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

than or equal to 5 mm of induration at 48 hours. Induration of less than 5 mm should be interpreted as a negative result but not as an exclusionary criterion for latent TB infection.

>5 mm induration is considered positive tuberculin skin test	**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

3. The whole-blood interferon-γ release assays may be considered in immunocompetent individuals with a history of BCG vaccination.

Consider whole-blood interferon-γ release assays if history of BCG vaccination	**Evidence level**
Winthrop KL. Ann Rheum Dis 2005; 64:iv29-30.	IV
Mazurek GH., et al. MMWR Recomm Rep 2005;54:49-55.	IV
Lebwohl M., et al. J Am Acad Dermatol 2008;58:94-105.	IV

4. If a patient is diagnosed with latent TB infection, then latent TB infection prophylaxis with 9 months of isoniazid should be initiated. Although it is preferable to complete the 9 months of therapy, immunosuppressive/immunomodulatory therapy may be initiated after 1 to 2 months if the patient's clinical condition requires as long as he or she is strictly adhering to and tolerating treatment with isoniazid.

Initiate immunologic therapy after 1-2 months of latent TB infection prophylaxis	**Evidence level**
Gardam MA., et al. Lancet Infect Dis 2003;3:148-55.	IV
Winthrop KL., et al. Arthritis Rheum 2005;52:2968-74.	IV
Mariette X., et al. Ann Rheum Dis 2003;62:791.	IV
Carmona L., et al. Arthritis Rheum 2005;52:1766-72.	IV

5. Adequate prophylaxis of latent TB infection has been shown to prevent up to 60% to 70% of patients from developing active TB. It is important to ensure that patients strictly follow the recommended latent TB infection treatment regimen and to maintain vigilance for active TB infection.

Ensure patients strictly follow latent TB infection prophylaxis regimen and to maintain vigilance for active TB infection	**Evidence level**
Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep 2004;53:683-6.	IV
Winthrop KL., et al. Arthritis Rheum 2005;52:2968-74.	IV

6. Patients with active TB should be referred to a specialist for standard 4-drug treatment. Concurrent immunosuppressive/immunomodulatory therapy should be avoided in this population before anti-TB therapy is completed unless the patient's clinical condition absolutely requires.

Complete therapy for active TB before initiating immunologic therapy	**Evidence level**
Gardam MA., et al. Lancet Infect Dis 2003;3:148-55.	IV

7. TB screening is recommended before initiation of therapy with any TNF-α inhibiting medication and at yearly intervals thereafter.

TB screening is recommended prior to initiating therapy with TNF-α inhibitors	**Evidence level**
Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep 2004; 53:683-6.	IV
Winthrop KL., et al. Arthritis Rheum 2005;52:2968-74.	IV
Gardam MA., et al. Lancet Infect Dis 2003;3:148-55.	IV
British Thoracic Society Standards of Care Committee. Thorax 2005;6:800-5.	IV
Carmona L., et al. Arthritis Rheum 2005;52:1766-72.	IV
Lebwohl M., et al. J Am Acad Dermatol 2008;58:94-105.	IV

8. Methotrexate (MTX) has been associated with reactivation of latent TB infection in patients with psoriasis and those with rheumatoid arthritis. Therefore screening for latent TB infection is recommended before initiation of MTX treatment for psoriasis.

MTX is associated with reactivation of latent TB infection	Evidence level
Smith JD, Knox JM. Br J Dermatol 1971; 84:590-3.	III
Di Girolamo C., et al. Br J Rheumatol 1998;37:1136-7.	III
Binyman K, Kooper RG. Rheumatology (Oxford) 2001;40:341-2.	III

9. Cyclosporinehas been reported to cause reactivation of latent TB infection in the higher doses utilized in the transplant population. Given that cyclosporine is known to be immunosuppressive, screening for latent TB infection is recommended before initiation of cyclosporine treatment for psoriasis.

Screen for latent TB infection prior to initiating CsA treatment	Evidence level
Lebwohl M, et al. J Am Acad Dermatol 2008;58:94-105.	IV

10. Medications that block T cell activation, alefacept and efalizumab, have not been reported to cause reactivation of latent TB infection. However, since they are associated with mild immunosuppression, it is recommended that latent TB infection screening be considered before initiating treatment with these therapies.

