A Practical Approach to Monitoring Patients on Biological Agents for the Treatment of Psoriasis

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ABSTRACT

Psoriasis is a chronic, systemic, inflammatory skin condition that manifests predominantly as well-demarcated, erythematous, scaly plaques on the elbows, knees, and scalp. While mild cases (minimal body surface) often respond to various topical treatments and light therapy, patients with extensive disease (larger body surface and possibly joint involvement) may require systemic medications for remission. The development of biological agents provides dermatologists valuable ways to help treat psoriatic disease quite efficiently, but literature regarding the monitoring of patients on biological treatments is sparse. Clinical practice varies widely since there is modest strong evidence to recommend or refute most tests currently recommended by the United States Food and Drug Administration. The purpose of this article is to present a practical approach to monitoring patients on biological therapy based on the most up-to-date literature. (*J Clin Aesthetic Dermatol.* 2010;3(8):20–26.)

The use of biological treatments has grown significantly since their introduction and now account for a significant proportion of the systemic therapies used for the treatment of psoriasis. Biological therapies target precise segments of the immune system, offering the advantage of being less immunosuppressive compared to the traditional systemic therapies that broadly cause immunosuppression. Currently, five biological agents (e.g., alefacept, etanercept, infliximab, adalimumab, and ustekinumab) are approved by the United States Food and Drug Administration (FDA) for the treatment of psoriasis, and other newer agents (e.g., ABT-874) are in various stages of development and clinical trials (Table 1).[1–6] The biologicals at present are divided into either tumor necrosis factor alpha (TNF-α) or T-cell lymphocyte inhibitors. Recently, CD4+ T helper (Th) 17 cells and interleukins (IL)-12 and IL-23 have been important in the pathogenesis of T-cell mediated disorders, such as psoriasis, and have influenced the development of medications that specifically target these key immunological players. Both IL-12 and IL-23 stimulate differentiation of naive T-cells into Th1 and Th17 cells, key cells that regulate the production of other pro-inflammatory cytokines significant in the pathogenesis of psoriasis.[7,8] Understanding of these immune cascade complexities has divulged this new class of biological agents that target cytokines (e.g., ustekinumab) important in the pathogenesis of inflammatory skin disease. Each drug class that is used in the treatment of psoriasis works by blocking different steps along the same immune-dysregulation pathway leading to psoriatic disease.

Biological agents have changed the treatment of psoriasis by giving dermatologists additional therapeutic options that are potentially less toxic to the liver, kidneys, and bone marrow, and are not teratogenic compared to the traditional systemic therapies for psoriasis, such as acitretin, methotrexate, and cyclosporine. Concerns of increased cholesterol, hair loss, and mucous membrane dryness seen with acitretin; liver and bone marrow toxicity, risk of lymphoma or cancers, and risk of serious infections seen with methotrexate; and increased blood pressure and increased cholesterol, electrolyte disturbance, risk of lymphoma and cancers, and risk of serious infections seen

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TABLE 1. Currently approved biological medications for the treatment of psoriasis[1–4,6]

DRUG NAME	TRADE NAME	MECHANISM OF ACTION	DOSING	FDA-APPROVED INDICATIONS	FDA APPROVAL FOR PSORIASIS
Anti-TNF-α					
Adalimumab	Humira	Recombinant human IgG1 monoclonal antibody	80mg initial dose, followed by 40mg EOW starting one week after initial dose	RA, JIA, PsA, Ps, AS, CD	2008
Etanercept	Enbrel	Dimeric fusion protein linked to Fc portion of human IgG1	50mg SQ BIW for three months, followed by a reduction to a maintenance dose of 50mg per week	JIA, RA, PsA, AS, Ps	2004
Infliximab	Remicade	Chimeric IgG1 monoclonal antibody	5mg/kg IV infusion followed by additional doses at two and six weeks after the first infusion, then every eight weeks thereafter	RA, PsA, CD, Ps, UC, AS	2006
T-cell Inhibitor					
Alefacept	Amevive	Dimeric fusion protein of CD2/LFA-3 linked to Fc portion of human IgG1	15mg IM weekly for 12 weekly injections	Ps	2003
Anti-IL*					
Ustekinumab	Stelara	Human IgG1 monoclonal antibody specific to p40 protein subunit of interleukin-12 and -23 cytokines	45mg or 90mg initially and four weeks later, followed by 45mg or 90mg every 12 weeks	Ps	2009

