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### Recomendações para o diagnóstico e tratamento das tuberculoses latente e activa nas doenças inflamatórias articulares candidatas a terapêutica com fármacos inibidores do factor de necrose tumoral alfa. Revisão de Março de 2008\*

### *Recommendations for the diagnosis and treatment of latent and active tuberculosis in inflammatory joint diseases candidates for therapy with tumor necrosis factor alpha inhibitors – March 2008 update\**

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#### Resumo

A Sociedade Portuguesa de Reumatologia e a Sociedade Portuguesa de Pneumologia actualizaram as recomendações para o diagnóstico e a terapêutica das tuberculoses latente (TL) e activa (TD) em doentes com doenças inflamatórias articulares (DIA), candidatos a tratamento com antagonistas do factor de necrose tumoral alfa (TNF $\alpha$ ). Com o objectivo de reduzir o risco de reactivação da tuberculose (TB) ou nova infecção, recomenda-se o rastreio de TD e TL tão precocemente quanto possível, preferencialmente no momento do diagnóstico da DIA, e repetir a avaliação do doente antes de iniciar terapêutica anti-TNF $\alpha$ . O tratamento da TD e TL deve ser sempre su-

#### Abstract

The Portuguese Society of Rheumatology and the Portuguese Society of Pulmonology have updated the guidelines for the diagnosis and treatment of latent tuberculosis infection (LTBI) and active tuberculosis (ATB) in patients with inflammatory joint diseases (IJD) that are candidates to therapy with tumour necrosis factor alpha (TNF $\alpha$ ) antagonists. In order to reduce the risk of tuberculosis (TB) reactivation and the incidence of new infections, TB screening is recommended to be done as soon as possible, ideally at the moment of IJD diagnosis, and patient assessment repeated before starting anti-TNF $\alpha$  therapy. Treatment for ATB and

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pervisionado por um especialista em TB. Quando houver indicação para terapêutica de TB, esta deverá ser cumprida integralmente antes de se iniciar o anti-TNF $\alpha$ . No caso da actividade da DIA o exigir, o anti-TNF $\alpha$  poderá ser iniciado após dois meses de terapêutica antibacteriana, no caso de TD, ou após um mês, no caso de TL.

Todos os doentes devem realizar radiografia do tórax. Alterações compatíveis com complexo de Gohn devem ser tratadas como TL. Lesões residuais obrigam a excluir TB activa. Se se suspeitar de lesões em actividade, o diagnóstico de TD deve ser excluído e o tratamento adequado instituído.

A prova tuberculínica (PT), com 2 unidades de tuberculina RT23, deverá ser efectuada em todos os doentes. Se a induração for <5 mm, a prova deve ser repetida dentro de 1 a 2 semanas no antebraço oposto, e considerada negativa apenas se o segundo resultado for igualmente <5 mm. As PT positivas obrigam a tratamento de TL, excepto se o doente tiver sido previamente tratado de forma adequada. Se a PT é realizada apenas em fase de imunodepressão, mesmo que seja negativa, deve ser equacionado o tratamento de TL antes de iniciar terapêutica anti-TNF $\alpha$ , após ponderar a relação risco/benefício.

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**Palavras-chave:** Guidelines, Sociedade Portuguesa de Reumatologia, Sociedade Portuguesa de Pneumologia, tuberculose, anti-TNF $\alpha$ .

LTBI must be done under the care of a TB specialist. When TB treatment is indicated, it should be completed prior to starting anti-TNF $\alpha$  therapy. If the IJD activity justifies the need for immediate treatment, anti-TNF $\alpha$  therapy can be started two months after antituberculous therapy has been initiated, in the case of ATB, and one month after in the case of LTBI. Chest X-ray is mandatory for all patients. If Gohn's complex is present, the patient should be treated for LTBI; healed lesions require the exclusion of ATB. In cases of suspected active lesions, ATB should be excluded/confirmed and adequate therapy initiated.