Screen for latent TB infection before initiating alefacept/efalizumab treatment	Evidence level
Lebwohl M, et al. J Am Acad Dermatol 2008;58:94-105.	IV

11. Topical therapies for psoriasis and phototherapy are not associated with reactivation of TB, and screening for latent TB infection is not necessary before initiation of these therapies for patients with psoriasis. Therefore, phototherapy and topical therapies may offer alternative options for patients with certain comorbidities.

Topical therapies for psoriasis and phototherapy are not associated with reactivation of TB	Evidence level
Expert opinion of National Psoriasis Foundation Medical Board	IV

Screening for TB

In 2004, the CDC published interim recommendations for the prevention of TB in patients commencing therapy with TNF-α antagonists.[23] Before initiating therapy, the physician should obtain a history to screen for TB risk factors, such as birth in a country where TB is prevalent, residence in a congregate setting (prison, homeless shelter, or long-term care facility), a prior positive tuberculin skin test result, substance abuse (injection or noninjection), healthcare employment in a setting with TB patients, and prior chest radiographic findings consistent with TB.[23]

After a careful history is obtained, the patient should be administered a tuberculin skin test, the standard screening test for latent TB infection in high-risk populations.[24] Testing all individuals who are to receive anti-TNF therapy will result in testing some individuals who are at low risk of infection. The positive predictive value of the tuberculin skin test in low-frequency populations is less than 50%. However, given the risk of development of active disease, erring on the side of caution is appropriate.[21]

Current recommendations from the CDC state that skin indurations of 5 mm or more at 48 to 72 hours should be interpreted as a positive result in any patient considered for anti-TNF therapy.[25] However, it should be noted that there is global variation in the diameter of skin induration that is interpreted as a positive result based on frequency of TB in the population and BCG vaccination, which can cause false-positive tuberculin skin test results. For example, the British Thoracic Society recommends the use of a threshold diameter of 15 mm in any person with a history of BCG vaccination.[26]

The whole-blood interferon-γ release assays, QuantiFERON TB Gold (Cellestis Limited, Abbotsford, Victoria, Australia) and T-SPOT TB (Oxford Immunotec Limited, Oxford, UK), might offer a more specific alternative to tuberculin skin test in regions of BCG vaccination since they assess immune responses to antigens that are highly specific for TB that are not found in BCG.[27] These assays are also more sensitive and more specific than the tuberculin skin test in diagnosing latent TB infection in immunocompetent individuals.[28,29] Although the CDC has endorsed the use of the Quantiferon TB-Gold test to screen most populations for latent TB infection,[30] the test is not currently recommended for screening before initiating anti-TNF therapy.[25]

Individuals who are immunocompromised because of immunosuppressive medications or medical conditions may experience anergy to the tuberculin skin test; consequently, an induration less than 5 mm should not be considered an exclusionary criterion for *M tuberculosis* infection.[23] Although immunosuppressive, anti-TNF treatment does not suppress the dermal induration that is the measure of a positive

