

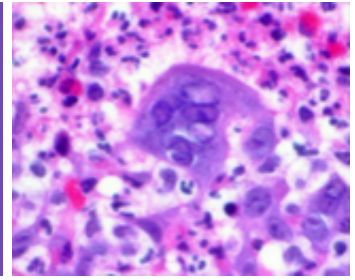


eLITERATURE REVIEW

eMedicalDermatology Review

Presented by
The Johns Hopkins University
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Supported by an Educational
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November 2009: VOLUME 2, NUMBER 2

Safety of Biologic Agents



In this Issue...

In this issue, we review several articles highlighting the safety of and screening measures for biologic agents used in patients with skin disease. Although these therapies provide a promising alternative to such older treatments as methotrexate, cyclosporine, and ultraviolet (UV) radiation, they are still relatively new to the market and long-term studies on their risk profiles are ongoing. Additional information on the safety, efficacy, and screening requirements for biologic therapies will become available as more practitioners incorporate them into their clinical practice.

- Commentary from our Guest Authors
- Long-Term Safety and Efficacy of Etanercept in Patients With Psoriasis Treatments and the Risk for Malignancy
- Screening and Monitoring of Patients Taking Biologic Agents for the Treatment of Psoriasis
- Tuberculosis Screening and Biologic Agents Presentation and Management of Tuberculosis in Patients Undergoing Biologic Therapy

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Release Date

November 17, 2009

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At the conclusion of this activity, participants should be able to:

- Identify specific risks associated with use of the new biologic therapies.
- Describe tuberculosis in the setting of biologic therapy, including screening requirements, necessary treatment for latent infection, and recognition of active disease.
- Evaluate the current screening and safety testing that should be performed in patients prior to and while undergoing biologic therapy.

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- **Mark Lebwohl, MD** has disclosed that he has received grants for clinical research, Advisory Board, speaker honorarium for/from Abbott, Amgen/Wyeth, Astellas, Centocor, Galderma, Genentech, Novartis, GlaxoSmithKline, Triax,

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- Elizabeth Sloand, PhD, CRNP has disclosed no relationships with commercial supporters.

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COMMENTARY

The new class of biologic therapies represents an exciting and promising alternative for patients with skin disease. Recommendations regarding screening tests and safety concerns continue to evolve as more information becomes available on the long-term use of these agents. Although initial reports have been promising regarding the safety and efficacy of biologics in dermatology patients, many areas still require further investigation. Of note, efalizumab was recently removed from the market due to an increased risk of progressive multifocal leukoencephalopathy that was only discovered once large-scale data was available on this rare occurrence. While many of the articles in this review reference efalizumab as one of the biologic therapies, the reader should keep in mind that this drug is no longer on the market. Currently, the best available safety follow-up studies have been in patients with rheumatoid arthritis (RA). Whereas these studies provide valuable data, extrapolating that data to other groups (ie patients with psoriasis) should be performed with caution. Patients with RA are frequently taking other immunosuppressive medications in addition to biologic agents and do not have the same comorbidities as do other patient populations. Psoriasis, for example, has been linked to obesity, alcohol consumption, and increased incidence of smoking,¹ all of which may change a patient's risk for drug-related adverse events. Patients with psoriasis may also have a higher risk for certain malignancies, both as a result of prior therapies and because of the inherent risk associated with the disease itself. Therefore, studies of biologic agents as a treatment for specific dermatologic conditions, such as psoriasis, warrant special attention. We review one such study, by Tying and colleagues, on the safety and efficacy of etanercept for patients with moderate to severe psoriasis, with a follow-up period of 96 weeks. As with similar studies in patients with RA, this report shows that the rate of adverse events with etanercept use is very low and the agent does not appear to be associated with any cumulative risk following long-term use.

An increased risk for malignancy is theoretically associated with any therapy that suppresses the immune system, because of the decreased surveillance of abnormal cells

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by the body's natural defenses. Thus, malignancy is of particular concern in patients taking any of the new biologic therapies. The US Food and Drug Administration (FDA) recently issued a black box warning for tumor necrosis factor (TNF) inhibitors after concluding that the agents are associated with an increased risk for malignancy in children and adolescents. The risk for malignancy with these therapies, compared with several older treatments, is examined in the review by Patel and associates. According to the authors, overall, biologic therapies appear to confer a low risk compared with other psoriasis treatments. However, there are limited data and most of the studies were not conducted in patients with psoriasis. Additional research is needed to draw meaningful conclusions.