TNF=tumor necrosis factor, mg=milligram, EOW=every other week, RA=rheumatoid arthritis, JIA=juvenile idiopathic arthritis, PsA=psoriatic arthritis, Ps=plaque psoriasis, AS=ankylosing spondylitis, CD=Crohn's disease, SQ=subcutaneous, BIW=twice weekly, kg=kilogram, IV=intravenous, UC=ulcerative colitis, IM=intramuscular, IL=interleukin. *The authors are categorizing ustekinumab and related medicines as a class called anti-IL for the purposes of this article.

with cyclosporine, have essentially been shattered with the introduction of biological drugs. Even so, traditional systemic therapies continue to play an important role in the treatment of psoriasis with their oral route of administration and low cost, making them an important treatment option in the appropriate patient. Phototherapy is very efficacious, but requires a heavy time commitment and a phototherapy unit, may increase the risk of skin cancer, and involves the diligence of a physician who has experience making frequent use of this therapy. Biological agents have grown increasingly popular for the treatment of moderate-to-severe disease, as clinical studies have shown these agents to be free of the major organ toxicities of methotrexate and cyclosporine and successful in treating those who may have been unresponsive or unable to tolerate traditional therapies. Although the majority of patients on biological agents have few complications, associated side effects are of real concern, and cautious monitoring with frequent laboratory testing, pristine patient education, and regular office visits, are necessary.

Several consensus statements and literature reviews have been published to reconcile differences among dermatologists and provide recommendations for the care of patients on biologicals.[9–13] Current agreement mandates a diligent screening process prior to initiating any biological agent including a thorough medical history and physical examination, with particular attention to the review of systems; specifically, the neurological, cardiovascular, gastrointestinal, and musculoskeletal systems. Important information from the past medical history includes history of previous or current serious or opportunistic infection,[1–6] malignancy including skin cancers and lymphomas,[14–23] demyelinating disorders such as multiple sclerosis,[24–31] heart disease such as congestive heart failure,[32,33] liver disease such as hepatitis B[13,34–37] and C,[38–40] immunosuppressive disorder such as HIV,[1–5,34,41,42] joint disease such as psoriatic arthritis, and vaccination status.[10,13] A detailed social history should also be emphasized, specifically a past or current history of illicit substance and tobacco abuse, as well as pregnancy status.

It has been established that psoriasis is associated with several comorbidities, including depression, psoriatic arthritis, and malignancy. Rapp et al[43] reported that the impact of psoriasis on patient quality of life was comparable to that of other chronic conditions, such as heart failure, diabetes, and arthritis. Therefore, physicians should consider screening for these associated comorbidities including a screening for depression, particularly in patients with severe psoriasis. More recently, many publications have highlighted the link between psoriasis and conditions

such as obesity, cardiovascular disease, diabetes, and metabolic syndrome. It is hypothesized that dysregulation of T-cells and over expression of pro-inflammatory cytokines such as TNF-α and IL-6, which leads to the hyperproliferation of keratinocytes and activation of neutrophils and endothelial cells within the skin, is also responsible for the increased prevalence of cardiovascular disease and metabolic syndrome in patients with psoriasis.[44,45] In some cases the dermatologist may be the "first responder" and have a unique opportunity to evaluate for these associated conditions and subsequently refer patients to a primary care physician who can follow up with the crucial concomitant treatment. Only by approaching psoriasis as a potentially multisystem disorder can dermatologists facilitate optimal medical wellbeing.[46,47]

Baseline laboratory studies should be performed and evaluated prior to initiating therapy with a biological agent, and these tests should include a comprehensive metabolic panel with liver function tests, a complete blood count, and a hepatitis panel. Baseline levels are important because hematological and metabolic disturbances have been reported (rarely) during biological therapy. Efalizumab, which was removed from the market in June of 2009 because of a potential risk to patients of developing progressive multifocal leukoencephalopathy (PML)—a rapidly progressing infection of the central nervous system that can lead to death or severe disability—has been shown to cause leukocytosis and possibly thrombocytopenia and hemolytic anemia[5,48–51]; infliximab can cause elevated liver function tests[3,52,53]; and alefacept can cause a specific CD4+ leucopenia.[4,54,55] Screening for antinuclear antibodies (ANA) prior to initiating a biological agent is controversial and should not preclude a patient from starting anti-TNF-α therapy.[12,56–62] The Centers for Disease Control and Prevention (CDC) recommends screening for tuberculosis (TB) prior to starting therapy with any TNF-α blocker and if positive, the patient is to begin prophylaxis TB therapy with isoniazid.[63–65]