Tuberculin skin test, with two units of RT23, should be performed in all patients. If the induration is <5 mm, the test should be repeated within 1 to 2 weeks, on the opposite forearm, and will be considered negative only if the result is again <5 mm. Positive TST implicates LTBI treatment, unless previous proper treatment was provided. If TST is performed in immunosuppressed IJD patients, LTBI treatment should be offered to the patient before starting anti-TNF- $\alpha$  therapy, even in the presence of a negative test, after risk / benefit assessment.

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**Key-words:** Guidelines, Portuguese Society of Rheumatology, Portuguese Society of Pulmonology, Tuberculosis, Anti-TNF $\alpha$  drugs.

### Introduction

Tumor necrosis factor alpha (TNF- $\alpha$ ) inhibitors are used to treat inflammatory joint diseases (IJD) such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). In populations with a high incidence of tuberculosis (TB), there have been an increased number of TB cases

reported in patients undergoing these therapies.<sup>1</sup> In fact, the relative risk (RR) of developing TB is 19 times higher in RA patients under anti-TNF- $\alpha$  therapy than in RA patients not undergoing such therapy.<sup>1</sup> However, it is important to point out that RA patients treated with conventional immunosuppressive drugs have a RR for TB that

is 4 times higher than in the general population.<sup>1</sup>

In patients treated with anti-TNF- $\alpha$  drugs, ATB usually results from the reactivation of a latent infection. TB onset usually occurs during the first months of treatment and often presents an atypical behavior, which may pose difficulties to the diagnosis.<sup>2</sup> In countries with high incidence of TB, cases caused by new infections are particularly frequent. TNF- $\alpha$  is fundamental for the immunological defence against *Mycobacterium tuberculosis*, specially in the formation and maintenance of granulomas. Animal models show that it is possible to reactivate TB after administering anti-TNF- $\alpha$  antibodies.<sup>3</sup>

The currently available anti-TNF- $\alpha$  drugs are adalimumab, etanercept and infliximab. These three drugs have been approved for use in RA, AS, PsA and psoriasis. In addition, etanercept has also been approved for use in juvenile idiopathic arthritis and infliximab and adalimumab for use in Crohn's disease.

Because of its greater epidemiological impact, as compared to other IJDs, RA has been considered a model for introducing new biotechnology derived drugs that interfere with the immune system.<sup>4,5</sup> RA affects around 1% of the world population and might have a very aggressive course, leading to disability, increased co-morbidity and mortality.<sup>6,7</sup> For this reason, the use of disease modifying anti-rheumatic drugs – DMARDs – should be started as early as possible and methotrexate (MTX) is the first treatment option for this therapeutic strategy. However, in cases where MTX is contra-indicated or where it is impossible to use an adequate dose due to intolerance or

toxicity, other immune modulating drugs may be used, such as leflunomide, cyclosporine and sulphasalazine. In patients who continue to present active disease, despite of the use of MTX at the maximum tolerated dose, alternative therapeutic measures should be taken, specifically the introduction of an anti-TNF- $\alpha$  drug. This approach is supported by international recommendations<sup>8</sup> and by the guidelines for using biologic agents in RA therapy<sup>9</sup> published by the Rheumatoid Arthritis Study Group (Grupo de Estudos de Artrite Reumatóide – GEAR) of the Portuguese Society of Rheumatology (SPR). The Portuguese experience on the use of biologic therapies in the treatment of RA has been recently reviewed by the SPR.<sup>10</sup> The SPR also sponsored guidelines for initiating biologic therapy in AS<sup>11</sup> and published the Portuguese experience on the use of biologic therapies in the treatment of this disease.<sup>12</sup> There are no specific guidelines on when to start biologic therapy in PsA, but in general, polyarticular forms similar to RA are treated according to the SPR recommendations for RA, and cases that are predominantly axial are treated according to the SPR recommendations for AS.

