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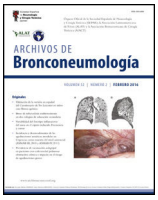

Editorial

Screening for Latent Tuberculosis and Biological Therapy☆

Cribado de la tuberculosis latente y terapia biológica

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The introduction of biologics drew attention to the need for diagnosis and treatment of latent tuberculosis infection (LTBI) by specialists not usually involved with this pathology. Tumor necrosis factor (TNF) treatments, known as anti-TNF therapy, radically improved the quality of life and clinical progress of patients with immunological, gastrointestinal, rheumatological, and dermatological diseases. However, reports of increased rates of tuberculosis (TB) in patients treated with infliximab uncovered a need to study the risk of reactivation of TB infection in these individuals,[1,2]

TNF plays an important role in the anti-tuberculosis response by increasing the phagocytic capacity of macrophages and cell recruitment for the formation of granulomas and containment of the tubercular infection.[3] TNF inhibitors promote the disintegration of granulomas and the activation and dissemination of the bacilli, so patients receiving these drugs, especially the monoclonal antibodies infliximab and adalimumab, have a high risk of reactivation of tuberculosis infection.[4]

It is now generally accepted that before starting treatment with biologics the risk of exposure to tuberculosis should be stratified, the presence of active disease or untreated residual disease should be ruled out, and preventive treatment should be offered to individuals who show evidence of LTBI.[5] Preventive treatment, according to some studies, is associated with a 74% reduction in the risk of tuberculosis reactivation.[6]

The key question is how to diagnose LTBI in individuals whose cell response is inhibited by their underlying disease or by the combination of corticosteroids with different immunosuppressive drugs.[7] Different scientific societies have published their own guidelines and consensus documents to address this often complex diagnosis.[8–13]

The initial test for tubercular infection in our setting remains the classic purified protein derivative (PPD) tuberculin skin test. This well-known skin test measures the delayed hypersensitivity reaction to the intradermal inoculation of PPD, a mixture of more than 200 proteins present in *Mycobacterium tuberculosis (M. tuberculosis)*. Because PPD antigens are also found in other mycobacteria, its specificity is low in individuals who have received Bacille Calmette-Guérin (BCG) vaccination. Moreover, PPD sensitivity in the diagnosis of LTBI may be compromised in patients receiving immunosuppressive therapy, and the rate of false negatives is high.

In vitro tests (interferon gamma release assay [IGRA]) quantify the cellular immune response by detecting gamma interferon produced by previously sensitized T cells when stimulated with specific antigens of the tubercular bacillus, i.e., early secretory antigen target-6 (ESAT-6) and culture filtrate protein 10 (CFP-10). These antigens secreted by the *M. tuberculosis* complex are absent in the BCG vaccine and in most of the environmental mycobacteria, conferring them greater specificity. IGRAs can rule out false positives on PPD in patients with normal immunity who are vaccinated with BCG and have no known risk factor for exposure to TB, while candidates for anti-TNF agents who already receive some type of immunosuppressive treatment are classified as high risk and are considered to be infected if a positive result is obtained with either technique (PPD or IGRA). Some studies have shown that IGRA sensitivity was superior to that of PPD in immunocompromised patients,[14] so an *in vitro* test should also be performed in immunocompromised patients who do not react to the PPD.

In addition to PDD or IGRA, it is important to assess individual risk factors for exposure to tuberculosis, such as age, country of birth, occupational exposure, travel to countries with a high incidence of the disease, or recent contact with a case of confirmed tuberculosis.

All patients who react to one or more tests should undergo a radiological study. The presence of residual lesions indicative of tuberculosis in the standard chest X-ray or CT scan may complicate management, as complete information about the treatment received previously is not always available. Chemoprophylaxis will be postponed until the presence of active disease is definitively ruled out from the microbiological analysis of respiratory secretions obtained by spontaneous or induced sputum or bronchoscopy.

In the event of a diagnosis of active tuberculosis, the specific treatment must be completed before biologics are started. Some forms of tuberculosis, predominantly extrapulmonary and disseminated forms, can be severe.

The most widely accepted LTBI treatment regimen worldwide continues to be monotherapy with isoniazid for 6 months. According to recent World Health Organization guidelines, acceptable

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alternatives to the recommended 6 months of isoniazid in countries with a low incidence of tuberculosis are 9 months of isoniazid, 3–4 months of isoniazid plus rifampin, 3–4 months of rifampicin alone, or 3 months of weekly isoniazid plus rifapentine (not available in Spain).[15]

There are discrepancies in the minimum time necessary for the treatment of LTBI before biologics can be safely started. Most guidelines suggest that 1 month would be sufficient, although in the case of short regimens, completion of 3-month course is preferable to avoid toxicities and interactions, if permitted by the patient's clinical situation.

Infected patients who cannot receive treatment should be monitored to rule out progression or reactivation if they present respiratory symptoms, particularly in the first 2 years, when the disease manifests itself most frequently.

In 2016, Archivos de Bronconeumologia published a practical consensus statement drawn up by a panel of respiratory, dermatology, rheumatology, gastroenterology, and infectious diseases specialists, setting out the main recommendations on the diagnosis, treatment and control of LTBI.[13] However, a recent anonymous online survey sent to various medical societies showed poor general adherence to the recommendations. Most of the 747 respondents performed LTBI screening at the right time in the right patients (93.7%); however, only 36.6% of respondents requested the appropriate diagnostic test, and only 56.3% correctly prescribed treatment of LTBI. Although 96% were familiar with the recommended LTBI treatment regimens, only 63.9% initiated them at the right time. Rheumatologists were more widely involved in LTBI screening and examined most patients for the possibility of LTBI (54%). In most cases, pulmonologists were involved on an advisory basis. The authors conclude that the incidence of tuberculosis in patients who are scheduled to receive biologics could be further reduced by emphasizing the importance of the correct diagnostic test and the use of the diagnostic algorithm for the LTBI.[16]

General guidelines for the diagnosis and treatment of LTBI in patients who are candidates for the use of biological agents are based on current clinical evidence. The optimal screening strategy will eventually be determined on the basis of accumulated evidence. Common sense and experience in the management of tuberculosis are currently the best guarantees for the correct evaluation of these patients.

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