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The Treatment of Moderate-to-Severe Psoriasis: Prescreening and Monitoring Psoriatic Patients on Biologics

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The development of biologics has dramatically altered the treatment of moderate-to-severe psoriasis while also introducing new standards of care for therapeutic monitoring. Currently, the biologics approved by the US Food and Drug Administration are divided into 3 classes: T-cell modulators, tumor necrosis factor-α inhibitors, and interleukin-12/23 inhibitors. Although the US Food and Drug Administration has established recommendations for pre- and peri-treatment screening evaluations, much of the evidence comes from clinical trials evaluating the short-term safety and efficacy of each medication, rather than long-term data, or studies that summarize either the appropriateness or feasibility of screening. Instead of following a blanket algorithm, providers must understand the evidence as it relates to each medication to determine which tests are appropriate for any specific patient. This chapter summarizes the current body of evidence and recommends a practical approach for monitoring psoriasis patients who are receiving biologic therapies.
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The development of biologics has revolutionized the treatment of psoriasis while introducing new standards of care for therapeutic monitoring. Currently, the biologics approved by the US Food and Drug Administration (FDA) are divided into 3 classes: T-cell modulators, tumor necrosis factor (TNF)-α inhibitors, and interleukin (IL)-12/23 inhibitors. Although the FDA has established recommendations for pre- and peri-treatment screening evaluations, much of the evidence comes from clinical trials looking at the overall safety and efficacy of the medication, rather than data summarizing either the appropriateness or feasibility of screening. Instead of following a blanket algorithm, providers must understand the evidence as it relates to each medication to determine which tests are appropriate for any specific patient. This chapter summarizes the current body of evidence and recommends a practical approach for monitoring psoriasis patients who are receiving biologic therapies.

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Specifically, we will review the literature for adverse effects of systemic biologic agents (alefacept, etanercept, adalimumab, infliximab, golimumab, and ustekinumab) for moderate-to-severe psoriasis and psoriatic arthritis, and suggest which screening tests and other monitoring should be offered to patients using each systemic biologic treatment (Table 1).

Alefacept

Alefacept was the first biologic agent to be approved for the treatment of moderate-to-severe plaque psoriasis.[1] A human dimeric fusion protein, alefacept prevents T-cell activation and promotes the reduction of proinflammatory CD45RO$^-$+ cells in the circulation via a natural killer cell–mediated apoptosis.

Alefacept has been found to induce or exacerbate bacterial infection, lymphoma, human immunodeficiency virus (HIV), and hepatitis B and C.[2-5] Circulating CD4 T-lymphocytes in the blood are potentially immunoprotective and decrease in a dose-dependent manner in response to alefacept therapy.[6-7] But reduced CD4 T-lymphocyte counts have not been shown to correlate with the incidence of infection.[2-5] In fact, there are no published reports to date of patients taking alefacept who have developed opportunistic infections. Because the clinical trials for alefacept substituted placebo for active drug in any patient demonstrating very low CD4$^+$ T-lymphocyte levels (<250 cells/mL), the risk of continuing alefacept treatment in this setting is not known.

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Table 1 Recommendations for Prescreening and Monitoring Your Patients on Biologics

Biologic	Pretreatment Screening	Subsequent Visits
T-Cell modulators		
Alefacept		Every 6 weeks
History	X (Including past medical and surgical histories)	X
Review of systems (side effects/adverse events after treatment initiation)	X	X (Weekly at visit for injection)
Focused physical examination	X	X
List of medications	X	X
PGA and BSA	X	X
Complete blood count	X	
Liver function tests	X	X
Hepatitis B and C serology	X	
CD4 T lymphocytes	X	X (Every other week during therapy)
TNF-α inhibitors		
		Every 3 months unless otherwise indicated
History	X (Including past medical and surgical histories)	
Review of systems (side effects/adverse events after treatment initiation)	X	X
Focused physical examination	X	X (Skin exam bi-annually in first year, annually thereafter)
List of medications	X	
PGA and BSA	X	X
Body weight and height	X	
Complete blood count	X	X
Liver function tests	X	X
PPD test	X	X (Yearly)
IL 12/IL 23 Inhibitor		
Ustekinumab		Every 3 months
History	X (Including medical and surgical histories)	
Review of systems (side effects/adverse events after treatment initiation)	X	X
Focused physical examination	X	X
List of medications	X	
PGA and BSA	X	X
Complete blood count	X	X
Liver function tests	X	X
Hepatitis B and C serology	X	
PPD test	X	X (Yearly)