APPROACH TO MONITORING PATIENTS ON BIOLOGICAL AGENTS

The purpose of this report is to provide suggested guidance concerning the monitoring of patients on biological medications. Despite various recommendations from the FDA and other consensus statements, few monitoring laboratory tests are strongly recommended. Since the completion of several randomized clinical trials, new long-term safety concerns have arisen, such as the development of opportunistic infections (i.e., tuberculosis [TB], cytopenias, lymphoma, skin cancer, demyelinating disease, drug-induced lupus, congestive heart failure, and hepatotoxicity). Efalizumab was removed from the market after isolated cases of PML were documented in patients who had received the drug. Thus, it is practical that meticulous monitoring be done in patients on continuous biological therapies. Although most of these complications are rare, prolonged follow up with post-marking analysis will further elucidate their prevalence and give future insight to more detailed recommendations.

Cytopenias, including anemia and thrombocytopenia, have been uncommonly associated with the TNF-α blockers[13] and mostly reported with the T-cell lymphocyte inhibitor efalizumab.[5,48–51] The onset of thrombocytopenia was found to occur within 2 to 3 months after the first dose of efalizumab, thus routine laboratory monitoring of platelets was standard for early detection of asymptomatic thrombocytopenia. The evidence illustrated that patients who developed efalizumab-related thrombocytopenia did not develop bleeding, returned to normal platelet counts after discontinuation of medication, and rarely needed any systemic treatment interventions (corticosteroids, immune globulin, and platelet transfusion). Consensus statements have concluded that routine baseline complete blood count be done prior to starting biological therapy and that repeat complete blood cell counts be considered every 3 to 6 months.

The evidence mandates that CD4+ T-cell count be checked every two weeks in patients taking alefacept, since alefacept can result in a dramatic reduction of CD4+ T-cells.[4,54,55] CD4+ T-cell count can be checked at the time of intramuscular injection and then the next dosage can be held if the CD4+ T-cell count is lower than 250cells/μL. If the CD4+ T-cell count remains below 250cells/μL for four consecutive weeks, therapy should be discontinued. Evidence is insufficient to determine the actual effect of keeping patients on alefacept with CD4+ T-cell counts lower than 250cells/μL, since clinical trials have substituted placebo or therapy discontinuation in this setting. Interestingly, it appears as if the incidence of infection is unrelated to CD4+ T-cell counts as there are very few reported cases of opportunistic infections in patients on alefacept.[66–68]

Most of the TNF-α inhibitors have not been shown to be hepatotoxic, although patients taking infliximab are at an increased risk for elevations in liver function tests.[3,52,53] Most cases are transient and asymptomatic, but rare cases have been reported of severe liver injury (acute liver failure with jaundice and autoimmune hepatitis with cholestasis) and reactivation of hepatitis B.[13,34–37] The benefit of screening and monitoring patients on TNF-α inhibitors is not clear, as those who experience an elevation in liver function tests are often asymptomatic. A practical approach is to do baseline chemistry with liver function tests at screening with interval monitoring (every 3–6 months) in patients without risk factors for liver injury and more frequent testing for those at high risk. Infliximab therapy must be discontinued and further evaluation performed for patients with chronically elevated liver function tests or those who become symptomatic. Consensus does not warrant hepatitis screening unless the patient undergoing treatment has risk factors or elevated liver function tests at baseline.

