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POSITION PAPER

Position paper on tuberculosis screening in patients with immune mediated inflammatory diseases who are candidates for biological therapy

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KEYWORDS
Tuberculosis screening;
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Abstract Chronic immunosuppression is a known risk factor for tuberculosis. Our aim was to reach a consensus on screening and prevention of tuberculosis in patients with immune mediated inflammatory diseases who are candidates to biologic therapy.
Methods: Critical appraisal of the literature and expert opinion on immunosuppressive therapies and risk of tuberculosis.
Results and conclusion: The currently recommended method for screening is the tuberculin skin test and the interferon gamma assay, after exclusion of active tuberculosis. Positively screened patients should be treated for latent tuberculosis infection. Patients may start biological therapy after 1–2 months, as long as they are strictly adhering to and tolerating their preventive regimen.

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PALAVRAS-CHAVE
Rastreio da tuberculose;
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Terapêutica biológica;
Terapêutica anti-TNF;
Doenças inflamatórias imuno-mediadas

Rastreio da tuberculose em portadores de doenças inflamatórias imunomediadas candidatos a terapêutica biológica

Resumo A imunossupressão crónica é um reconhecido factor de risco para a tuberculose. O nosso objectivo foi o de obter um consenso para o rastreio e prevenção da tuberculose em portadores de doenças inflamatórias imunomediadas candidatos a terapêutica biológica.
Métodos: Revisão crítica da literatura e opinião de peritos acerca das terapêuticas imunossupressoras e risco de tuberculose.
Resultados e conclusão: O método actualmente recomendado para o rastreio é o teste cutâneo da tuberculina e o doseamento do interferão gama, após exclusão da tuberculose activa. Doentes com rastreio positivo devem receber tratamento para a tuberculose latente. Estes doentes podem iniciar a terapêutica biológica após 1 a 2 meses, desde que a sua adesão seja rigorosa e apresentem boa tolerância à terapêutica profilática.

Introduction

In populations with high incidence of tuberculosis (TB), there have been an increased number of TB cases reported in patients treated with tumor necrosis factor antagonists (anti-TNF).[1] In fact, the relative risk (RR) of developing TB is 1.6–25.2 times higher in Rheumatoid Arthritis (RA) patients under anti-TNF therapy than in RA patients treated with conventional immunosuppressive therapy, depending on the clinical setting and the anti-TNF used.[1–7]

Active TB in the context of anti-TNF therapy usually results from the reactivation of a latent infection, shortly after the beginning of the treatment.[5,8] TB often presents an atypical behavior, which may pose difficulties to the diagnosis.[9] In countries with high incidence of TB, cases caused by new infection are also particularly frequent. TNF is fundamental for the immunological defence against *Mycobacterium tuberculosis*, especially in the formation and maintenance of granulomas. Animal models confirmed that it is possible to reactivate TB after administering anti-TNF antibodies.[10]

Besides anti-TNFs, other biological agents were approved for immune mediated inflammatory disease's treatment. Data about the risk of developing TB infection in patients treated with these other agents are scarce. Even though this risk might be lower for some of the biological agents that do not interfere with TNF until more data is available this group assumed that this position paper should be applied to all biological treatments.

Preventive chemotherapy can significantly reduce the incidence of active TB in individuals with latent infection, identified by positive tuberculin skin test (TST) or interferon-γ release assay (IGRA).[11]

The currently available evidence about the best management to prevent TB in patients receiving biological therapy is limited. In this position paper on the screening and prevention of TB in patients treated with biological therapy, delegates from the Tuberculosis Committee (TC) of the Portuguese Pulmonology Society (SPP), the Rheumatoid Arthritis Study Group (GEAR) of the Portuguese Society of Rheumatology (SPR), the Portuguese Society of Dermatology and Venereology (SPDV) and the Portuguese Society of Gastroenterology (SPG), have revised and updated recommendations that had been previously developed by the GEAR – SPR and by the TC – SPP, first published in 2006[12] and latter updated in 2008.[13]

The main objective of this position paper is to contribute for the reduction of the number of cases of reactivated TB and new TB infections in patients with immune mediated inflammatory diseases who are candidates for treatment with biological therapy in Portugal. An additional objective is to standardize the procedures used to screen and prevent TB in the initial assessment of these patients, preferably at disease onset, before the beginning of any immunosuppressant therapy.

Recommendations

Who should be screened?

