

# A Review of Complications of Biologic Therapy for Psoriasis

Therapeutic success requires clinicians to understand emerging and established safety concerns.

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The development of biologic therapies in the treatment of psoriasis has dramatically advanced our management of psoriasis and psoriatic arthritis. Along with these significant advances have evolved concerns for potential side-effects from biologic therapies. The FDA has issued warnings related to biologic agents used in the management of psoriasis over the past two years. These warnings have focused on infectious,<sup>1</sup> neurologic,<sup>2</sup> and malignancy related concerns.<sup>3</sup> Evaluating the true risk of complications of biologic agents in the management of psoriasis is challenging because many reports of complications from use of these agents have occurred in the management of other diseases, such as rheumatoid arthritis and inflammatory bowel disease, rather than psoriasis. These diseases may have a greater inherent risk for developing infections or malignant complications compared to psoriasis. Many complications of these biologic agents have occurred in patients on concomitant immunosuppressive therapies.

The biologic agents in the treatment of psoriasis can be categorized into agents that inhibit T-cells, inhibit tumor necrosis factor alpha, and that target interleukin 12 and interleukin 23. Complications of biologic therapy may be directly related to some extent to the mechanism of action of the biologic agent.

Alefacept (Amevive, Astellas) and efalizumab (Raptiva, Genentech) are T-cell inhibiting agents. Efalizumab was recently withdrawn from the market voluntarily by the manufacturer Genentech.<sup>4</sup> Alefacept is a fully human LFA-3/IgG1 fusion protein that targets CD2. This results in inhibition of T-cell activation and induces selective apoptosis of memory T-cells (CD45RO+).<sup>5</sup> Efalizumab is a recombinant humanized monoclonal IgG1 antibody directed against the  $\alpha$  subunit (CD11a) of LFA-1 on the surface of T-cells. This blocks LFA-mediated T-cell adhesion.<sup>6</sup> Etanercept (Enbrel, Amgen Wyeth), infliximab (Remicade, Centocor), and adalimumab (Humira, Abbott) target tumor necrosis factor alpha. Etanercept is a receptor fusion protein antibody that binds to soluble TNF- $\alpha$ . Infliximab is a chimeric monoclonal antibody that binds soluble and membrane-bound TNF- $\alpha$ . Adalimumab is a recombinant, fully human monoclonal IgG1 that binds to TNF- $\alpha$ . Ustekinumab (Stelara, Centocor) is a fully human monoclonal antibody that targets interleukin 12 and interleukin 23. The drug binds with high affinity to their shared p40 subunit and targets the Th1 and Th17 arms of the immune system.<sup>7</sup>

## Malignant Complications

Determining the risk of developing malignancies with the use of biologic agents in the treatment of

psoriasis is difficult due to the nature of the disease and the concomitant use of immunosuppressive agents. Psoriasis is a chronic inflammatory disorder that may inherently place the patient at risk of developing certain cancers. In a British cohort study, patients with psoriasis who were over the age of 64 had a three-fold increased risk of developing lymphoma as compared to those without psoriasis.<sup>8</sup> A further investigation evaluated the cancer rates in those with severe psoriasis as defined by receiving systemic therapies versus those with mild psoriasis as defined as not taking systemic therapy.<sup>9</sup> Their analysis demonstrated that all patients with psoriasis faced an increased risk of lymphoma with higher relative risks for Hodgkin's lymphoma (HL) and cutaneous T-cell lymphoma (CTCL). Patients with mild psoriasis had a relative risk of 1.42 of developing Hodgkin's lymphoma and 3.18 of developing CTCL. In comparison, patients with severe psoriasis had a relative risk of 4.10 of developing Hodgkin's lymphoma and 10.75 of developing CTCL.

