Screening and Monitoring of Latent Tubercular Infection in Patients Taking Tumor Necrosis Factor-α Blockers for Psoriatic Arthritis

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ABSTRACT. Patients with arthritis who need treatment with biologics are carefully screened for possible previous exposure to tuberculosis to detect any latent tubercular infection (LTBI). The traditional method of screening for LTBI is not specific, because positivity could also depend on infection by atypical mycobacteria and bacillus Calmette-Guerin vaccination. In addition, the screening does not show high sensitivity, frequently presenting a false negativity because of immunosuppression caused by drugs used for arthritis. Recently, interferon-γ release assays (IGRA) have been used to screen LTBI with more sensitivity and specificity before treatment with anti-tumor necrosis factor-α drugs. Moreover, in our experience, IGRA are potentially useful in monitoring LTBI during biologic therapy. (J Rheumatol 2012;39 Suppl 89:82–5; doi:10.3899/jrheum.120252)

Key Indexing Terms:
PSORIATIC ARTHRITIS LATENT TUBERCULAR INFECTION
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Several events have changed the context in which the rheumatologist works today: migration phenomena, social changes and the increase in poverty, and the development of new drugs with potential interference from infectious diseases. In this context, tuberculosis (TB) represents a challenge we must not underestimate.

The global prevalence of this disease is still close to 9 million, mainly in underdeveloped countries[1]. This condition is believed to affect one–third of the world's population, with a natural history showing a progression to active disease in only 5% of cases[2]. However, the development of novel diagnostic modalities for latent TB infection (LTBI) is a significant advance in this field. The evolution of LTBI, in particular with regard to rheumatology, may be greatly affected by the use of tumor necrosis factor-α (TNF-α) blockers.

TNF-α is a potent inflammatory cytokine that controls immunity against several bacterial infections, including tuberculosis[3]. TNF-α blockers, used for the treatment of inflammatory diseases such as psoriatic arthritis (PsA), are associated with progression from an LTBI to overt disease[4,5]. There are 4 licensed TNF-α blockers currently in clinical use for the treatment of PsA: infliximab, adalimumab, and golimumab, which are monoclonal antibodies, and etanercept, a blocker of the receptor of TNF-α.

There are significant differences in the pharmacological profile of these agents. In fact, while etanercept binds only trimeric soluble TNF, infliximab, adalimumab, and golimumab bind both monomeric and trimeric TNF[6]. In addition, monoclonal antibodies bind membrane-bound TNF more strongly than does etanercept[7]. These characteristics may help to explain the different propensity they have to cause reactivation of TB[8]. In fact, membrane-bound TNF, expressed by activated macrophages and T lymphocytes, is essential in protecting against TB infection[9].

The reactivation of LTBI represents an intriguing clinical topic, because in these cases TB is often extrapulmonary or disseminated[10]. Therefore, before starting such a therapy, patients must be appropriately screened, while during treatment careful monitoring is mandatory. This article will discuss these aspects and propose a screening and monitoring flow chart.

SCREENING OF TB IN PATIENTS WITH PsA WHO NEED BIOLOGIC THERAPY

Patients with arthritis who need treatment with biologics are carefully questioned about their medical history, focusing on possible previous exposure to TB and/or vaccination (Figure 1).