All patients with immune mediated inflammatory diseases who are candidates for the use of biological therapy should be screened for latent TB infection (LTBI) prior to starting therapy (Evidence level C).

Patients eligible for anti-TNF therapy have an increased risk of developing TB upon starting this treatment. TB in this setting can present with severe, atypical and life-threatening manifestations. This risk exists not only due to the biological importance of TNF in the initiation and maintenance of the response against *M. tuberculosis*, but also because the underlying diseases (e.g. RA) and concomitant treatments (e.g. steroid therapy) increase the risk of TB per se.[14–18] Most of the active TB cases in patients treated with anti-TNF are due to reactivation of LTBI. It is well known that screening for LTBI before starting anti-TNF therapy is effective in preventing reactivation of TB.[17] Therefore, all national guidelines recommend the exclusion of active TB disease and LTBI in patients in whom biological therapy is considered.[19–21]

When to screen?

Patients with immune mediated inflammatory diseases should be screened for TB before starting biologic treatment and ideally when the disease is diagnosed (Evidence level C).

Any candidate to biological therapy should be screened for the presence of specific immune response to *M. tuberculosis* (including TST and IGRA) before starting these drugs and ideally when the immune mediated inflammatory disease is diagnosed, except in patients with mild forms of psoriasis, treated with topical drugs.[19–21]

It has been shown that certain diseases, such as RA, as well as chronic immunosuppressive therapy, such as corticosteroids (>15 mg/day for more than 2 weeks) increase the risk of TB. In addition, it is also well known that immunosuppressive therapy compromises the sensitivity of the TST and IGRA, this being especially true for TST.[16,18,22–25] Therefore, it is highly desirable that the first screen for TB should be done at the moment of diagnosis, before any kind of immunosuppressive treatment or phototherapy is started.

Which tests should we use?

After exclusion of active TB, LTBI should be screened with TST and IGRA (Evidence level C and D).

In the light of current knowledge, and in the absence of a *gold standard* test for LTBI diagnosis,[19] the screening process for LTBI requires a combination of a detailed medical history (which should include ethnicity, country of birth, history of or recent exposure to TB, previous TB and respective treatment, co-morbidities associated with increased risk of TB, professional activities with increased risk of exposure to TB), travel to endemic areas, chest radiograph (searching for changes indicative of active or residual previous TB) and tests for immunological memory against *M. tuberculosis* (TST and IGRA).[19] In erythrodermic psoriasis TST may be impossible to perform, reinforcing the need of IGRA in these cases.

The sensitivity of both tests may be compromised in patients receiving immunosuppressive therapy, although published evidence suggests that IGRA has a higher sensitivity than TST in patients with immune mediated inflammatory diseases, even after starting immunosuppressive therapy.[26–30]

Currently, different guidelines are adopted regarding the use of TST and IGRA, reflecting the difficulty of choosing the best strategy.[19,24,31–33] Over-treatment, implying the risk of drug toxicity due to a false-positive screening and under-treatment due to a false-negative screening are the main concerns.

Since the increase in sensitivity and specificity provided by IGRA in different studies is controversial and their positive and negative predictive values are yet to be defined, the role of IGRA is still under investigation. In this sense, IGRA cannot yet be used as a single test for immunological memory to *M. tuberculosis*. Thus, currently it is prudent to use both TST and IGRA in order to maximize sensitivity.[19,24,31]

Since patients may have false negative TST due to immunosuppression, a two step approach is advised—repeat TST 1–3 weeks after the initial negative screening.

How to exclude active tuberculosis in patients with Crohn's disease?

Acid fast bacilli smear and culture should be performed in endoscopic biopsies (Evidence level C).

The distinction between Crohn's disease and intestinal TB is a diagnostic challenge, as they present similar clinical, radiological, endoscopic and histological features.Investigation of patients with suspected Crohn's disease should always include differential diagnosis with intestinal TB. Acid fast bacilli smear and culture are warranted in pathological examination of endoscopic biopsies. Other tests such as nucleic acid amplification, immunohistochemistry or in situ hybridization are promising techniques that have been evaluated in some studies, but they are not widely available and require further validation.[34–51]

How to interpret the tuberculin skin test?

TST is considered positive if induration is $\geq$5 mm in previously immunosuppressed patients and if $\geq$10 mm in patients not previously exposed to immunosuppressors (Evidence level D).