Developing a new malignancy while receiving alefacept is rare, and does not mandate additional laboratory monitoring (such as a complete cell count or a lactate dehydrogenase level).[8] In fact, malignancy rates have been studied by the Assessment and Tracking of Long-Term Alefacept Safety trial, which followed approximately 1200 patients taking alefacept for moderate-to-severe psoriasis compared with the general psoriatic population and found that the rates of malignancy and lymphoma were similar in the 2 groups.[9]

Additionally, rare cases of hepatotoxicity, including reactivation of hepatitis B or C, nonspecific coagulopathy associated with transaminitis, and worsening cirrhosis have been reported in the postmarketing experience of alefacept. Infrequent (every 6-12 weeks during therapy) monitoring of the liver function tests might be justified.

Based on the available evidence, a thorough pretreatment history should survey a patient's history of infection, malignancy, lymphoma, hepatitis, and HIV status. Pretreatment testing should include baseline CD4 T-lymphocyte counts, comprehensive metabolic evaluation and a complete blood count. Screening for pre-existing hepatitis B and C infection would be prudent. HIV testing should occur when the clinical history suggests its possibility. During appointments, which occur weekly for alefacept administration, a brief review of systems should evaluate for symptoms and signs of infection or malignancy (ie, fever, unexplained weight loss, night sweats). CD4 T-lymphocyte counts should be conducted every other week. The liver function tests should be evaluated every 6-12 weeks during therapy, and every 3-4 months during intervals between alefacept courses. Persis-

tently (4 weeks or longer) reduced CD4 lymphocyte counts (<250 cells/mL) mandates discontinuation of the drug.

TNF-α Inhibitors

There are 4 TNF-α inhibitors that are FDA-approved for the treatment of psoriatic disease: etanercept, infliximab, adalimumab, and golimumab (approved only for psoriatic arthritis). As a class, these drugs have been associated with the reactivation of latent tuberculosis (TB), development of opportunistic infections, malignancies such as lymphoma and non-melanoma skin cancer (NMSC), hepatitis-B activation, lupus-like syndromes, worsening of congestive heart failure, and the development or worsening of demyelinating disease such as multiple sclerosis.

Reactivation of Latent Tuberculosis

The link between anti-TNF-α therapy and TB reactivation is well-established. Therefore, although the history and physical is the mainstay of screening before commencing anti-TNF-α therapy, both pretreatment and yearly purified protein derivative (PPD) placement are recommended for patients on these medications.[10] In most cases, the PPD is considered positive if greater or equal to 5 mm; the patient must then have a chest x-ray and sputum culture. If determined to have latent TB and treatment is deemed necessary, the patient should receive isoniazid or another acceptable antituberculous therapy for at least 1 month before starting the anti-TNF-α agent.[11] The antituberculous therapy then should be continued as per established recommendations.

In addition to the PPD test, there is recent evidence highlighting the efficacy of the QuantiFERON-TB Gold (QFT-G) test as a pretreatment measure for the presence of latent TB. In fact, the QFT-G blood test detects both latent and active *Mycobacterium tuberculosis* infection based on interferon-γ concentrations in test samples. The PPD test has a documented specificity of 49% and sensitivity of 33%, while the Centers for Disease Control and Prevention describes the specificity of the QFT-G test to be between 67% in an immunocompromised population to 98.1% in a healthy population and sensitivity ranging from 81% to 98% in these same populations.[12] Each QFT-G result and its interpretation should be considered in conjunction with other epidemiologic, historical, physical, and diagnostic findings. This test's advantages over the PPD include a single patient visit to draw a blood sample, results within 24 hours, lack of boost responses measured by subsequent tests, an objective result that does not depend on provider interpretation, and lack of cross-reactivity with previous Bacille–Calmette–Guérin vaccination.[12]

