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Latent tuberculosis and the use of immunomodulatory agents

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Latent *Mycobacterium tuberculosis* infection (LTBI) is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of active tuberculosis.[1] The World Health Organization estimates that one fourth of the world population is infected with *M. tuberculosis*.[2] The main strategy for reducing the risk of developing the disease in individuals infected with *M. tuberculosis*, who are at increased risk of progression to active tuberculosis, is LTBI treatment,[1] which is able to reduce this risk by 60-90%[3] and is one of the main components of the World Health Organization's End TB strategy.[4]

Between 5% and 10% of individuals with LTBI will progress to active tuberculosis in their lifetime, most within the first 5 years after infection.[5] The remainder of infected individuals will be able to contain the infection through an effective cellular immune response, which is dynamic.[6] The greatest risk factor for progression to active tuberculosis is poor immune status.[7] Therefore, HIV-infected individuals are at increased risk of progression to active tuberculosis, as are patients with chronic renal failure, patients with silicosis, and patients on immunosuppressive therapy.

TNF is a pro-inflammatory cytokine that plays an essential role in containing mycobacterial infection. TNF-α is initially produced by macrophages and monocytes activated by various stimuli, including viral and bacterial infections.[8] The release of TNF-α in response to mycobacterial infection increases phagocytosis and killing of mycobacteria,[9] and its production is required for the formation of granulomas, which engulf mycobacteria and prevent their proliferation.[10] In addition, TNF-α helps control mycobacterial infection by inducing apoptosis of ineffective macrophages, thus preventing these cells from becoming intracellular sanctuaries.[10]

The treatment of rheumatic diseases has undergone a drastic transformation since the introduction of biological agents, which are able to reduce the inflammatory process and inhibit progressive structural damage.[11] TNF inhibitors are biological agents that reduce inflammation and are able to modify the progression of chronic inflammatory diseases by inhibiting TNF-α. Despite the numerous benefits of using these agents in this population, the development of active tuberculosis should be expected when any biological agent with anti-TNF activity is used.[6] Therefore, screening for and treatment of LTBI are recommended in patients with chronic inflammatory diseases for which treatment with anti-TNF biological agents is indicated.

In this issue of the JBP, Lopes et al.[12] provide information on the risk of developing tuberculosis in patients with LTBI receiving immunomodulators and anti-TNF biological agents. The authors followed patients with chronic inflammatory diseases and LTBI, the mean follow-up period being 3 years (range, 6 months to 4 years). In the study, treatment with biological agents and other immunomodulators was initiated no sooner than 1 month after initiation of isoniazid therapy. There were only 6 cases of active tuberculosis among 101 patients with LTBI. The risk of developing tuberculosis was 1.39 times higher in patients treated with biological agents than in those treated with other immunosuppressants (although the statistical significance of this estimate was not confirmed, possibly because of the small number of active tuberculosis cases). In addition, the patients who developed active tuberculosis were diagnosed with the disease 10 months after the initiation of biological therapy. A history of contact with a tuberculosis case was strongly associated with the development of tuberculosis, which demonstrates that recently acquired infection is a risk factor for the development of active tuberculosis.[5] The most commonly used biological agent, prescribed in 58% of the cases, was infliximab. Of the 5 patients who developed tuberculosis while on biological agents, 4 used infliximab, which is described in the literature as the biological agent that poses the greatest risk of development of active tuberculosis.[6]

Another very interesting result of the study was the high LTBI treatment completion rate.[12] LTBI treatment with isoniazid was offered as a way to reduce the risk of developing tuberculosis in patients with a positive tuberculin skin test result and no signs or symptoms of active tuberculosis. More than 95% of the patients completed the treatment. The authors reported only one case of treatment abandonment, which is an excellent result, given that LTBI treatment abandonment is the most commonly reported reason for treatment failure. In addition, the low incidence of adverse effects in the study population, which caused treatment discontinuation in only 4% of the cases, is of note.

These results, found at a referral facility, underscore the need to screen patients who are referred for immunosuppressive therapy for LTBI and to offer LTBI treatment, which proved to be safe and for which the adherence rate was high in patients with chronic inflammatory diseases. Nevertheless, monitoring for tuberculosis symptoms is required throughout the period of treatment with biological agents, particularly in patients who need to be on immunosuppressants for more than 9 months.

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REFERENCES

1. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018.
2. World Health Organization. Global tuberculosis report 2019. Geneva: World Health Organization; 2019.
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Manual de Recomendações para o Controle da Tuberculose no Brasil. Brasília: Ministério da Saúde; 2019.
4. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new end TB strategy. Lancet. 2015;385(9979):1799-1801 https://doi.org/10.1016/S0140-6736(15)60570-0
5. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol. 1974;99(2):131-8. https://doi.org/10.1093/oxfordjournals.aje.a121593
6. Gardam MA, Keystone EC, Menzies R, Manners S, Skamene E, Long R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis. 2003;3(3):148-55. https://doi.org/10.1016/S1473-3099(03)00545-0
7. Getahun H, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis Infection. N Engl J Med. 2015;373(12):1179-80. https://doi.org/10.1056/NEJMra1405427
8. Papadakis KA, Targan SR. Tumor necrosis factor: biology and therapeutic inhibitors. Gastroenterology. 2000;119(4):1148-57. https://doi.org/10.1053/gast.2000.18160
9. Denis M. Tumor necrosis factor and granulocyte macrophage-colony stimulating factor stimulate human macrophages to restrict growth of virulent Mycobacterium avium and to kill avirulent M. avium: killing effector mechanism depends on the generation of reactive nitrogen intermediates. J Leukoc Biol. 1991;49(4):380-7. https://doi.org/10.1002/jlb.49.4.380
10. Kindler V, Sappino AP, Grau GE, Piguet PF, Vassalli P. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. Cell. 1989;56(5):731-40. https://doi.org/10.1016/0092-8674(89)90676-4
11. Bonafede M, Fox KM, Watson C, Princic N, Gandra SR. Treatment patterns in the first year after initiating tumor necrosis factor blockers in real-world settings. Adv Ther. 2012;29(8):664-74. https://doi.org/10.1007/s12325-012-0037-5
12. Lopes DMA, Pinheiro VGF, Monteiro HSA. Diagnosis and treatment of latent tuberculosis infection in patients undergoing treatment with immunobiologic agents: a four-year experience in an endemic area. J Bras Pneumol. 2019;45(6):e20180225. https://doi.org/10.1590/1806-3713/e20180225