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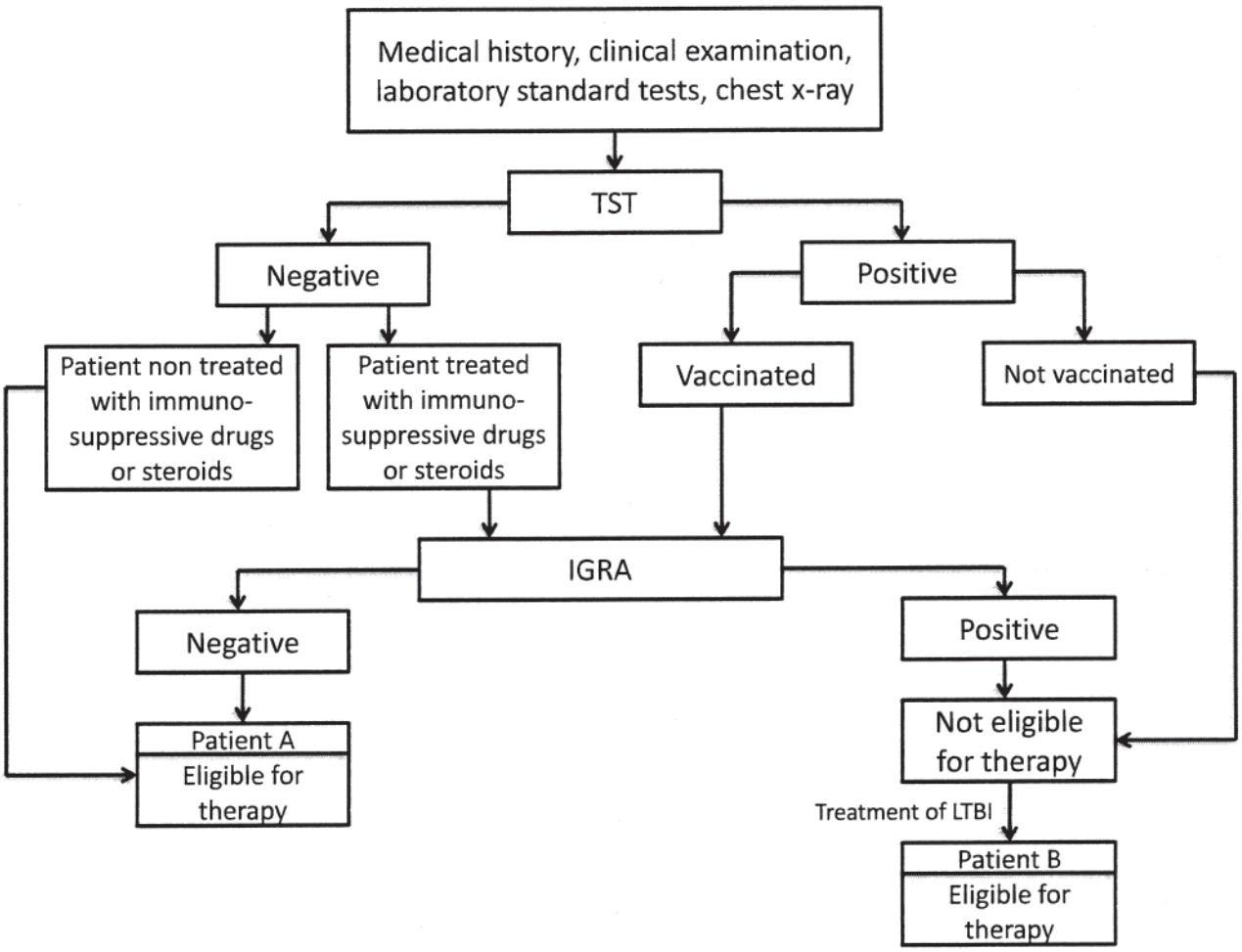

Figure 1. Flow chart of screening for latent tubercular infection and the appropriate approach to biologic therapy. TST: tuberculin skin test; IGRA: interferon-γ release assays. Modified from J. Ruiz-Manzano, et al. Diagnosis and treatment of tuberculosis. [Spanish]. Arch Bronconeumol 2008;44:551-66; with permission.

After clinical examination, they undergo chest radiography and a tuberculin skin test (TST) to detect a cutaneous delayed-type hypersensitivity response to purified protein derivative (PPD). TST is not a specific test. In fact, the antigens present in PPD cross-react with other mycobacteria, including atypical strains, and particularly bacillus Calmette-Guerin (BCG)[11]. In addition, TST sensitivity could be greatly decreased by the anergy caused by disease or by treatment with immunosuppressive drugs[12]. To obviate these limitations regarding sensitivity and specificity, in cases in which we may suppose a possible false-negative response to TST or a false-positive result due to BCG vaccination, we have to use blood tests, based on the measure of the release of interferon-γ (IFN-γ) by T cells, stimulated *in vitro* with *Mycobacterium tuberculosis*-specific antigens[13,14]. Currently, 2 tests are commercially available in agency-approved formats: the T-SPOT, which measures the number of IFN-γ-secreting T cells in terms of spots; and quantiFERON TB gold In-Tube (QFT-GIT), which measures the concentration of the secretion of IFN-γ. These tests are more sensitive and specific tools for the demonstration of TB infection, and their performances are not confounded by prior BCG vaccination[15,16]. If an IFN-γ release assay (IGRA) test is negative, then biologic therapy can begin.

In the case of an IGRA-positive patient at screening (having had a negative chest radiograph), we start treatment of LTBI, prescribing as first choice isoniazid for 9 months. TNF-α blockers, if suitable, can start only after the first 45 days of therapy. Alternatively, we suggest a 3-month isoniazid plus rifampin regimen before starting biological therapy.