In order to increase the sensitivity of TST (at the expense of lower specificity) different guidelines recommend, in the immunocompromised population, an induration of $\geq$5 mm to be the cut-off for a positive TST.[19,21,52,53]

The Tuberculosis Network European Trials Group (TBNET) recommends a cut-off value of 10 mm, stating that the loss of sensitivity to detect infection by increasing the cut-off from 5 to 10 mm is marginal, while the gain in specificity is substantial.[19] Taking this into consideration, TBNET suggests that a TST $\geq$ 10 mm should lead to LTBI treatment, without requiring IGRA confirmation. This evidence is based on results of non-controlled and non-randomized trials and on observational studies.

According to the Portuguese clinical practice, patients with immune mediated inflammatory diseases, who are candidates for anti-TNF therapy, should undergo a TST: the test is considered positive in previously immunosuppressed patients if the induration is $\geq$5 mm and in patients not previously exposed to immunosuppressors if the induration is $\geq$10 mm.

Who should start latent tuberculosis infection treatment?

Patients with epidemiological risk factors for TB (history of exposure to TB, previous TB, emigrants from high TB prevalence areas, residents in high incidence areas, co morbidities associated with increased risk of TB, professional activities with increased risk of exposure to TB, travel to endemic areas), or chest X-ray sequelae of untreated previous TB, or positive TST and/or IGRA, should start LTBI treatment, after exclusion of active TB (Evidence level C and D).

Whenever there is evidence of exposure to TB (regardless the results of the screening and after exclusion of active TB) or LTBI (positive TST and/or IGRA or changes in chest radiograph suggestive of previous untreated TB), after exclusion of active TB, preventive treatment should be offered before initiating biological therapy, as these patients have a high risk of progression to disease.[19,21,54–57]

Due to the risk of serious forms of disease, treatment must be offered to candidates for biological therapy regardless of age and presumed date of infection.

Which latent tuberculosis infection treatment regimen should be used?

Isoniazid for 9 months (Evidence level C and D).

Several therapeutic strategies have been proposed. Isoniazid is classically recommended as this drug in immunocompromised patients has proven to be effective (data derived from multiple studies in HIV patients).[58–60] Isoniazid for a period of 9 months is the most commonly used regimen and has an estimated efficacy of around 90%. This regimen is recommended by the American Thoracic Society (ATS)[61] and Canadian Tuberculosis Standards,[62] while the 6 months regimen, in which effectiveness varies between 65 and 69%, is proposed by the National Institute for Health and Clinical Excellence (NICE).[63]

TBNET recommends treatment with isoniazid for 9–12 months or isoniazid and rifampicin for 3 months (3HR).[19] However, the later is associated with a lower efficacy (around 60%). Some studies indicate that 4 months of rifampicin (4R) are at least as effective as 3HR and this regime has the advantage of being better accepted by patients, having fewer adverse effects when compared with regimens based on isoniazid and is associated with a lower cost to the health system.[64–68] These are very relevant advantages but effectiveness remains uncertain, as this regimen has not yet been tested extensively in randomized trials.

In the light of current knowledge, treatment with isoniazid for 9 months is the most consensual option.[19,59,60] One month is defined as the minimum LTBI treatment duration before starting biological drugs.[19] This recommendation is based on expert opinion.

Evaluation of the risk for toxicity due to latent tuberculosis infection treatment

Patient education, clinical monitoring, baseline and monthly laboratory testing of liver enzymes (Evidence level C and D).

Given the high risk of TB in patients starting anti-TNF, the risk of age-related hepatotoxicity[69] should not prevent patients from receiving treatment for LTBI. In addition to liver toxicity, isoniazid is associated with toxicity to the nervous system.[70] Vitamin B6 reduces central and peripheral effects of isoniazid and should be given to individuals with a history of alcoholism, diabetes, pregnant, postpartum, infants, malnourished, HIV-positive, people with active liver disease, cancer or history of pre-existing peripheral neuropathy.[71]

In case of choosing rifampicin-based regimens, interactions with other drugs should be considered, since this drug is a potent inducer of CYP450.[72]

Besides patient education and clinical monitoring, baseline and monthly (or biweekly) laboratory testing of liver enzymes is recommended for people older than 35 years, chronic alcohol abusers, HIV-infected persons, females during pregnancy and within 3 months after delivery and for those with chronic liver disease or taking potentially hepatotoxic concomitant medications. Transient transaminase elevations are common and may reflect the process of hepatic adaptation. However, isoniazid and/or rifampicin should be withheld as recommended if the serum transaminase level is higher than three times the upper limit of normal in a symptomatic patient or five times the upper limit of normal in the absence of symptoms.[60,61]

A change of the therapeutic regimen for a less hepatotoxic one (as 4R, at the expense of effectiveness) should be considered when serious hepatotoxicity is limiting LTBI treatment with isoniazid.