Keeping patients on anti-TNF- $\alpha$  therapy depends on documenting its efficacy. The three TNF- $\alpha$  antagonists seem to display similar clinical effectiveness in the diseases mentioned above. However, there are differences from the molecular point of view, and the mechanisms whereby each drug acts are not entirely equal. Etanercept is a dimeric fusion protein consisting of the extracellular ligand of the p75 TNF receptor combined with the Fc portion of human IgG1. It forms stable bonds with the soluble trimeric

forms of TNF- $\alpha$  and TNF- $\alpha$  (lymphotoxin), keeping them from interacting with their respective receptors. It also interacts with monomeric TNF- $\alpha$  and with trans-membrane TNF- $\alpha$ , but in this case the affinity is low and has a transient effect (90% of trans-membrane TNF- $\alpha$  is released from the etanercept binding within 10 minutes). Etanercept is administered at a dose of 25 mg twice weekly or 50 mg once weekly, as a subcutaneous (SC) injection. Etanercept may be used for RA treatment as monotherapy or in association with MTX (in this case the literature reports enhanced effectiveness<sup>13</sup>).<sup>14</sup> It has been approved as monotherapy against AS and PsA<sup>14</sup>, but is generally used together with MTX to treat PsA. Infliximab is a chimeric monoclonal antibody with a high affinity and specificity for TNF- $\alpha$ , forming stable complexes with monomeric and trimeric TNF- $\alpha$ , and with trans-membrane TNF- $\alpha$ . Infliximab has no affinity for TNF- $\alpha$ (lymphotoxin). The binding to trans-membrane TNF- $\alpha$  induces cell lyses, mediated by complement dependent cytotoxicity or antibody dependent cellular cytotoxicity. It can also induce apoptosis by mechanisms that are not fully understood, but known to involve the caspases.<sup>15</sup> These cellular effects lead to a reduction in the number of TNF- $\alpha$  producing cells (monocytes and CD4 and CD8 lymphocytes), that is not observed with etanercept.<sup>16</sup> Infliximab is administered intravenously in doses that vary according to the disease and clinical response.<sup>17</sup> In RA it is used in association with MTX, usually in doses of 3 mg/kg every 8 weeks.<sup>17</sup> In PsA it is used in association with MTX, usually in doses of 5 mg/kg every 8 weeks.<sup>17</sup> In AS, it is used as monotherapy in doses of 5 mg/kg

every 6 weeks.<sup>17</sup> Adalimumab is a human recombinant monoclonal IgG1 antibody, with a mechanism of action similar to infliximab. It is administered subcutaneously at 40 mg doses every other week.<sup>18</sup> Adalimumab may be used for the treatment of RA as monotherapy or in association with MTX<sup>18</sup> (in this case the literature reports enhanced effectiveness).<sup>19</sup> Adalimumab has been approved for use as monotherapy<sup>18</sup> in PsA and AS.

In the US, where the annual incidence of TB is 6.2 cases per 100,000 inhabitants, the incidence of TB in patients treated with infliximab is 54 per 100,000 and, with etanercept, 28 per 100,000. This difference may merely be due to the different risk of reactivating TB in the populations exposed to these two anti-TNF- $\alpha$  drugs.<sup>20</sup> However, the different mechanism of action could also explain the lower risk of TB reactivation in patients treated with etanercept. In fact, the above described effect of anti-TNF- $\alpha$  monoclonal antibodies on the cells expressing TNF- $\alpha$ , and their ability to irreversibly inhibit receptor p75 and p55 signaling, constitutes a hypothetical reason for a reduced preservation of granuloma integrity during continuous therapy with infliximab and adalimumab.<sup>21</sup>

Since 2002, specific guidelines for screening candidates to anti-TNF- $\alpha$  therapy for active and latent TB<sup>9</sup> have been followed. However, in spite of this, there have been cases of TB in this group of patients, especially among those on monoclonal antibody therapy (infliximab and adalimumab). This has been observed in Portugal in a study performed by the SPR.<sup>22</sup>