The medical literature evaluating the risk of cancer associated with the biologics in the treatment of psoriasis lacks the power of large clinical trials as well as long-term follow up.<sup>10</sup> In a study evaluating the adverse events in 1,200 patients treated with alefacept for severe psoriasis, the incidence of reported malignancies and lymphomas was within the expected rate for the psoriatic population.<sup>11</sup> A review of almost 3,000 patients with moderate to severe psoriasis treated with efalizumab showed an incidence of malignancy similar to placebo and consistent with rates in patients with moderate to severe psoriasis.<sup>12</sup> With all of the TNF- $\alpha$  inhibitors, drug inserts report more cases of lymphomas in clinical trials compared to control patient and the general population.<sup>13,14,15</sup> With the exception of non-melanoma skin cancer, the incidence of malignancies was similar to the general population. According to a recent review article, the current data is not sufficient to completely rule out or firmly establish a causal relationship between biologics and lymphoma. Short-to intermediate term treatment with biologics (up to four years) appears to be very safe with respect to lymphoma risk.<sup>16</sup>

The FDA issued an alert on August 4, 2009, warning healthcare professionals of the increased risk of lymphoma and other malignancies in children and adolescents treated with TNF blockers.<sup>17</sup> The FDA reviewed 48 cases of malignancy in children and adolescents. Approximately 50 percent of the malignancies were lymphoma (Hodgkin's, non-Hodgkin's); other malignancies included leukemia, melanoma, and solid organ cancers. Of concern were reports of malignancies typically rare in children, including leiomyosarcoma, hepatic malignancies, and renal cell cancer. The majority of patients (88 percent) were on other immunosuppressive medications, especially azathioprine and methotrexate. There were 11 deaths in the 48 reported malignancies. Nine deaths were due to hepatosplenic T-cell lymphoma. All of these patients were treated with infliximab, along with azathioprine or 6-mercaptopurine and had underlying inflammatory bowel disease. The FDA concluded that there was an increased risk of malignancy in children and adolescents with the use of TNF blockers but was unable to fully characterize the strength of the association. On August 4, 2009, the FDA also warned of the possible association of leukemia and TNF blockers.<sup>17</sup> The FDA reviewed 147 post-marketing reports of leukemia in patients using TNF blockers. These reports included 44 cases of acute myeloid leukemia, 31 cases of chronic lymphocytic leukemia, and 23 cases of chronic myeloid leukemia. There were 30 deaths out of 147 patients, and the average time to onset of leukemia was one to two years. Most patients who developed leukemia were also receiving other immunosuppressive therapies. The FDA concluded there was a possible association between treatment with TNF blockers and the development of leukemia.

The risk of malignancies with ustekinumab is difficult to ascertain, due to limited clinical trial data. In placebo controlled psoriasis studies and non-controlled studies, 0.4 percent of ustekinumab subjects reported malignancies, excluding non-melanoma skin cancers. Non-melanoma skin cancer was reported in 0.8 percent of patients treated with ustekinumab. Serious malignancies included breast, colon, head

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and neck, kidney, prostate, and thyroid cancers.<sup>18</sup>

### Neurologic Complications

Efalizumab was voluntarily withdrawn from the market by Genentech after three confirmed cases of progressive multifocal leukoencephalopathy (PML).<sup>4</sup> PML is a progressive neurologic disorder associated with the John Cunningham virus (JC virus). It is associated with scattered demyelination of the brain. The JC virus resides in the latent form in up to 80 percent of healthy adults and typically causes PML in HIV positive patients.<sup>19</sup> The first two cases of PML associated with efalizumab occurred in elderly patients (over age 70) who were treated with efalizumab for greater than three years.<sup>20</sup> In both cases, the patients died. A third case involved a 47-year-old male who received efalizumab for over three years.<sup>21</sup> In all cases, the diagnosis was confirmed by detection of JC viral DNA in the CSF, neurologic symptoms, and MRI studies. PML should be suspected in patients on biologic agents who demonstrate acute onset of visual deficits, mental impairment, dementia, personality changes, confusion, and motor weak-

ness. PML has been associated with 57 patients treated with rituximab.<sup>22</sup>

One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed during the clinical development of ustekinumab.<sup>18</sup> The subject received 12 doses of ustekinumab over approximately two years and presented with headaches, seizures, and confusion. After ustekinumab was withdrawn, the patient fully recovered. RPLS is not caused by demyelination or a known infectious agent, but fatal outcomes have been reported. RPLS may manifest with headaches, seizures, confusion, and visual disturbances.