With the increasing use of biologic therapies, standard screening and safety measures continue to evolve. The available information on this topic has been reviewed by Huang and coworkers, who report that standard screening measures (such as the tuberculin skin test (TST), the basic metabolic panel, and urinalysis) are poorly supported by the available research. They find inadequate evidence strongly recommending for or against any particular screening practices, although they do offer recommendations based on what is standard for most physicians. Hopefully, these recommendations can be updated once more patient treatment-years have accrued on these therapies. Although there is an increasing amount of evidence supporting the safety and efficacy of biologic agents, a lack of information still exists regarding the utility of the screening tests themselves. It is important to remember that each test carries a financial burden; there is also a risk for emotional stress, as in the case of false-positive results with routine use of the TST.

Tuberculosis (TB) is of particular concern among patients receiving biologic therapies, especially TNF- α inhibitors. These agents interfere directly with an important part of the body's cell-mediated defense against such intracellular pathogens as *Mycobacterium* spp. With most dermatologists not accustomed to seeing reactivated latent TB or acute active disease, the article by Hernandez and colleagues provides a helpful review of the presentation, diagnosis, and management of TB infection. The newest guidelines for TB screening, recently published by Doherty and associates on behalf of the National Psoriasis Foundation, are also reviewed in this newsletter. It is strongly advised that physicians prescribing biologic therapies be familiar with this information.

As the data continue to accumulate, biologic therapies appear to be a very safe and valuable new tool for the treatment of dermatologic diseases. Trials in patients with RA are helpful and reassuring, but should be interpreted with caution in other patient populations. More research is still needed in all areas relative to these therapies, especially with regard to the efficacy of current screening practices. Practitioners must evaluate each patient on an individual basis, considering the patient's underlying risk factors in the context of current treatment recommendations.

Commentary References

1. Higgins E. [Alcohol, smoking and psoriasis](#). *Clin Exp Dermatol.* 2000; 25(2):107-110.

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LONG-TERM SAFETY AND EFFICACY OF ETANERCEPT IN PATIENTS WITH PSORIASIS

Tyring S, Gordon KB, Poulin Y, et al. **Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis.** *Arch Dermatol.* 2007;143(6):719-726.

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Tyring and colleagues conducted a phase 3, randomized, double-blind trial with an open-label extension period. The 12-week, placebo-controlled portion of the study included 618 adult patients with moderate to severe psoriasis, with 591 of them entering the open-

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label extension. The results of the 12-week, double-blind portion of the study have been previously reported.¹ This article reports on the safety and efficacy data from the subsequent 84-week, open-label period. Compared with standard incidence ratios calculated for expectations in age- and sex-matched cohorts from the general population, observed numbers of total malignancies in the study population did not differ significantly from what would be expected in the general population. With the exception of injection-site reactions, the rate of adverse events in the etanercept treatment group was similar to that in the placebo group. In patients originally randomized to etanercept, long-term exposure was not associated with increased rates of adverse events, with the rates being similar at week 12 and at week 96. Nonneutralizing antibodies to etanercept were observed in 18.3% of the patients, with the presence of these antibodies not affecting the safety or efficacy of the agent in these individuals. No opportunistic infections, TB, or demyelinating diseases were reported. Two patients experienced worsening of congestive cardiac failure.

A 75% reduction in Psoriasis Area and Severity Index (PASI) score was observed in 51.1% of the original etanercept group and 51.6% of the original placebo group following 96 weeks of open-label treatment. The PASI response rate peaked at week 48, with 63% and 61.1% of the etanercept/etanercept and placebo/etanercept groups, respectively, achieving a PASI75 (ie, a PASI score of at least 75%). Dermatology Life Quality Index (DLQI) and patient global assessment of psoriasis were used as measures of patient-reported outcomes. At week 96, the authors reported that 75.7% of placebo/etanercept patients and 77.0% of etanercept/etanercept patients were categorized as DLQI responders. At week 96, 78% of patients in both groups achieved a patient global assessment of psoriasis score of 0 to 2.