The incidence of TB in the general Portuguese population (29.4/100,000 inhabit-

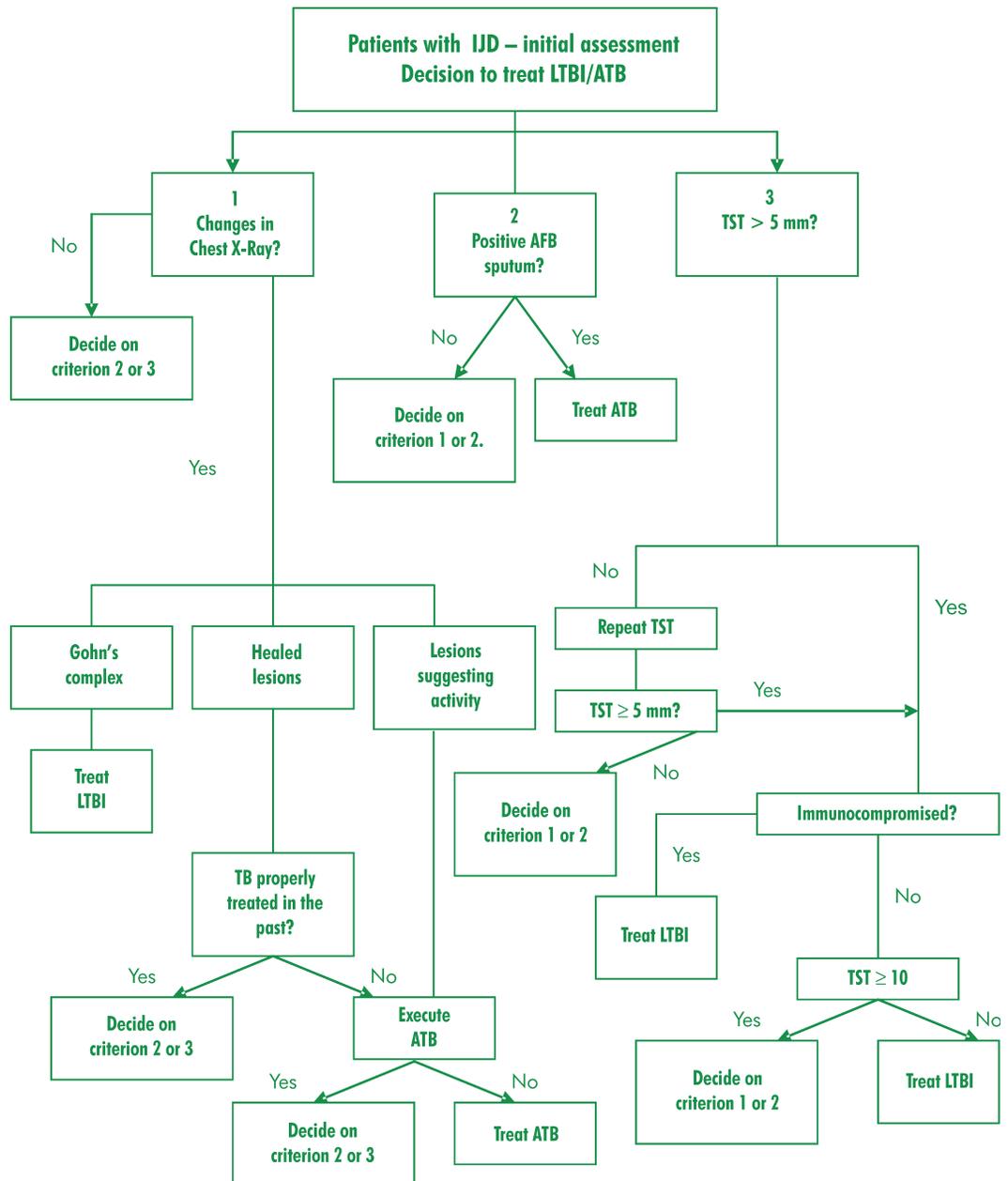
ants in 2006)<sup>23</sup> is much higher than the rate in the US and in most European countries. This fact requires that the international recommendations concerning screening and treating these patients for TB should be adapted to the Portuguese reality.

For these reasons, SPR's GEAR and the Tuberculosis Committee (TC) of the Portuguese Pulmonology Society (SPP) have elaborated recommendations for the diagnosis and treatment of LTBI and ATB in IJD patients treated with anti-TNF- $\alpha$  and other immunosuppressant drugs.