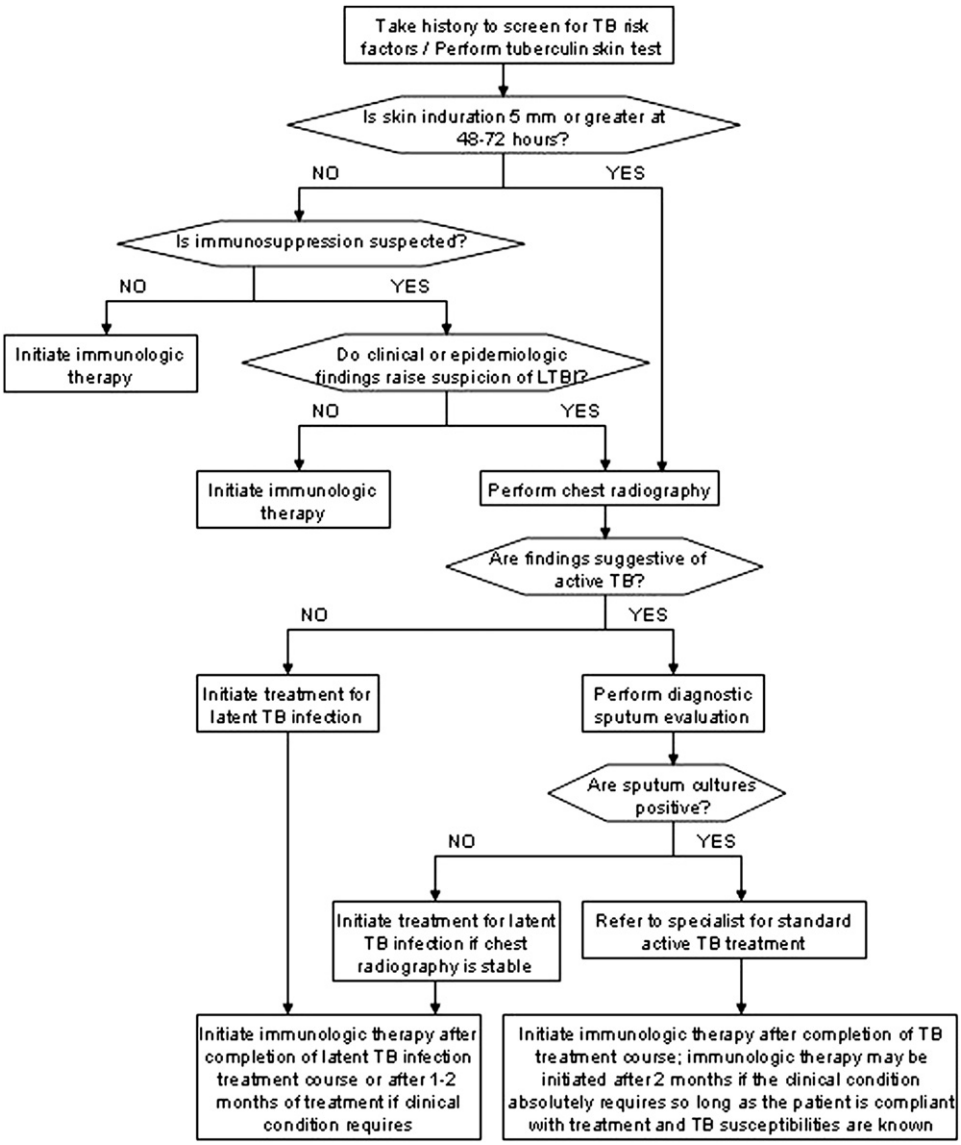

Fig 1. Screening for tuberculosis infection before initiating immunosuppressive/immunomodulatory therapy for psoriasis.

response to the tuberculin skin test.[31] Both anergy testing (determining skin reactivity to a panel of control antigens that should normally elicit a response) and "two-step" or "booster" tuberculin tests are not currently recommended in immunocompromised individuals in the United States.[25] The whole-blood interferon-γ release assays have demonstrated a better diagnostic performance than the tuberculin skin test in immunosuppressed individuals,[32] but they are not recommended at this time.

Individuals may have a positive tuberculin skin test secondary to latent TB infection or active TB. Active disease must be ruled out before therapy for latent TB infection or anti-TNF therapy can be considered.[21] Chest radiography is an important screening test to differentiate these conditions. The CDC recommends that chest radiography should be performed in all individuals with a positive tuberculin skin test result or in any individual with a negative tuberculin skin test who has clinical or epidemiologic findings that raise suspicion of latent TB infection.[24] Findings suggestive of TB should trigger diagnostic sputum evaluation (microscopic examination of a stained sputum smear for acid-fast bacilli and culture for *M tuberculosis*).[33] Those patients with a chest radiograph of normal findings or patients with a chest radiograph showing stable abnormal findings with negative sputum cultures should receive treatment for latent TB infection. Patients with active TB should be referred to a specialist familiar

with the diagnosis and management of TB and should be treated with a standard 4-drug regimen. The individual with active disease must have documented completion of therapy before anti-TNF therapy can be started.[21] Although it is preferable to delay TNF blockade until a full course of antituberculosis treatment has been completed, some recommendations state that anti-TNF treatment may be initiated sooner if the patient's clinical condition absolutely requires. In these situations, therapy should not be initiated until it is certain that the patient is compliant with antituberculosis medications for at least 2 months and the drug susceptibility profile of the organism in those with a positive culture is known.[26]