MONITORING OF PATIENTS WITH ARTHRITIS DURING TREATMENT WITH TNF-α BLOCKERS

Patient A (Figure 2) is directly eligible for TNF-α blocker therapy and has to be clinically evaluated every 3 months with standard laboratory tests. Every 12 months, in cases of healthcare workers or others potentially at risk of exposure to TB infection, we suggest a repeated IGRA test. Such a recommendation applies also during the periods in which TNF-α blocker therapy is temporarily discontinued, owing

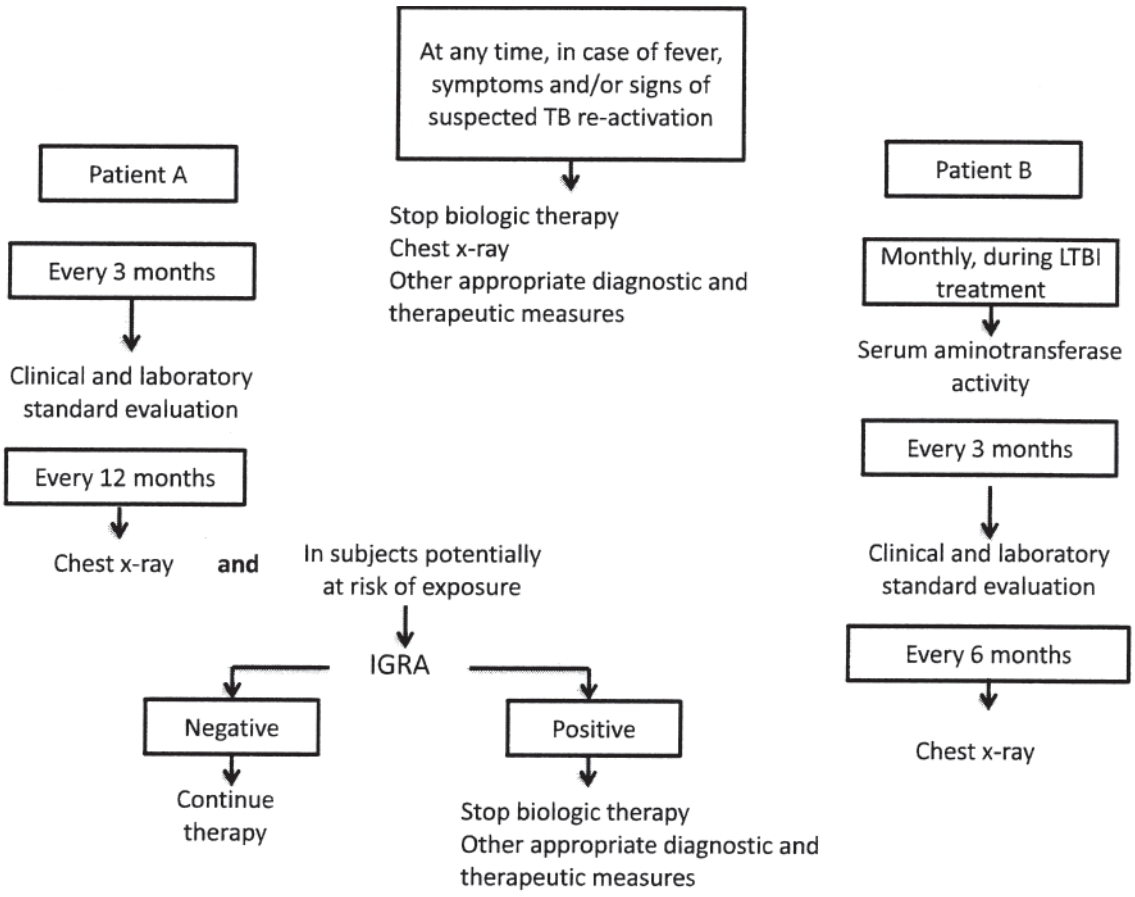

Figure 2. Flow chart of monitoring of latent tubercular infection (LTBI) in patients treated with biologic therapy. IGRA: interferon-γ release assays.

to a good control of the disease. Ringrose, *et al*[17], instead suggests that all patients with negative baseline TST and QFT-GIT results do not need further followup tests during the treatment. Our flow chart describes a safer approach in the screening of LTBI, to diagnose a recent TB infection. However, at present, guidelines do not clarify the effective cost/benefit ratio in such cases; therefore different strategies are plausible. In the case of a negative result, as a second step, TNF-α blockers are continued.

A chest radiograph should be performed in all subjects every year (or at any time, in case of respiratory symptoms). If the IGRA test becomes positive, biologic therapy should be stopped, a chest radiograph performed, and appropriate diagnostic and therapeutic measures taken, if indicated.

Patient B (Figure 2) is eligible for TNF-α blocker therapy only after treatment of LTBI because of positivity of TST and/or IGRA. For such patients, serum activity of aminotransferases during LTBI treatment must be evaluated every month; every 3 months they should undergo clinical and laboratory standard evaluation, and every 6 months, a chest radiograph.

In all patients, at any time, in case of fever, symptoms, and/or signs of a suspected TB reactivation, biologic therapy should be stopped and appropriate diagnostic and therapeutic measures taken.

Screening and constant monitoring of LTBI during TNF-α blocker therapy is critical for continued treatment of PsA, to avoid risks of reactivation of tubercular disease.

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