The main objective of these recommendations is to contribute for the reduction of the number of cases of reactivated TB and new TB infections in patients who are candidates for treatment with TNF- $\alpha$  antagonists in Portugal. An additional objective is also to standardize the procedures used to screen and prevent tuberculosis in the initial assessment of IJD patients, preferably before the onset of any immunosuppressant therapy.

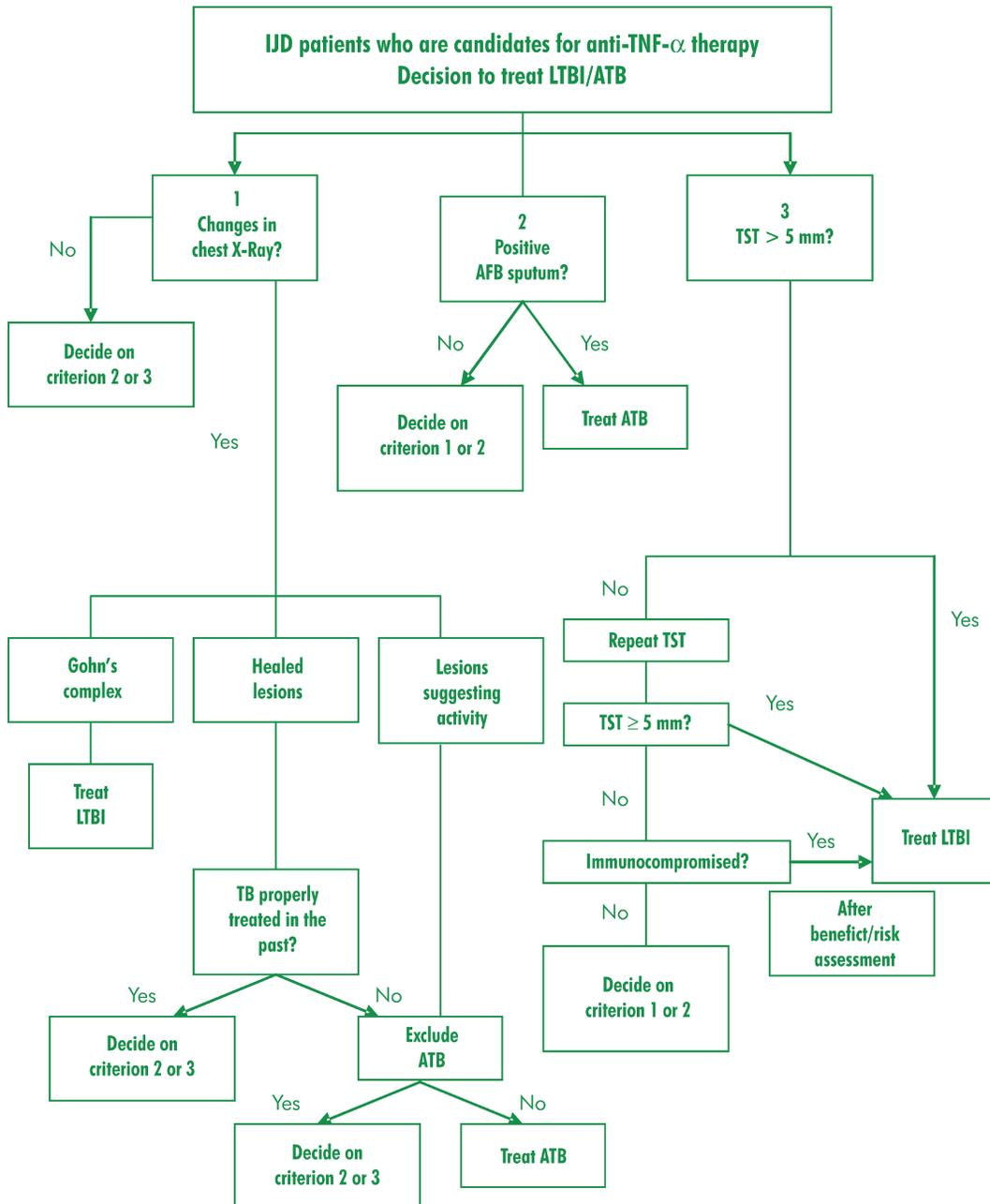
A group of experts was appointed by SPR's GEAR and SPP's TC to develop these recommendations. The group made an extensive review of the literature using the *PubMed/Medline* search engine and the following keywords: tuberculosis and TNF- $\alpha$  antagonists – 199 publications; tuberculosis and infliximab – 184 publications, tuberculosis and adalimumab – 48 publications,