Infliximab, a chimeric monoclonal antibody targeting soluble and membrane-bound TNF-α,[13] has the highest association with TB reactivation of the TNF-α inhibitors. More than 300 cases of reactivated TB associated with infliximab therapy have been reported between 1998 and 2002,[13] with an incidence of 54:100,000.[11] Postmarketing surveillance reports in 2001 identified 70 cases of reactivated TB, most thought to be reactivation of latent TB, among 147,000 patients who were treated with infliximab for Crohn's disease, rheumatoid arthritis (RA), and other forms of inflammatory arthritis. Of these 70 cases, 48 occurred within the first 3 infusions. Of the 70 patients, 55 were also on one or more additional immunosuppressive agents (methotrexate, cyclosporine, azathioprine, or corticosteroids).[14,15] Based on these studies the risk of TB with infliximab is estimated to be 6 times the risk related to patients not receiving treatment.

Etanercept, a dimeric, fully human TNF-α-receptor fusion protein that binds to and inhibits the effects of TNF-α,[16] also has been linked with TB reactivation, although to a lesser degree than infliximab. There have been 38 reports of disseminated TB infection worldwide from 1998 to 2002 in patients with a history of TB taking etanercept, estimating the incidence to be 28:100,000.[11]

The association between TB reactivation and drug therapy is less well established for adalimumab and golimumab.[17] This may be because these drugs were developed and approved for use after etanercept and infliximab; thus, less adverse event data of this nature exist as clinical practice standards evolved. Regardless, until more data are available, the pharmacologic similarities between adalimumab, golimumab, infliximab, and etanercept mandate the identical pre- and during-treatment evaluation for the presence of latent and newly acquired TB for all of the TNF-α inhibitors.

Hepatitis

The TNF-α inhibitors have also been implicated in the development of liver function test (LFT) abnormalities and, rarely, clinically significant hepatic injury. Clinical trials have demonstrated that patients with RA, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriatic arthritis, and psoriasis who were treated with infliximab experienced elevated aspartate transaminase and alanine transaminase tests at a greater frequency than those treated with placebo.[18] Generally, these abnormalities are transient and asymptomatic. However, rare cases of severe liver injury, including acute liver failure and autoimmune hepatitis, have been reported in patients receiving infliximab.[19] The net benefit of screening is unclear, as most patients who experience elevated LFTs are asymptomatic and have a return to normal levels, and it is not possible to predict those most prone to developing hepatic injury.

Despite the uncertain benefit of LFT screening, both baseline LFTs and hepatitis B and C serologies should be measured before starting anti-TNF-α treatment. If the hepatitis serologies are positive, the patient should be referred to an internist or gastroenterologist to assess the appropriateness of the anti-TNF-α therapy, keeping in mind that hepatitis C positivity does not necessarily preclude the use of this class of drugs.[20-22] If the LFTs are normal and the patient does not have a baseline risk of developing liver injury, then the LFTs do not need to be monitored for the duration of therapy in the absence of symptoms or signs of new hepatotoxicity. If the baseline LFTs are normal but the patient is at risk for liver injury (eg, history of alcohol abuse, fatty liver, or nonalco-

holic fatty liver disease), the clinician should consider LFT monitoring at regular intervals, such as every 12 weeks. Persistently elevated LFTs (>1.5 times the upper limit of normal) necessitate discontinuation of therapy until further evaluation via appropriate referral to determine the nature of the problem.[18]

Malignancies

Initiating therapy with any of the anti-TNF-α biologics in a patient who has a history or risk of developing certain malignancies necessitates close follow-up.[23] Postmarketing reports have recorded cases of NMSC and lymphoma appearing in patients undergoing therapy with each of the TNF-α inhibitors. It still is unclear if malignancies that occur in the context of TNF-α inhibitor therapy are drug-related or instead are inherently more likely to occur in patients with psoriasis, with or without therapy.