All the TNF- $\alpha$  inhibitors and efalizumab have been associated with reports of new or exacerbated symptoms of demyelinating disorders.<sup>13-15</sup> The demyelinating conditions have included transverse myelitis, Guillian-Barre syndrome, multiple sclerosis (MS), optic neuritis, and seizures. All the TNF- $\alpha$  biologic agents used in the treatment of psoriasis urge caution in the treatment of patients with pre-existing or recent onset of central nervous system (CNS) demyelinating disorders.<sup>13-15</sup> It has been demonstrated that sib-

### Incorporating a New Psoriasis Option into Practice

The approval this fall of ustekinumab (Stelara, Centocor Ortho Biotech) represents a new direction in the field of biologic therapies for psoriasis. The novel inhibitor of IL-12 and IL-23 offers a mechanism of action that is different from that of previously-approved biologics and is likely just the first of its kind. Phase III data reported by the company upon FDA approval of ustekinumab show that a significantly higher proportion of patients receiving Stelara (45mg for patients weighing 220 lbs. or less or 90mg for patients weighing more than 220 lbs.) achieved at least a PASI 75 at week 12 compared to placebo controls. With every-12-week Stelara maintenance therapy, the majority of patients achieving a PASI 75 improvement maintained substantial skin clearance for one year.

Pooled analysis of safety data from Phase 2 and 3 clinical trials was presented in poster form at the 28th Anniversary Fall Clinical Dermatology Conference in Las Vegas in October. Results showed that in more than 3,000 patients treated with ustekinumab for up to three years, there was no evidence of cumulative toxicity. Rates of adverse events and infections were similar across three groups:

patients receiving ustekinumab 45mg, those receiving ustekinumab 90mg, and placebo controls. Rates of serious infection for all subjects were consistent with rates anticipated in the population of patients with psoriasis. Furthermore, rates of non-melanoma skin cancer were no higher among treated patients than among controls.

These efficacy and safety data combined with the convenience of therapy—ustekinumab is injected subcutaneously at weeks 0 and 4, followed by every-12-week dosing—have led to significant patient interest in the new agent. Although there are no medical considerations that would prevent dermatologists from initiating ustekinumab in a psoriasis patient who has not previously undergone biologic therapy, Paul Yamauchi, MD, PhD, medical director of the Dermatology Institute and Skin Care Center of Santa Monica and Clinical Assistant Professor of Dermatology at David Geffen School of Medicine at UCLA, says that insurance restrictions in the short-term may restrict the use of ustekinumab in biologic-naïve patients. "Because it's a brand new drug, there are going to be some inevitable problems with insurance approval and access," Dr.

lings of patients with MS have a significantly higher risk of predisposition to developing MS.<sup>23</sup> It is important to obtain a pre-treatment family history for demyelinating disorders prior to therapy and to inform the patients of potential risks. The causal relationship between TNF- $\alpha$  inhibitors and demyelinating disorders has not been firmly established. TNF- $\alpha$  levels in the cerebrospinal fluid have been strongly correlated with multiple sclerosis activity.<sup>24</sup> Interestingly, the blood-brain barrier probably prevents the entry of TNF- $\alpha$  antagonists into the cerebrospinal fluid, however, TNF- $\alpha$  antagonists may increase the activity of autoreactive T-cells. This could stimulate enhanced autoimmune responses and provide a mechanism for exacerbating MS disease activity.<sup>25</sup> Demyelinating disorders should be considered in patients on biologics experiencing visual changes, sensory loss, weakness, paresthesias, ataxia, and seizures.

### Infectious Complications

Increased rates of infection have been reported in patients being treated with all of the TNF blockers and alefacept.<sup>13-15,26,27</sup> Upper respiratory infections are

the most common infection. Each of the TNF inhibitors has a black box warning concerning the occurrence of mycobacterium tuberculosis (TB), bacterial sepsis, invasive fungal disease, and other opportunistic infections. During biologic treatment of psoriasis, patients should be advised to seek immediate medical attention if they develop signs or symptoms of infection. In the event of any serious infection (one in which antibiotic therapy is necessary) the biologic therapy should be discontinued until complete resolution of the infection.

TNF alpha is known to have an essential role in granuloma formation. Destabilization of granulomas in patients infected with TB can result in disseminated disease.<sup>28,29</sup> TB has occurred at higher rates than in controls during clinical trials with the monoclonal antibodies infliximab and adalimumab.<sup>14,15</sup> TB reactivation while receiving the fusion protein receptor agent etanercept has been found to occur less commonly than with the other TNF inhibitors.<sup>30</sup> Common symptoms in patients presenting with TB include fever, cough, night sweats, weight loss, anorexia, general malaise and weakness.<sup>31</sup>

Yamauchi says. He notes, however, that Centocor Ortho Biotech's ACCESS 1 program is helpful for achieving pre-authorization of all patients. Furthermore, he says, specialty pharmacies have proven remarkably adept at processing pre-certifications.