tuberculosis and etanercept – 89 publications, isoniazid and methotrexate – 26 publications. In addition, the group reviewed the following information: TB in patients undergoing anti-TNF therapy<sup>22</sup>, data on TB<sup>23</sup> published by the General Directorate of Health (“Direcção Geral de Saúde”), national standards for the treatment of LTBI<sup>24</sup> and the international recommendations for screening and preventing TB in candidates for TNF- $\alpha$  antagonists therapy.<sup>25-28</sup> The recommendations were also based on the operational capacity of the Pulmonology Diagnostic Centers (Centros de Diagnóstico Pneumológico – CDP) and the Pulmonology and Rheumatology Departments. When the recommendations were ready, but before the final document was concluded, they were submitted to the review of two Spanish specialists responsible for the evaluation of the effectiveness of the Spanish recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists (LC and JGR)<sup>26</sup>, and also to a specialist in infectious diseases experienced in the treatment of tuberculosis (Dr. Germano do Carmo). The recommendations were presented and submitted to a public debate at a round table organized specifically for this purpose in the Portuguese Rheumatology Congress (April, 2006) and during a national meeting in the World TB Day (March, 2006).



**Fig. 1 – Patients with IJD – initial assessment.** Decision to treat LTBI/ATB. If criteria 1, 2 and 3 are negative, do not treat for LTBI/ATB

IJD: Inflammatory Joint Disease; TB: Tuberculosis; LTBI: Latent tuberculosis infection; ATB: Active tuberculosis; AFB: Acid-fast bacilli; TST: Tuberculin skin test



**Fig. 2.** IJD patients who are candidates for TNF- $\alpha$  treatment decision to treat LTBI/ATB. If criteria 1, 2 and 3 are negative, do not treat for LTBI/ATB

IJD: Inflammatory Joint Disease; TB: Tuberculosis; LTBI: Latent tuberculosis; ATB: Active tuberculosis; TST: Tuberculin skin test; AFB: Acid-fast bacilli

In June 2006, the initial draft version of the recommendations was placed on the SPR Internet website to enable further public debate. The recommendations included the suggestions and criticisms received as part of this final public debate process.

The first version of these guidelines was published in September 2006<sup>29,30</sup> and placed on the General Directorate of Health Internet website in December 2006. This first review was based on the clinical experience obtained on the use of these recommendations during 2007 and on new data recently published.

The applicability, effectiveness and safety of these recommendations will be regularly reviewed by the Sponsoring Societies (SPR and SPP); the recommendations will be reviewed whenever warranted by new data or evidence.

### Recommendations

Due to the compromised immunity observed in RA and other IJD patients, as a consequence of the physiopathology of the disease itself and of immunosuppressant therapies,<sup>26</sup> rheumatologists should screen for ATB and LTBI (Fig. 1) as early as possible, preferably at the moment of the diagnosis of an IJD. The objective is to obtain an evaluation of each patient before any immunosuppressant therapy is started. At this time the diagnostic accuracy of the tuberculin skin test is similar to the one obtained in the general population, thus enabling the treatment to be focused on the individuals with the highest probability of having LTBI. However, even if patients have been screened at the onset of disease, screening should be repeated before start-

ing treatment with anti-TNF- $\alpha$ . If the initial assessment was negative, the second screening will recognize any LTBI or ATB that may have occurred in the meantime. In individuals that have been treated for LTBI before, this second screening will identify any possible ATB. If correctly performed, LTBI treatment should only be done once in the lifetime.