The increased efficacy of higher-dose etanercept therapy with no corresponding increase in adverse events has been previously demonstrated,² but efficacy data for this duration of time and in this number of patients were not available. The long-term safety data on etanercept for the treatment of patients with psoriasis lag behind the data available on use of the agent in individuals with RA. This is the longest study conducted to date on the safety and efficacy of high-dose etanercept therapy for the treatment of psoriasis.

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1. Tying S, Gottlieb A, Papp K, et al. [Etanercept and clinical outcomes, fatigue, and depression in psoriasis: a double-blind placebo-controlled randomised phase III trial.](#) *Lancet.* 2006;367(9504):29-35.
2. Leonardi CL, Powers JL, Matheson RT, et al; Etanercept Psoriasis Study Group. [Etanercept as monotherapy in patients with psoriasis.](#) *N Engl J Med.* 2003;349(21):2014-2022.

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PSORIASIS TREATMENTS AND THE RISK FOR MALIGNANCY

Patel RV, Clark LN, Lebwohl M, Weinberg JM. **Treatments for psoriasis and the risk of malignancy.** *J Am Acad Dermatol.* 2009;60(6):1001-1017.

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Patel and associates reported on the risk for malignancy associated with the most common systemic psoriasis therapies based on a review of the available data. A diagnosis of psoriasis in the absence of systemic therapy appears to be associated with an increased risk for certain malignancies, such as nonmelanoma skin cancer (NMSC) and lymphoproliferative disorders, although the true risk is not easy to determine because

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of the difficulty involved in finding patients with moderate to severe psoriasis who have not received treatment with systemic therapy.

- **Psoralen and ultraviolet A (PUVA):** Patients treated with ≥ 337 PUVA treatments exhibit a 100-fold increased risk for squamous cell carcinoma (SCC) compared with expected population incidence rates. PUVA is also associated with an increased risk for melanoma, especially in persons with skin types I and II. The risk for basal cell carcinoma, however, is not dramatically increased.
- **Ultraviolet B (UVB) therapy:** Most of the available data suggest that neither the newer narrowband nor the traditional broadband UVB therapies are associated with an increased skin cancer risk.
- **Methotrexate:** Studies in patients with RA treated with methotrexate have demonstrated a well-documented increased carcinogenic risk, specifically for melanoma, non-Hodgkin's lymphoma, and lung cancer. Less data are available in patients with psoriasis, but there have been multiple reports of Epstein-Barr virus-associated lymphomas among these individuals.
- **Cyclosporine:** The incidence ratio for malignancies in patients taking cyclosporine is 2.1 compared with the general population. A 6-fold increased risk for skin malignancy, mostly SCC, is the most common form of malignancy reported with the use of cyclosporine.
- **Mycophenolate mofetil:** The evidence for increased malignancy risk associated with mycophenolate mofetil use has been established in transplant patients, but data are lacking in individuals with psoriasis.

Biologic Agents and Malignancy Risk

- **T-cell modulators (alefacept and efalizumab):** A long-term safety study of alefacept use found no increase in the carcinogenic risk compared with the general psoriasis population. A large study of efalizumab-pooled data from phase 3 studies also demonstrated no increased risk, although several case reports have suggested the association of this agent with lymphoproliferative disease.
- **TNF- α antagonists (etanercept, adalimumab, and infliximab):** Although some safety data are available on these agents in the psoriasis population, the largest long-term studies have been in patients with Crohn's disease or RA. One large study of patients with RA treated with either adalimumab or infliximab showed an odds ratio for malignancy of 3.3. Evidence is available that suggests a link between TNF- α inhibitors and lymphoma, NMSC, reactivation of various latent malignancies, and hematologic malignancies. The increase in risk appears to be slight, however.
- **Ustekinumab:** Ustekinumab is an interleukin (IL)-12 and IL-23 inhibitor proposed for the treatment of adult plaque psoriasis; use of the agent has not yet been approved by the FDA. Although there is a well-established carcinogenic effect of this drug in the mouse model, studies in humans and primates thus far have demonstrated no increased risk for cancer.

Overall, a thorough assessment of the malignancy risk associated with the newer biologic therapies will require more long-term follow-up in dermatologic populations. The results of clinical trials thus far, however, seem to indicate that the risk is not significantly higher than that of older therapies such as PUVA, methotrexate and cyclosporine. Among all therapies reviewed in this article, UVB appears to be the safest therapy in terms of carcinogenic risk.