How should follow up be performed?

Patients should be re-screened for LTBI if the previous screen had been negative and the patient had not started biologicals, to exclude possible infection in the meantime (in the absence of a known contact with a TB patient, the screen would be valuable for 6 months). In the event of contact with active TB, TB screening should be promptly performed and in the absence of disease and LTBI, chemoprophylaxis should be guaranteed.[19]

Annual testing is recommended for patients, who live, travel or work in environments where TB exposure is likely, while they continue treatment with biologic agents. Patients who tested positive for TST and IGRA should only be monitored for clinical signs of TB.

Summary

1. All candidates for biologic therapy should be screened for TB.
2. TB screening procedures should include risk assessment, evaluation of TB signs and symptoms, chest radiography, TST and IGRA.
3. After exclusion of active TB, the presence of a positive TST ($\geq$10 mm in immunocompetent or $\geq$5 mm in immunocompromised conditions) or positive IGRA indicates the possibility of LTBI and LTBI therapy should be offered.
4. The existence of an untreated or inadequately treated previous TB (determined by chest X-ray sequelae and/or clinical history) should be evaluated for active TB and, if that is excluded, LTBI treatment should be given.
5. In the event of a recent exposure to a TB patient, LTBI therapy should be offered, even in the presence of negative screening tests.
6. The recommended regimen for LTBI treatment is 9 months of isoniazid.
7. Annual testing is recommended while on biological treatment.

Anexo 1. Protocolo de actuação para rastreio de doentes candidatos a tratamento imunosupressor.

Data: ____/____/_____	N.º Processo: _____	Médico: _____

1. Identificação do doente

Nome: _____

Sexo: M ☐ F ☐	Data nascimento: ____/____/_____	Profissão: _____
Hábitos tabágicos: Não ☐ Sim ☐ (_____ UMA) Consumo álcool: Não ☐ Sim ☐ (_____ g/dia)		Observações: _____ _____

2. Informação sobre a doença

Diagnóstico: _____	Data do diagnóstico: ____/____/_____

Tem indicação actual para iniciar tratamento imunosupressor? Sim ☐ Não ☐

Se medicação biológica, qual? _____

Se outros imunosupressores, quais? _____

VIH positivo ou outro estado de imunosupressão? _____

Medicação em curso ou suspensa há menos de um mês				
Medicamento	Sim	Não	Dose	Data início/Data fim
Corticóides				____/ ____/ _____; ____/ ____/ _____
Metotrexato				____/ ____/ _____; ____/ ____/ _____
Ciclosporina				____/ ____/ _____; ____/ ____/ _____
Azatioprina				____/ ____/ _____; ____/ ____/ _____
Ciclofosfamida				____/ ____/ _____; ____/ ____/ _____
Outros				____/ ____/ _____; ____/ ____/ _____

3. Informação sobre antecedentes

Exposição anterior a caso de TB? Sim ☐ Não ☐

Se sim, em que ano? _____ Tipo de exposição: _____

Rastreio TB anterior? Sim ☐ Não ☐	Se sim, resultados: _____
Fez tratamento de infecção latente por Mt? Sim ☐ Não ☐	Se sim, durante quanto tempo (meses)? _____
Antecedentes de TB activa? Sim ☐ Não ☐	Se sim, em que ano? _____
Fez tratamento de TB activa? Sim ☐ Não ☐	Se sim, qual o tratamento e durante quanto tempo (meses)?