New-onset squamous cell carcinoma of the skin has been observed in patients immediately after initiation of etanercept.[24,25] Interestingly, after approximately 8-10 weeks no new squamous cell carcinomas were reported with more than 1 year of follow-up in patients who remained on the medication. Similarly, in a review of patients taking adalimumab, 17 of the pooled 1469 patients developed a malignancy (3 melanoma, 10 NMSC, 2 breast, 1 gastric adenocarcinoma, 1 non-Hodgkin lymphoma).[17] In a pooled analysis of golimumab-treated patients some patients developed malignancies, mostly NMSC and lymphoma.[26,27] Again, it is unclear whether these malignancies represent an inherent background rate specific to the treated population, and therefore are unrelated to drug exposure. In fact, the incidence of lymphoma is increased in people suffering from chronic diseases, including RA and psoriasis, independent of medical therapy. For example, in a Swedish Cancer Registry, patients with RA on TNF-α blockers compared with age- and sex-matched patients with RA on conventional therapies display no increased risk of developing lymphoma.[28]

While it is unknown whether the increased incidence of lymphoma is secondary to the disease state or anti-TNF-α therapy, physicians prescribing anti-TNF-α therapy for their psoriatic patients should monitor for new onset lymphoma and NMSC during routine follow-up. The practitioner should screen for systemic symptoms (such as weight loss, fatigue, or anorexia) and conduct lymph node and skin examinations at baseline, every 6 months for the first year, and then yearly to monitor for newly arisen malignancies. Patients with a history of lymphoma should not be prescribed TNF-α inhibitors without a careful consideration of the potential risks.

Opportunistic Infections

TNF-α–inhibitor therapy is associated with the development of opportunistic infections. Of the 3 TNF-α–inhibitor therapies currently available, infliximab may be the most likely drug to induce these infections, especially in patients with HIV.[29] Examples of such infections include listeria,[30] histoplasmosis, and sepsis.[31-33] Patients taking any of the TNF-α inhibitors should be instructed to be sensitive to skin changes suggestive of cutaneous infection or respiratory infections that persist longer than usual and to seek medical care promptly. Febrile illness always warrants evaluation of the patient before continuing therapy with the TNF-α inhibitor.

Autoimmunity

In a recent report from the Biomediques Group on Autoimmune Diseases project, a multicenter study devoted to collecting data on the use of biologic agents in adult patients with systemic autoimmune diseases, 105 patients were identified who developed systemic lupus erythematosus or lupus-like disease after starting anti-TNF-α therapy with infliximab, etanercept, or adalimumab. Infliximab was more commonly associated with lupus-like features than etanercept or adalimumab.[34]

The lupus-like syndrome that tends to develop in patients taking anti-TNF-α therapy presents with malar butterfly rash, discoid lupus, serositis, arthritis, or general malaise.[34] In these instances, the patient may develop antinuclear antibodies and antibodies against double-stranded (ds) DNA, all of which resolve with drug cessation. In other situations, laboratory testing may reveal positive antinuclear antibody and anti-ds DNA in the absence of lupus-like symptoms or signs.[35] Based on these reports, routine checking of antibody titers on patients being treated with anti-TNF-α therapy is not necessary unless the patient presents with signs or symptoms suggestive of a lupus-like illness. If a patient develops a lupus-like syndrome and is found to have both positive antinuclear antibody and anti-ds DNA titers, the medication should be discontinued and the patient should be referred for evaluation. Importantly, in most documented cases cessation of drug therapy led to resolution of symptoms, and initiation of another anti-TNF-α inhibitor did not trigger a recurrent lupus-like syndrome.[36]

Other Adverse Events

The TNF-α inhibitors as a class have also been associated with common adverse events, including pharyngitis, chills, and headache.[37] Infusion reactions are most common with infliximab therapy and typically affect 20% of all patients treated within the first 1-2 hours of the infusion. Rarely does the reaction cause anaphylaxis. Management includes decelerating the infusion rate and occasionally administering antihistamines and corticosteroids. Pretreatment with antihistamines and acetaminophen is commonly used. Other less common adverse events associated with TNF-α inhibitors include congestive heart failure exacerbations and demyelinating syndromes.[38]

Despite the relatively frequent incidence of common adverse events, there is currently no evidence to suggest that patients with multiple drug allergies require additional screening or monitoring when commencing anti-TNF-α therapy. Furthermore, evidence from clinical trials, postmarketing surveillance, and case reports does not support routine pretreatment screening with urinalysis, chest radiograph, or metabolic panels before initiation of any of the anti-TNF-α agents. Regardless, pretreatment blood tests could include a

comprehensive metabolic panel with a complete blood count. The rationale for this would be to establish the full baseline health status of the patient and assess any future laboratory abnormalities in relation to the baseline results.