Treatment of latent TB infection

Individuals with latent TB infection should receive prophylactic treatment before anti-TNF therapy is initiated.[33] The treatment recommended by the CDC for latent TB infection remains isoniazid, 300 mg daily, for 9 months, although 4 months of rifampin therapy (600 mg daily), either alone or in combination with isoniazid, is an acceptable alternative regimen.[10,34] The recommendation of daily rifampin and pyrazinamide for 2 months was discontinued[34] after it was shown to have unacceptable liver toxicity.[35] The CDC has issued no clear recommendation on how long latent TB infection prophylaxis must be given before a TNF-α inhibitor may be added, but it is preferable for a patient to receive the full 9-month course of therapy. However, the patient's clinical course may require earlier initiation of therapy, and the clinician must balance the possible increased risk of active TB with the morbidity suffered from protracted disease.[21]

Because the organism burden in latent TB infection is low, a prolonged delay in anti-TNF therapy in patients with latent infection may be unnecessary. Some authors have recommended that anti-TNF therapy should be withheld, at the very least, until the patient is adhering to an appropriate prophylactic regimen.[27] Gardam et al[21] recommend that latent TB infection treatment be given for 1 to 2 months to ensure that the antituberculosis therapy is well tolerated. French guidelines suggest that latent TB infection prophylaxis should be started at least 3 weeks before the initiation of TNF blockers.[36] Recommendations from the Spanish National Health Service in collaboration with the Spanish Society of Rheumatology recommend 1 month of latent TB infection prophylaxis before initiation of TNF blockers.[37] The effect of various regimens in preventing active TB in the setting of anti-TNF medications has not been studied. It is not clear if prophylactic regimens with shorter durations of therapy may show benefit if TNF-α inhibitors are started during the treatment course.

Treatment of latent TB infection has been shown to prevent up to 60%[38] to 70%[37] of patients from developing active TB. Even with strict adherence to prophylactic treatment recommendations, some cases of active TB may occur.[37-40] However, the incidence of active TB has been reported to be 7 times higher when latent TB infection treatment recommendations are not followed precisely than when they are strictly followed.[39] In addition to ensuring that patients strictly follow the recommended latent TB infection treatment regimen, it is also important to maintain vigilance for active TB infection and atypical presentations of active TB infection in all individuals receiving anti-TNF therapy. If a patient develops active TB while taking TNF inhibitors, the anti-TNF therapy should be stopped and standard 4-drug therapy for TB should be initiated.[33]

Evaluation before initiating latent TB infection prophylaxis should emphasize the importance of adhering to the treatment regimen and should review possible adverse effects of the medications. Baseline laboratory testing is not routinely indicated; however, patients with a history suggestive of liver disease should have evaluation of baseline serum aspartate aminotransferase, serum alanine aminotransferase and bilirubin levels. Patients should be carefully monitored during treatment for signs of hepatitis. Periodic laboratory monitoring is necessary only for individuals with baseline abnormalities or individuals experiencing new symptoms.[10]

Selection of TNF-α antagonist

The TNF-α inhibitors have different mechanisms of action and may, therefore, have variable risks for the development of TB. Infliximab and adalimumab are monoclonal antibodies to TNF-α, whereas etanercept is a dimeric, soluble recombinant fusion protein constructed from the extracellular domain of the human p75 TNF receptor and the Fc fragment of human IgG1.[40] All 3 agents bind to TNF-α, but infliximab binds to TNF more avidly than etanercept.[41] Adalimumab has the longest half-life (2 weeks).[19] The half-life of infliximab is 8 to 9.5 days[18] and etanercept has the shortest half-life (4 days).[42]

In a review of the FDA's adverse events database from January 1998 through September 2002, Wallis et al[43] found 335 cases of infliximab-associated TB and 39 cases of etanercept-associated TB worldwide. The cumulative incidence of reported TB among patients receiving these drugs in the United States was estimated at 54/100,000 for infliximab and

28/100,000 for etanercept. Additionally, the authors found that the time to onset of active TB in the reported cases was shorter with infliximab than with etanercept.[33] However, this review is limited by the voluntary reporting of adverse events and possible variations in the populations receiving each medication. Furthermore, atypical presentations of TB, including disseminated and extrapulmonary disease, are much more common in patients who have been treated with any of the 3 anti-TNF biologic therapies.