Given practical considerations linked to insurance coverage, most patients using ustekinumab will be transitioning from another biologic therapy that yielded inadequate response, Dr. Yamauchi suggests. Transitioning from a TNF or T-cell agent to ustekinumab is rather straightforward, Dr. Yamauchi says; there is no need for any "wash-out" period. However, there will likely be a period of one to three weeks from the time the patient and physician decide to transition to the completion of preauthorization processes and start of treatment. However, Dr. Yamauchi adds, there is no need for an add-on therapy to bridge between the two systemics, as patients should not experience any rebound during the brief interruption of therapy.

Another role for ustekinumab may be in the management of moderate to severe psoriasis patients in whom another biologic is contraindicated due to specific safety concerns or contraindications.

"Given that there are no boxed warnings associated with the novel agent, we can certainly use it in patients who are ineligible to receive a TNF due to MS or history of congestive heart failure," Dr. Yamauchi says.

Patient convenience or preference may also be a suitable indication to switch to ustekinumab, according Dr. Yamauchi, even if response to current therapy is adequate. "Quite a few of my patients do a lot of travelling for their jobs, for example, and bringing needles with them on trips has been a burden." With injections limited to two in the first four weeks of treatment and then every 12 weeks thereafter, ustekinumab may be an attractive treatment option for patients hindered by frequent injections and/or those who are needle phobic.

"Ustekinumab gives a new and unique mechanism of action which we need to help our psoriasis patients," Dr. Yamauchi says. "For patients with psoriatic arthritis, the TNF inhibitors do play a significant role in managing psoriasis and psoriatic arthritis, but I think the different mechanism of action is welcome to treat psoriasis."

—Paul Winnington

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Patients may present with disseminated or extrapulmonary disease during reactivation of TB while being treated with the TNF inhibitors, including etanercept.<sup>32,33</sup> The FDA recommends screening all patients before starting on a TNF inhibitor or ustekinumab, however, the Medical Board of the National Psoriasis Foundation recommends screening for TB in patients who are placed on any of the biologics that may cause immunosuppression.<sup>34</sup>

Before starting treatment, patients should be screened for latent TB by taking a history of travel, recent sick contacts, physical exam, and a tuberculin-PPD (5mm should be considered positive). Patients who are Bacille Calmette-Guerin (BCG) vaccinated are good candidates for the QuantiFERON-TB Gold assay, which has a greater specificity and at least as good sensitivity as the PPD.<sup>35</sup> If infection is suspected or the PPD is positive, a chest radiograph should be obtained. If there is a high suspicion for infection, contact a physician with expertise in the treatment of tuberculosis to help in the treatment process.<sup>14,36</sup> Debate over how long one should wait before starting anti-TNF therapy for psoriasis after beginning treatment for latent TB continues. Recommendations range from two weeks to six months.<sup>37</sup>

Once the patient is started on a biologic therapy, a majority of dermatologists recommend performing an annual PPD, particularly in those at highest risk of infection.<sup>34</sup> Monitoring for signs and symptoms of infection during and after treatment is warranted as well. There are reports of patients with false negative PPDs who developed infection while being treated with TNF inhibitors.<sup>35</sup> If a patient develops any signs or symptoms of TB while being treated it is currently recommended that the drug be withheld and expert opinion in the treatment of TB be obtained.

Cell-mediated immunity and TNF- $\alpha$  are critical for defense against fungal infections due to histoplasma, coccidioides, candida, cryptococcus, aspergillus and pneumocystis.<sup>38-42</sup> Inflammatory cell recruitment to the site of infection and granuloma formation and maintenance are several of the key roles TNF- $\alpha$  plays in host defense.<sup>43</sup> Second to *Staphylococcus aureus*, fungal infections are among the most common seri-

ous infections encountered during treatment with TNF inhibitors.<sup>31,43</sup>

In September of 2008, the FDA issued a warning that healthcare professionals were not recognizing invasive fungal infections early enough in patients treated with the TNF inhibitors. In 240 cases of histoplasmosis reviewed, there were at least 21 reports identified where unrecognized infection resulted in delay of treatment. Twelve of these patients died.<sup>36</sup> Maintaining close follow up with patients and recognizing risk factors should aid in earlier diagnosis of fungal infections in this patient population.

