless of the tuberculin test. It

is believed that, in these cases, the benefit of preventing TB overcomes the risks of a preventive treatment.

#### **When using biopharmaceuticals, patients with rheumatoid arthritis with no history of contact with a case of pulmonary TB should receive treatment for TBLI without a tuberculin test?**

A negative history of contact does not exclude TBLI. In these cases, and in the absence of a tuberculin test, IGRA is recommended for obtaining a diagnosis of latent infection. In the case of unavailability of both tests, the decision about TBLI treatment should be individualized, and the physician will take into consideration its risks and benefits. When assessing the potential benefit of this treatment, we must consider the factors discussed (above) with respect to the question of a positive epidemiology for tuberculosis. In particular, the increased epidemiological risk (high disease burden in the convivial environment) and the synergism of risk factors for progression to TB disease should be evaluated.

In the assessment of risk associated with treatment, we must consider the hepatotoxic potential of isoniazid, especially in individuals aged  $> 35$  years, frequent alcohol users, patients with previously abnormal liver function tests, and in those individuals on concomitant use of other hepatotoxic drugs. However, generally speaking, liver disease due to isoniazid is an uncommon occurrence, and the concomitant use of hepatotoxic drugs is not an absolute contraindication to isoniazid use. However, the use of this agent requires liver function test monitoring.

Finally, one must consider the potential for microbial resistance induction, thanks to the indiscriminate use of isoniazid. After the evaluation, if the treatment of TBLI is deemed unnecessary, a monthly clinical monitoring for early detection of active TB is recommended, with special attention to signs such as cough, fever, sweating and weight loss. The investigation of symptomatic patients should be refined to include at least a radiographic study of chest, in addition to bacilloscopy and sputum culture; and an expert evaluation (by a pulmonologist, phthisiologist or infectologist) should also be considered.

#### **The performance of IGRA for diagnosing TBLI is comparable to the tuberculin test?**

The accuracy of IGRA is similar or superior to the tuberculin skin test for diagnosis of TBLI. There is a potential advantage of IGRA in BCG-vaccinated individuals and in immunodepressed patients due to disease and/or treatment – situations where the tuberculin test accuracy decreases due to false positives and false negatives, respectively. There is debate about the performance of IGRA in populations with high prevalence of TB. There is also the possibility of indeterminate results, which should be evaluated with caution; with such an occurrence, a conduct of TBLI treatment should be considered. Despite such considerations, given the current unavailability of the tuberculin skin test, the BSR advocates the incorporation of IGRA in the list of procedures of the Brazilian Unified Health System and supplementary health care.

***In the absence of TST, and with availability of IGRA, this latter test is suitable for the establishment of a TBLI diagnostic in all patients with rheumatoid arthritis using immunobiologicals?***

Yes. IGRA is indicated in the same situations in which the tuberculin skin test would apply, replacing it. Therefore, if IGRA is available, its use is recommended for TBLI screening in all patients with rheumatoid arthritis, when in use of an TNF- $\alpha$  inhibitor, in the absence of the tuberculin test. If there is limited availability, we should prioritize IGRA for patients with a negative or uncertain history of contact with a case of pulmonary TB.

***With the prolonged use of a TNF- $\alpha$  inhibitor, or with an exchange of biologicals in patients who completed treatment for TBLI in the past, there is need to repeat the treatment with isoniazid?***

As a rule, once treated fully and effectively, TBLI does not require retreatment. Exceptions occur when there is a known re-exposure to *M. tuberculosis*; in this case, retreatment is indicated. Based on expert opinion, we can consider a periodic retreatment every 2 or 3 years in areas of high TB prevalence, when a persistent state of immunodepression prevails.<sup>11</sup> However, a Brazilian study evaluated the efficacy of long-term TBLI screening and treatment in 202 patients with rheumatoid arthritis in use of different TNF- $\alpha$  inhibitors.<sup>13</sup> In this protocol, no regular retreatment for TBLI nor repetition of the tuberculin skin test were carried out in asymptomatic patients, and this conduct was continued for over 3 years of follow-up.

***Should be treated for TBLI those patients with respiratory symptomatology and with a positive history of contact with a pulmonary TB case, when in the use of a TNF- $\alpha$  inhibitor?***

The prophylactic schemes are contraindicated, thanks to the likelihood of TB disease emergence through inefficiency and/or potential microbial resistance induction. The treatment of TBLI involves an active TB exclusion in all instances. Contacts with respiratory symptomatology deserve an extended investigation. In such cases, an assessment by a TB specialist (pulmonologist, phthisiologist or infectologist), with full treatment, when indicated, prior to the use of TNF- $\alpha$ , is recommended.

***Once the possibility of TB disease was ruled out, patients with a history of contact with a case of multidrug-resistant TB should receive treatment for TBLI, when using biological DMARDs?***

The treatment of TBLI in multidrug-resistant TB contacts is not recommended. In symptomatic contacts, tuberculosis should be investigated. In asymptomatic subjects, after ruling out TB, a monthly clinical and half-yearly radiographic follow-up is recommended in the first two years. Isoniazid prophylaxis should not be attempted. In such cases, the use of

a not-TNF- $\alpha$  inhibitor biological agent should be considered, independently of the tuberculin skin test or IGRA.

### Conflicts of interest

The authors declare no conflicts of interest.

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Licia Maria Henrique da Mota\*, Bóris Afonso Cruz, Cleandro Pires de Albuquerque, Deborah Gonçalves, Ieda Maria Magalhães Laurindo, Ivanio Alves Pereira, Jozélio Freire de Carvalho, Geraldo da Rocha Castelar Pinheiro, Manoel Barros Bertolo, Nilzio Antônio da Silva, Paulo Louzada Júnior, Ricardo Machado Xavier, Rina Dalva Neubarth Giorgi, Rodrigo Aires Corrêa Lima  
*Sociedade Brasileira de Reumatologia, São Paulo, SP, Brazil*

\*Corresponding author.

E-mails: [liciamhmota@gmail.com](mailto:liciamhmota@gmail.com), [licia@unb.br](mailto:licia@unb.br) (L.M.H. da Mota).

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