These patients should be assessed based on their clinical history, focusing on TB risk factors, as well as complementary tests to detect ATB or LTBI.

The following situations should be referred to a CDP:

Patients with indication for treatment of LTBI or ATB;

Patients with symptoms suggesting ATB;

Patients at high risk for TB;

Patients with Gohn's complex or healed lesions on chest X-rays and a history of untreated TB;

Patients with a positive tuberculin skin test, All patients with IJD patients who are anti-TNF- $\alpha$  candidates and are already immunosuppressed;

The tuberculin skin test should be performed and interpreted in a CDP, whenever possible.

When treatment for tuberculosis (LTBI or ATB) is indicated, this should preferably be completed before starting anti-TNF- $\alpha$ . However, if the IJD activity justifies the need for immediate treatment, anti-TNF- $\alpha$  therapy can be started two months after the beginning of antituberculous therapy in the case of ATB, and one month after the beginning of antituberculous therapy in the case of LTBI.<sup>25, 31, 32</sup>

### Clinical history

- a) Symptoms suggestive of ATB → if yes, refer to CDP
- b) Check personal history for TB risk factors → if yes, refer to CDP
  - i. previous TB
  - ii. recent immigrants coming from countries with a high incidence of TB
  - iii. recent contact with infectious patients
  - iv. health care professionals
  - v. IV drug users
  - vi. diabetes, HIV infection, leukemias, lymphomas, head, neck or lung cancer

### Complementary tests to be done

- c) Chest X-Ray that can be:
  - i. Normal
  - ii. Abnormal:
    - 1. Gohn's complex → treat for LTBI, refer to CDP
    - 2. Fibrotic lesions
      - a. Past history of properly treated TB → the decision will depend on other procedures
      - b. Past history of untreated or incorrectly or incompletely treated TB → exclude ATB → treat for LTBI, refer to CDP
    - 3. Active lesions → confirm ATB diagnosis → treat for ATB, refer to CDP
- d) In the presence of symptoms or X-Ray findings suggestive of active tuberculosis,

check for the presence of *Mycobacterium tuberculosis* (microscopic examination and culture of sputum and, if positive, perform drug susceptibility tests).

e) Tuberculin skin test (TST) should be interpreted as follows:

- i. < 5 mm – negative → repeat TST on the other forearm within the next 7 to 14 days. If the second test is positive ( $\geq 5$  mm), only this last result should be used.
- ii.  $\geq 5$  mm – positive in any patient who is about to start anti-TNF- $\alpha$  treatment or in the initial assessment of any IJD patient who fulfill the criteria for an immunosuppressed patient.
- iii.  $\geq 10$  mm – positive in the initial assessment of any IJD disease and in patients who do not meet the criteria for an immunosuppressed patient.

### Procedure following tuberculin test

-if positive (ii and iii) → treat for LTBI (except if a correct treatment was performed in the past), refer to CDP

– if negative:

- a) Patient not previously exposed to immunosuppressive drugs → initiate anti-TNF- $\alpha$
- b) Immunosuppressed patient → treat as LTBI, refer to CDP. This decision should be taken on an individual basis, after a benefit / risk assessment, taking into account the age of the patient, ethanol consumption, previous hepatic diseases and the evaluation of LTBI risk.

### Notes

- Immunosuppressed patients are those with established IJD, treated with steroids (prednisolone in doses higher than

10 mg/day) and/or with immunosuppressant drugs such as MTX, cyclosporine, azathioprine, leflunomide or cyclophosphamide, regardless of the dose.