An analysis of the German registry of patients receiving biologic agents that was controlled for variations between populations found no significant differences in the rate of TB in patients receiving infliximab versus etanercept. Only one case of TB was noted in this review, and it was in an infliximab-treated patient.[44] Information comparing adalimumab to the other agents is limited because of its more recent approval. A recent analysis of the Spanish BIOBADASER registry of patients receiving biologic agents revealed that there was not a significant difference in the rate of active TB among any of the 3 TNF-α antagonists.[39] No clear recommendation can be made at this time as to which particular anti-TNF agent should be used in the setting of latent TB infection, since this topic requires further study.

TREATMENT ALTERNATIVES

Although many other treatment options have likely been exhausted before initiation of therapy with TNF-α inhibitors, an understanding of the risk of reactivation of latent TB infection with other psoriasis treatments is important. Topical steroids, the most commonly used treatment for psoriasis, have never been reported to cause reactivation of latent TB infection. Likewise, other topical therapies, including calcipotriene, tazarotene, anthralin, tars, and salicylic acid as well as phototherapy, are not immunosuppressive and do not cause TB reactivation.

Some commonly used systemic therapies for psoriasis are immunosuppressive and have been reported to cause TB reactivation. Methotrexate (MTX) has been reported to cause reactivation of latent TB infection when used for the treatment of psoriasis[45] and rheumatoid arthritis.[46,47] There are no guidelines regarding TB testing before initiation of MTX therapy. One concern in patients who are found to have latent TB infection is the concomitant use of MTX and isoniazid; both of which are hepatotoxic medications. Although an earlier study reported a high incidence of hepatotoxicity with concomitant use,[48] a larger, more recent study reported no cases of severe hepatic failure and only a low incidence of mild, reversible elevations in liver function tests that was comparable to rates reported for isoniazid therapy alone.[49]

Cyclosporine is an immunosuppressive agent that inhibits T lymphocytes; in addition to its therapeutic use for psoriasis, cyclosporine is widely used in transplant patients.[50] Although reactivation of latent TB infection has been reported in transplant recipients,[51] no cases of reactivation of latent TB infection have been reported at the lower doses of cyclosporine used in dermatologic settings (up to 5 mg/kg per day).[50]

More recently, other biologic medications that block T-cell activation without inhibiting TNF-α, such as alefacept (Amevive, Astellas, Deerfield, Ill) or efalizumab (Raptiva, Genentech, Inc, South San Francisco, Calif), have been used in the treatment of psoriasis. Although these agents have not been reported to cause reactivation of latent TB infection, they are immunosuppressive, and the majority of advisors from the medical board of the National Psoriasis Foundation perform baseline TB testing before initiating therapy with either agent.[52]

In conclusion, the new biologic TNF-α inhibitors are very promising in the treatment of psoriasis and psoriatic arthritis. 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 before initiating any immunologic therapy. Screening consists of a carefully taken history and a tuberculin skin test, with chest radiography performed to rule out active disease in patients with a positive screening.

The recommended treatment for latent TB infection is 9 months of daily isoniazid. 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. Careful monitoring for TB and atypical presentations of TB is critical, especially during TNF blockade. These recommendations are largely based on level IV evidence and evidence-based studies on this subject are needed. Future recommendations and studies need to address the utility of whole blood interferon-γ release assays in these patients, the appropriate interval between initiation of latent TB infection prophylaxis and initiating immunosuppressive/immunomodulatory therapy, and what

variations exist, if any, in the risk of TB developing among the 3 TNF-α inhibitors.

Consensus

The medical board of the National Psoriasis Foundation reviewed and endorsed this manuscript by a majority vote on January 31, 2008 at the medical board meeting.

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