	_____

4. Rastreio actual

Sintomas? Sim ☐ Não ☐ Quais? _____	Observações: _____ _____
Rx tórax? Sim ☐ Não ☐ Resultado: _____	
Se sintomas sugestivos e/ou alterações compatíveis com TB no Rx:	
Baciloscopia? Sim ☐ Não ☐ Data: ____/____/_____	Resultados/Observações: _____ _____
TC tórax? Sim ☐ Não ☐ Data: ____/____/_____	Resultados/Observações: _____ _____

Se diagnóstico de Doença de Crohn, fez:

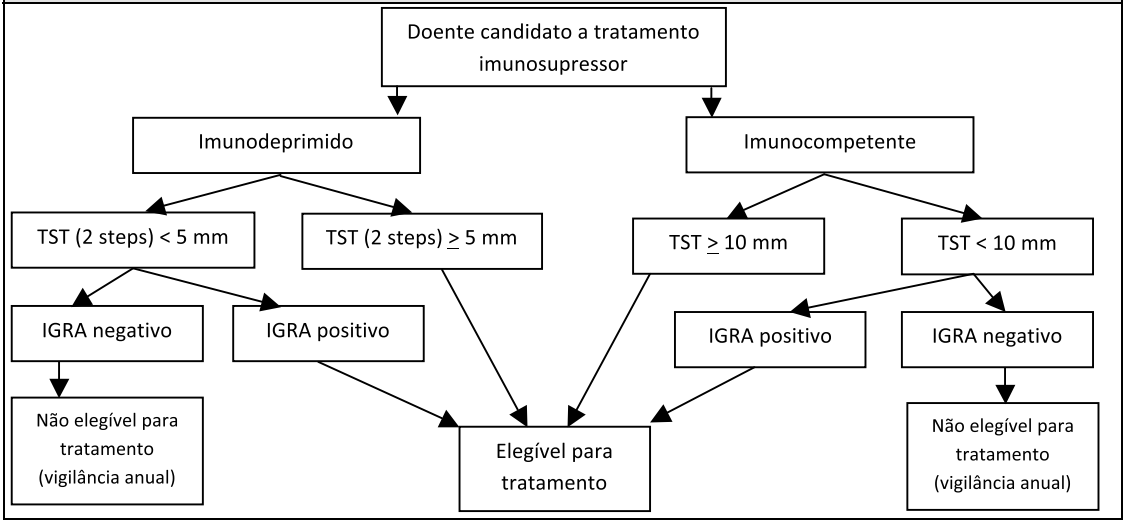
- Exame directo da biopsia intestinal? Sim ☐ Não ☐ Resultado/Observações: _____
- Cultura da biopsia intestinal? Sim ☐ Não ☐ Resultado/Observações: _____
- TAAN na biopsia intestinal? Sim Não Resultados/Observações:_____

Se foi excluída TB doença:

TST (*two steps*): Sim ☐ Não ☐ Resultado: _____ (mm)/ _____ (mm)

IGRA: Sim ☐ Não ☐ Resultado: _____

5. Algoritmo de decisão para elegibilidade para tratamento de infecção tuberculosa latente (Se sequelas de TB ou nódulos de Gohn em doente que nunca efectuou tratamento antibacilar ou se história de exposição a tuberculose ativa, passa a elegível para tratamento independentemente do resultado do TST ou do IGRA)



6. Risco de toxicidade

Consumo álcool: Não ☐ Sim ☐ (_____ g/dia)

Patologia hepática: Sim ☐ Não ☐ Observações: _____

Consumo habitual de medicamentos: Sim ☐ Não ☐ Quais? _____

Estudo analítico:

Análise	Data	Resultado
TGO	____/____/_____	
TGP	____/____/_____	
Outra	____/____/_____	

7. Proposta terapêutica (após avaliação do risco de toxicidade)

Tratamento de infecção tuberculosa latente: Sim ☐ Não ☐	Esquema: _____ Duração prevista: _____ (meses)
Tratamento de tuberculose activa: Sim ☐ Não ☐	Esquema: _____ Duração prevista: _____ (meses)

8. Vigilância do tratamento

Vigilância	Deve incluir	Em relação ao início do tratamento
Clínica	• Sinais ou sintomas de efeitos adversos	• 15 dias, 1 mês, 2 meses e depois de 2/2 meses
Laboratorial	• TGP/TGO • Hemograma e bilirrubina (se tratamento com R)	• 15 dias, 1 mês, 2 meses e depois de 2/2 meses • Mensal se VIH, álcool, doença hepática prévia, fármacos hepatotóxicos, gravidez ou pós-parto, utilizador de drogas, idade> 35 anos

Principais efeitos adversos

Isoniazida	Rifampicina
• Hepatite • Neuropatia periférica (parestesias, hipostesias, diminuição força muscuilar extremidades) • Sonolência, letargia • Rash cutâneo	• Hepatite (colestática) • Síndrome flu-like • Gastro-intestinais (dor abdominal, náuseas, vómitos) • Reacção cutânea generalizada • Púrpura trombocitopénica

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