Ustekinumab

An IL-12/IL-23 inhibitor, ustekinumab is the first approved drug of a new class of biologics. After 12 weeks of therapy with ustekinumab mild adverse events were noted in 62% of patients. These included events similar to those seen in patients taking the TNF-α blockers, including infection, gastrointestinal symptoms, and headache. Noteworthy were a 35-year-old woman who developed a myocardial infarction, a 63-year-old woman who had recurrent noncardiac chest pain, and a 55-year-old man who developed hemorrhagic gastric ulcers.[39] To date, there have been no cases of lymphoma or demyelinating disease in patients taking ustekinumab during a clinical trial.[40-42] Ustekinumab therapy has been linked with a solitary case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS), which resolved once the drug was metabolized and discontinued.[43] The etiology of RPLS is unclear, and is not believed to be related to an infectious etiology. Until further data become available, it is advisable to monitor patients taking ustekinumab every 3 months for signs and symptoms of infection, cardiovascular disease, bleeding, and symptoms of RPLS, such as headache, encephalopathy, seizures, and visual changes. No specific blood abnormalities were noted in the clinical trials for ustekinumab, but regular (every 3-6 months) monitoring of the comprehensive metabolic tests and a complete blood count is advisable.

Discussion

Any hospitalization for serious infections such as pneumonia, TB, or sepsis is generally an indication to discontinue biologic therapy. But before permanent discontinuation of the therapy there should be strong evidence that the adverse event is drug-related. Additionally, if a patient suffers either new-onset or worsening congestive heart failure or demyelinating neurologic illness the biologic should be discontinued until a full assessment of causality is completed. A patient may continue taking the biologic even with the development of NMSC or a melanoma in situ, both of which subsequently are fully treated, although if invasive malignant melanoma or any other type of malignancy arises during therapy then the biologic should be discontinued indefinitely.[44]

A possible complication of an abruptly discontinued therapy is a flare of psoriasis.[45-48] In this scenario, cyclosporine or methotrexate may be used for a few months to suppress disease[49] and a biologic may be used subsequently in combination with the "rescuing" systemic agent to gain better control of the psoriatic flare.

Discontinuing a specific biologic therapy for an extended amount of time and reinitiating the same drug when the adverse event resolves increases the likelihood of antibody formation against the drug, rendering it either less effective or ineffective after its reintroduction. In most patients, using another drug of the same class may re-establish disease control.[50] Importantly, a recurrent adverse event during treatment with any specific TNF-α inhibitor may occur with all other drugs within that class.[51]

Pregnancy should be queried in all appropriate patients. But all the approved biologic therapeutics for psoriasis are of pregnancy category B. The molecular structures of the approved biologics inhibit placental transfer during the first trimester. Although placental transfer cannot be excluded during the second and third trimesters of pregnancy, no evidence of teratogenicity has been observed in animal studies.[52] The option to continue the therapy through pregnancy is controversial, but the current registry data are comforting in that there is little to no evidence of teratogenicity or increase in spontaneous abortion. The data are strongest for the TNF-α inhibitors. The Organization of Teratology Information Specialists compiles evidence from women exposed to various medications during pregnancy and has demonstrated that exposure to TNF-α inhibitors during early pregnancy results in a comparable proportion of stillbirths and congenital anomalies as expected within the general population. However, a larger sample size and longer-term data are needed, and the decision to treat during pregnancy should be made on an individual basis and when the therapeutic need is great. Succinctly, the use of these drugs during pregnancy should be done with caution and a strong consideration of the specific clinical scenario.[53,54]

Conclusions

The monitoring recommendations presented in this chapter are sensible and, as much as possible, based on the available published data. For all the biologic therapies it is imperative that the patient undergoes regular surveillance for a range of possible adverse events. Most patients should be seen in follow-up every 3-4 months, and the emphasis should be on the detection of infection involving either common or rare, opportunistic pathogens. Of course, taking inventory for the presence of the rarer negative sequelae also is critical. Undoubtedly, appropriate screening and monitoring greatly augments the possibility of a positive therapeutic experience for the patient with psoriasis.

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