TB has been reported in patients treated with all the TNF-α inhibitors. Specifically, an increase of pulmonary TB in patients treated with infliximab and adalimumab and extrapulmonary TB in patients on etanercept has been noted.[1–3,69–71] As stated previously, the CDC recommends TB

TABLE 2. Key points in monitoring patients on biological therapies

LABORATORY TESTS
• Annual TB skin test; alternatives include the QuantiFERON®-TB gold blood test and chest x-ray if indicated
• CD4+ T-lymphocyte count every two weeks for alefacept
• Complete metabolic panel with liver function tests for each infliximab infusion and with any sign of hepatic injury
• +/- Complete metabolic panel every 3 to 6 months on all biological therapies
• +/- Complete blood count every 3 to 6 months on all biological therapies
• +/- Hepatitis screen and HIV testing when risk factors present on all biological therapies
VACCINATIONS
• +/- Influenza and pneumococcal vaccination (high-risk patients per CDC recommendations)
• +/- Standard vaccinations avoiding live and live-attenuated vaccines
• Vaccination may not be beneficial in patients taking efalizumab

testing before starting any treatment with a TNF-α blocker. Package inserts for the same medications mandate screening TB skin testing, but do not mandate any further TB testing.[1–3] Nonetheless, a majority of prescribing physicians perform annual TB skin testing, particularly in those patients at high risk for TB exposure, such as healthcare workers and those who travel to endemic areas. Efalizumab and alefacept have not been associated with the reactivation of latent TB; however, many physicians choose to perform TB skin tests while patients are on these therapies because of the inherent immunosuppression.[13,69,72–74]

It is logical to take any steps necessary to prevent infection in patients who are immunosuppressed by medications such as biological therapies.[75–77] It has been postulated that biological therapies may impair the immunological response to vaccinations, and studies have looked at the immunological responses to vaccinations in patients treated with TNF-α and T-lymphocyte inhibitors.[78–81] Currently, the package inserts for the biological medications caution against any vaccination during biological treatment and recommend it be done prior to or after therapy.[1–6] Little evidence shows harm in vaccination of patients on biological therapies, and the majority of recent clinical practice is based on the standard recommendations given for the treatment of transplant patients on immunosuppressive treatments. Recommendations include vaccination prior to trans-plantation and initiation of immunosuppressive therapy and the complete avoidance of live virus vaccines.[82] When the National Psoriasis Foundation surveyed physicians to elucidate current practice, it found that 50 percent of those surveyed advised their patients to have influenza vaccines annually. It was concluded that though it may be preferable to vaccinate patients prior to the initiation of biological therapy it is not always practical. Current consensus advocates withholding live and live-attenuated vaccinations (varicella, herpes zoster, measles-mumps-rubella, yellow fever, and inhaled influenza) during biological therapy and to consider routine influenza and pneumococcal vaccination in patients who are at high risk.[12,13] Table 2 shows the key tests and vaccinations to consider based on literature review and medication package inserts.

Ustekinumab, an anti-IL-12 and IL-23 inhibitor, is the newest biological agent approved for the treatment of psoriasis and is administered as a 45mg (≤100kg) or 90mg (>100kg) subcutaneous dosage initially and four weeks later, followed by 45mg or 90mg every 12 weeks thereafter. Ustekinumab has excellent documented safety and efficacy in three Phase 3 clinical trials (PHOENIX 1,[83] PHOENIX 2,[84] and ACCEPT[85]), although guidelines are not currently defined with regard to laboratory monitoring of patients on this medication. These studies all demonstrated ustekinumab was safe, well tolerated, and efficacious in treatment-naive patients, those who failed other immunosuppressive therapies, those who were unresponsive to phototherapy, or those who were unable to tolerate other therapies. In general, side effects from both PHOENIX 1 and 2 did not require treatment adjustment, did not appear to be dose related, and were considered mild. In PHOENIX 2, adverse-event reporting was not significantly different in patients taking drug versus placebo. The long-term side effects of ustekinumab are unknown, but the safety and tolerability over several years appears excellent,

and current clinical practice dictates following prescribing information and physician experience with routine blood work and TB testing prior to initiating therapy.

CONCLUSION

With improved understanding of the immunological basis of psoriasis, enhanced and targeted therapies have been developed for effective and safe long-term treatment. How patients on these medications should be screened and monitored is not fully characterized and clinical practices vary. Without proper clinical trials to help develop guidelines, practitioners must use evidence from the currently available, randomized, controlled, clinical trials and post-marketing surveillance that is documented in the literature. Since each biological medication has the potential for serious side effects, it is prudent that prescribers use caution when initiating and maintaining continuous therapy. A realistic approach includes a careful screening with history and physical exam, vaccination review, baseline laboratory tests, and TB skin testing. Interval monitoring with physical exam, laboratory tests, and annual TB skin test should be considered in all patients treated with biologicals; other specific tests should be determined on a case-by-case basis per the most current consensus recommendations.

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