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SCREENING AND MONITORING OF PATIENTS TAKING BIOLOGIC AGENTS FOR THE TREATMENT OF PSORIASIS

Huang W, Cordoro KM, Taylor SL, Feldman SR. **To test or not to test? An evidence-based assessment of the value of screening and monitoring tests when using systemic biologic agents to treat psoriasis.** *J Am Acad Dermatol.* 2008;58(6):970-977.

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Huang and coworkers examined the available literature on screening and monitoring of patients with psoriasis taking biologic therapies (ie, alefacept, efalizumab, etanercept, infliximab, and adalimumab). The value of screening tests was assigned A,B, C, and D evidence grades, similar to those given by the US Preventive Services Task Force. Overall, the authors reported that the evidence is inadequate to strongly recommend for or against any screening practices. No screening test received greater than a B rating, indicating moderate net benefit and a fair quality of evidence.

The authors found evidence to recommend against the purified protein derivative skin test for latent or active TB in patients beginning etanercept therapy. They did, however, conclude that this testing continue to be performed in any patient starting anti-TNF therapy, in light of the current recommendations by the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society, and the mechanism of action of these agents.

Evidence from clinical trials and postmarketing surveillance does not support routine pretreatment screening with urinalysis, chest radiography, and metabolic panels prior to initiation of therapy with any of the biologic agents. The authors recommend that clinicians assess the utility of the testing based on the individual patient. They also point out that it can be difficult to assess changes in a patient's laboratory results later on, while he or she is receiving therapy, if no baseline values have been obtained.

Although biweekly screening of CD4+ T lymphocytes is recommended by the FDA for patients being treated with alefacept, according to the authors, the risk for infection does not appear to be related to CD4+ counts and no cases of opportunistic infections have been reported. The potential benefits and harm are difficult to assess because of the lack of data; the authors suggest monthly, rather than twice-monthly, monitoring of such patients. In addition, the authors found evidence supporting routine platelet monitoring in patients taking efalizumab. The FDA recommends monthly monitoring initially, and then every 3 months thereafter for the duration of therapy.

In conclusion, overall data on the utility of screening tests in patients undergoing biologic therapy are lacking. Most of the authors' findings are based on efficacy and safety studies. The negative impact of screening tests, including false-negatives and false-positives; the resultant psychological stress; and the associated medical and financial damage are all significant. The authors advise caution and consideration of a patient's underlying risk factors when deciding on appropriate screening tests.

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TUBERCULOSIS SCREENING AND BIOLOGIC AGENTS

Doherty SD, Van Voorhees A, Lebwohl MG, Korman NJ, Young MS, Hsu S; **National Psoriasis Foundation consensus statement on screening for latent tuberculosis infection in patients with psoriasis treated with systemic and biologic agents.** *J Am Acad Dermatol.* 2008;5(2):209-217.

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Doherty and colleagues reviewed the literature on specific immunosuppressive therapies and their associated risk for TB, in order to evaluate the evidence supporting TB screening in patients receiving these treatments. Articles for review were retrieved via a MEDLINE search using the MeSH terms tuberculosis (TB) and infliximab, etanercept, efalizumab, adalimumab, methotrexate, cyclosporine, steroid, calcipotriene, tazarotene, anthralin, tar, salicylic acid, phototherapy, PUVA, and Bacillus Calmette-Guérin (BCG) vaccination. Evidence was graded on a scale established by Shekelle and associates,¹ with IA being the highest and representing evidence from a meta-analysis of randomized, controlled trials, and IV being the lowest and representing evidence from expert committee reports or opinions, or clinical experience from respected authorities.

The authors found grade IV evidence for the following regarding the screening of patients for TB prior to the initiation of immunologic therapy:

- TB screening before initiating immunologic therapy
- Induration of >5 mm as a positive finding on the TST
- Whole-blood interferon- γ release assays if there is a history of BCG vaccination
- Initiation of immunologic therapy after 1 to 2 months of prophylaxis for latent TB infection
- Ensuring that patients strictly follow latent TB prophylaxis and maintaining vigilance for active TB infection
- Treatment of active TB infection completed prior to initiation of immunologic therapy
- Latent TB screening prior to initiation of TNF- α therapy
- Latent TB screening prior to initiation of cyclosporine therapy
- Latent TB screening prior to initiation of alefacept/efalizumab therapy
- The use of topical therapies and phototherapy for the treatment of psoriasis is not associated with reactivation of TB

