National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents

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Background: Chronic immunosuppression is a known risk factor for allowing latent tuberculosis (TB) infection to transform into active TB. Immunosuppressive/immunomodulatory therapies, while highly efficacious in the treatment of psoriasis and psoriatic arthritis, may be associated with an increased rate of active TB in patients receiving some of these therapies.

Objective: Our aim was to arrive at a consensus on screening for latent TB infection in psoriasis patient treated with systemic and biologic agents.

Methods: Reports in the literature were reviewed regarding immunosuppressive therapies and risk of TB.

Results: Screening patients for latent TB infection before commencement of treatment is of utmost importance when beginning treatment with the tumor necrosis factor−α inhibitors, T-cell blockers, cyclosporine, or methotrexate. The currently recommended method for screening is the tuberculin skin test. It is preferable that positively screened patients be treated with a full course of latent TB infection prophylaxis before immunosuppressive/immunomodulatory therapy is initiated. However, in the opinion of many experts, patients may be started on the immunosuppressive/immunomodulatory therapy after 1 to 2 months, if their clinical condition requires, as long as they are strictly adhering to and tolerating their prophylactic regimen.

Limitations: There are few evidence-based studies on screening for latent TB infection in psoriasis patients treated with systemic and biologic agents.

Conclusions: The biologic TNF−α inhibitors are very promising in the treatment of psoriasis. However, because TNF−α is also an important cytokine in preventing TB infection and in keeping latent TB infection from becoming active disease, the use of TNF−α inhibitors has been associated with an increased risk of developing active TB. A higher incidence of TB has also been reported with other immunosuppressive/immunomodulatory treatments for psoriasis. It is, therefore, of utmost importance to appropriately screen all patients for latent TB infection prior to initiating any immunologic therapy. Delaying immunologic therapy until latent TB infection prophylaxis is completed is preferable. However, if the patient is adhering to his prophylactic regimen and is appropriately tolerating the regimen, therapy may be started after 1 to 2 months if the clinical condition requires. (J Am Acad Dermatol 2008;59:209-17.)

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INTRODUCTION

Tumor necrosis factor (TNF) antagonists, including infliximab (Remicade, Centocor, Malvern, Pa), etanercept (Enbrel, Amgen, Thousand Oaks, Calif), and adalimumab (Humira, Abbott, North Chicago, Ill) are biologic medications that have proven to be effective for the treatment of plaque-type psoriasis[1-4] and psoriatic arthritis.[5-7] All 3 medications are approved by the Food and Drug Administration (FDA) for the treatment of psoriatic arthritis; with adalimumab recently gaining FDA approval, all 3 are now FDA approved for the treatment of plaque-type psoriasis. These medications have been used off-label for a variety of conditions in dermatology, in addition to psoriasis, including granulomatous diseases, neutrophilic dermatoses, vasculitis, autoimmune connective tissue diseases, autoimmune blistering diseases, graft-versus-host disease, and other inflammatory dermatoses.[8]

The effects of TNF-α are not only important in inflammatory disorders, but also have a central role in the host defense against *Mycobacterium tuberculosis*.[9] The human immune response is highly effective in controlling primary infection resulting from exposure to *M tuberculosis*. However, all viable organisms might not be eliminated in some individuals. *M tuberculosis* is thus able to establish latency, a period during which the infected individual is asymptomatic but harbors *M tuberculosis* organisms, which are capable of causing disease later.[10,11] This condition, referred to as latent tuberculosis (TB) infection, affects an estimated 9.6 million to 14.9 million people residing in the United States.[12] TNF-α is involved in the killing of mycobacteria by activating macrophages[13] and preventing the dissemination of infection by stimulating granuloma formation.[14] Since TNF-α is involved in both protection against mycobacterial infection and TB pathogenesis, it is not surprising that the clinical use of TNF-α antagonists has been implicated in an increased rate of TB.[15] Additionally, atypical presentations of TB, such as disseminated and extrapulmonary disease, are much more common in the setting of treatment with all 3 of the anti-TNF-α therapies.[16,17] Both infliximab and adalimumab have black box warnings on their product labels citing this risk,[18,19] and discussion with the FDA is ongoing regarding an update to the package labeling for etanercept. The Centers for Disease Control and Prevention (CDC) recommends TB screening with a tuberculin skin test for all patients being treated with any TNF-α inhibitor.[20]

Although some of these cases may result from new infection, the majority are assumed to be caused by reactivation of latent TB infection.[21] An appreciation of the risk associated with the TNF inhibitors has also prompted review of other immunosuppressive agents, and a higher incidence of TB has been reported with these agents as well.

Abbreviations used:

CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
MTX: methotrexate
TB: tuberculosis
TNF: tumor necrosis factor

METHODOLOGY

Reports in the literature were reviewed regarding immunosuppressive therapies and risk of tuberculosis. Articles were retrieved via MEDLINE search for the MeSH terms TB and infliximab, etanercept, adalimumab, methotrexate, cyclosporine, alefacept, efalizumab, steroid, calcipotriene, tazarotene, anthralin, tar, salicylic acid, phototherapy, PUVA, BCG vaccination. Evidence was graded by using levels of evidence developed by Shekelle et al.[22] IA evidence includes evidence from meta-analysis of randomized controlled trials; IB evidence includes evidence from at least one randomized controlled trial; IIA evidence includes evidence from at least one controlled study without randomization; IIB evidence includes evidence from at least one other type of quasi-experimental study; III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

TREATMENT ALGORITHM

Evidence

See Fig 1.

1. All patients should be screened for TB risk before initiating treatment with immunosuppressive therapies.

Screen for TB risk	Evidence level
Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep 2004;53:683-6.	IV
American Thoracic Society. Am J Respir Crit Care Med 2000;161:S221-47.	IV
Gardam MA, et al. Lancet Infect Dis 2003;3: 148-55.	IV
Lebwohl M., et al. J Am Acad Dermatol 2008;58:94-105.	IV

2. Tuberculin skin tests are considered positive in patients about to initiate immunosuppressive/immunomodulatory treatments when they have greater