- For immunosuppressed patients, a negative tuberculin skin test does not exclude TB. For this reason, if the tuberculin test is conducted in an immunosuppressed phase, the patient should be treated for LTBI before starting anti-TNF- $\alpha$  therapy, even if the test is negative. This decision should be taken on an individual basis, after a benefit / risk assessment, taking into account the age of the patient, ethanol consumption, previous hepatic diseases and the evaluation of LTBI risk.
- Some authors<sup>33</sup> suggest that tuberculin skin test should not be conducted on immunosuppressed patients who are candidates for treatment with TNF- $\alpha$  antagonists, given the decision to treat them for LTBI regardless of the result of the tuberculin skin test. These recommendations defend the tuberculin skin test, as this information may be useful in the future to determine the sensitivity and specificity of the tuberculin skin test in such patients, and may help to assess the impact of LTBI treatment based on the tuberculin skin test result.
- The threshold for considering a positive tuberculin skin test was reduced from 10mm to 5mm in patients who will start therapy with TNF- $\alpha$  antagonists, even in the absence of depressed immunity criteria, because of the high risk of developing serious forms of TB associated with the use of these drugs.

### Treatment regimens for latent tuberculosis

- a) Isoniazid for 6 months (6H) – 60% efficacy. Level of evidence: A<sup>31</sup>
- b) Isoniazid for 9 months (9H) – 70% efficacy. Level of evidence: A<sup>26</sup>
- c) Isoniazid and Rifampicin for 3 months (3HR) – 50% efficacy. Level of evidence: A<sup>31</sup>
- d) Isoniazid, Rifampicin and Pyrazinamide for 2 months (2HRZ) – efficacy study currently underway. Level of evidence: D<sup>34</sup>

### Treatment regimens for active tuberculosis

- e) Isoniazid, Rifampicin, Pyrazinamide and Ethambutol for 2 months, followed by Isoniazid and Rifampicin for 4 months.<sup>35,36</sup>
- f) Other regimens may be proposed in specific cases (co-morbidities, such as liver or kidney failure, or if drug susceptibility testing indicates resistance to some of the first-line drugs).

### Comments

1. Patients should be screened and treated for LTBI or ATB when an IJD is first diagnosed and when the patient is a candidate for starting anti-TNF- $\alpha$  therapy.
2. Although prior screening is mandatory for all patients treated with TNF- $\alpha$  antagonists, none of the LTBI treatment regimens is 100% effective. In addition, patients contact with hospital environments, where there is a higher risk of contacting with TB patients, increasing the risk of new infections. For these reasons, patients should be carefully monitored for TB symptoms throughout the period they receive anti-TNF- $\alpha$  drugs and for six months after the drugs are discontinued.

This clinical vigilance should be complemented, whenever necessary, by X-Rays and other suitable complementary diagnostic tests.<sup>25</sup>

3. Therapy for ATB should be administered under direct observation (DOT).

4. For TST it should be used 2 units of RT23 Tuberculin.

5. There are new tests to diagnose LTBI, such as  $\gamma$ -interferon quantification; their usefulness in immunosuppressed IJD patients is currently being assessed.

6. Treatment for ATB and LTBI must be done under the care of a TB specialist, who will also address all diagnostic or therapeutic questions.

7. There is toxicity, especially liver toxicity, associated with LTBI therapy. The risk of liver toxicity increases with age. There is little data available on the risk of liver toxicity in IJD patients treated with DMARDs combined with anti-tuberculous drugs.<sup>37,38</sup> Patients should be carefully watched by a CDP specialist, both clinically and with laboratory tests, using the prevailing guidelines.<sup>24</sup>

8. In non-immunosuppressed patients, the risk of LTBI evolving to ATB is 10% over a patient's lifetime<sup>24, 39, 40</sup>. Treatment for LTBI reduces this risk to about 0.5%.<sup>39,40</sup>

9. In immunosuppressed patients, the risk of LTBI evolving to ATB is 8 to 10% per year.<sup>41</sup> In these patients, ATB may present atypically (making the diagnosis more difficult and often delayed) and it is generally more serious and associated with higher mortality rates.

10. LTBI therapy effect lasts for over 20 years. In fact, some authors even admit that the effect lasts for the patient's lifetime<sup>41</sup>. Because of this, patients are treated

for LTBI only once. LTBI treatment plans and duration are identical for all patients, regardless of being immunosuppressed or not.

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