The authors also found level III evidence (ie, evidence from nonexperimental descriptive studies) for the association of methotrexate with reactivation of latent TB infection. In conclusion, screening for latent TB infection is recommended prior to the initiation of any immunologic therapy. Screening consists of a careful history for risk factors, a tuberculin skin test, and a chest radiograph in cases of a positive skin test. For the treatment of latent TB infection, isoniazid should be prescribed for 9 months. Immunologic therapy should be delayed for as long as possible during prophylactic therapy but can be initiated after 1 to 2 months if necessitated by the patient's clinical condition.

Additional research on the utility of whole-blood interferon- γ release assays, on the appropriate interval between initiation of latent TB prophylaxis and immunologic therapy, and on the variation in risks associated with the available TNF- α inhibitors for the treatment of latent TB reactivation was recommended by the panel.

References

1. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. [Clinical guidelines: developing guidelines](#). *BMJ*. 1999;318(7183):593-596.

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PRESENTATION AND MANAGEMENT OF TUBERCULOSIS IN PATIENTS UNDERGOING BIOLOGIC THERAPY

Hernandez C, Cetner AS, Jordan E, Puangsuwan SN, Robinson JK. **Tuberculosis in the age of biologic therapy**. *J Am Acad Dermatol*. 2008;59(3):363-380.

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The focus of this review by Hernandez and associates was to update dermatologists on the diagnosis and treatment of latent and active TB infection in the setting of TNF- α inhibitor therapy.

An elevation in the rates of TB infection has been observed in patients being treated with infliximab, and vigilance for the signs of active TB infection is recommended for up to 6 months following the discontinuation of therapy because of the long half-life of the agent. Etanercept appears to be associated with a lower risk for TB reactivation than infliximab. However, the more aggressive, disseminated form of TB infection has been observed in patients taking both medications. Although less data are available, adalimumab also appears to increase an individual's risk for latent TB reactivation. Use of anti-T-cell therapy with alefacept or efalizumab, on the other hand, has not been associated with an increased risk for TB infection.

Latent TB infection is usually asymptomatic and radiographically silent. Symptoms of active infection include chronic nonproductive cough, fever, malaise, weight loss, and night sweats. Although pulmonary disease is most common, extrapulmonary disease occurs more often among immunocompromised patients. A detailed history for TB risk factors should include questions about the following: potential exposures; travel to areas where TB is endemic (ie, Central Asia, Sub-Saharan Africa, Eastern Europe, Central America); previous TST results, BCG vaccination; prior history of active TB infection, and type and duration of therapy; history of HIV infection or organ transplantation; and any exposure to the homeless, prisoners, or immigrants.

TB screening with either the TST or the whole-blood interferon- γ assay is recommended for all patients prior to initiation of anti-TNF therapy. The QuantiFERON[®]-TB Gold (QFT-G; Cellestis Inc, Valencia, CA) is a newer, more specific TB screening test than the TST. The QFT-G exhibits less cross-reactivity with the BCG vaccine and with other mycobacterium infections, and provides both added patient convenience and less intraobserver variance in interpretation. Its sensitivity is less clear, however, and additional data are still needed on the utility of the QFT-G in certain patient populations. The CDC has approved use of the QFT-G in place of or in the same circumstances as the TST. Chest radiography alone is not a sufficient screening test for TB, and should be used only to evaluate patients with a high clinical suspicion for active TB or after a positive TST.

Although no guidelines have been published regarding the need for TB rescreening in patients receiving anti-TNF therapies, the authors do recommend annual rescreening.

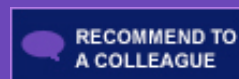
Diagnosis of active TB relies on examination of sputum samples for acid-fast bacilli, mycobacterial cultures, or nucleic acid amplification tests. The TST and QFT-G are insufficient for ruling out active TB if clinical suspicion is high.

The standard treatment for latent TB infection is 9 months of isoniazid. Whereas no research is available to confirm the practice, it is standard to allow at least 30 days of isoniazid therapy prior to initiating anti-TNF therapy, although a full 9 months would be preferable. In patients with active TB infection, at least 2 months of compliant TB treatment is advised prior to initiation of anti-TNF therapy.

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