Histoplasmosis has been the most commonly reported invasive fungal infection in patients treated with the TNF inhibitors.<sup>44</sup> The most common presentation is with acute pneumonia, although extra-pulmonary and disseminated disease are not rare initial presentations in immunosuppressed patients.<sup>45</sup> Infected patients who are immunosuppressed often present with fever, chills, malaise, dyspnea, cough, headache, weight loss and interstitial pneumonia on chest radiograph.<sup>45</sup> *Histoplasma capsulatum* is endemic to the Ohio River and Mississippi River Valleys and is found in soil and other materials contaminated with bird or bat feces. Those who live in this endemic area account for the majority of cases reported, although any patient with signs of infection and recent travel to this region should be evaluated for histoplasmosis.<sup>36,44</sup>

Coccidioidomycosis is another invasive fungal infection that has been associated with severe adverse events in patients treated with TNF inhibitors. In an endemic area, one study found patients treated with infliximab to have a relative risk of 5.23 for developing symptomatic coccidioidomycosis compared to normal residents.<sup>46</sup> This fungus is endemic to the Southwestern United States. It is especially common in the region between Phoenix and Tucson. Patients commonly present with the same symptoms as seen in histoplasmosis.<sup>36</sup>

At this time, there is no reliable screening method for fungal infections before starting biologic therapy because most patients acquire the disease after start-

ing treatment rather than reactivation of latent infection.<sup>44</sup> Patients who present with signs and symptoms of possible invasive fungal infection and live or have recently traveled to an endemic area should be carefully evaluated. Rapid techniques are the most valuable tool for detecting fungi in immunosuppressed patients because rapid deterioration has been known to occur.<sup>47</sup> Currently available rapid methods include urine or serum antigen testing and histopathological identification in tissue biopsies. These tests should always be confirmed by cultures of body fluids or tissues infected.<sup>48,49</sup> An infectious disease specialist should be involved in the treatment of infected patients and the biologic agent should be stopped immediately.<sup>36</sup> Patients with mild to moderate disease will typically require treatment with itraconazole or fluconazole alone over several months. Those who present with disseminated or severe infection will require IV Amphotericin B followed by months of itraconazole.<sup>44,45</sup>

Reactivation of hepatitis B or worsening of symptoms has been reported with all of the TNF inhibitors, and in some cases patients died.<sup>13,15,27,50,51</sup> The FDA states that limited data are available and all patients prescribed these medications should be evaluated for Hepatitis B virus prior to starting therapy. There are a limited number of studies, mostly case reports, in patients who are infected with Hepatitis B virus and treated with TNF inhibitors. In many of these cases, the patients are concomitantly treated with anti-hepatitis B medications, such as lamivudine, which has been shown to prevent increases in viral loads.<sup>52</sup> Infliximab more often causes HBV reactivation, compared to patients treated with etanercept and adalimumab. This is not unique, as it also is more likely to cause reactivation of TB and other opportunistic infections, when compared to etanercept and adalimumab.<sup>53,54</sup> Reactivation has been noted to most commonly occur after the third dose of infliximab.<sup>53,54</sup>

Patients infected with Hepatitis C have not been found to experience the same complications as those with Hepatitis B during anti-TNF alpha treatment,<sup>55</sup> however, long-term safety of TNF inhibitors

in patients with chronic hepatitis C is not well known.<sup>52</sup> The few studies that have reviewed patients with HCV infection and psoriasis treated with etanercept have demonstrated no change in HCV load or LFTs.<sup>56-60</sup> These studies suggest that etanercept is currently the safest of the TNF inhibitors to use in this patient population. Although infliximab has been shown to be effective and safe in patients with psoriasis and HCV, fewer data are available.<sup>56</sup>

At this time, there is no consensus on screening patients for Hepatitis B or C before starting them on TNF inhibitors. HBV is one of the most common forms of chronic viral infection and, therefore, a conservative approach would be to check serologies before starting TNF inhibitor therapy.<sup>37</sup> Patients who are carriers of HBV or HCV, but are without active disease, may still be treated for psoriasis with a TNF inhibitor.<sup>55,56</sup> These patients should have frequent monitoring of viral loads and LFTs. Treating infected patients with concurrent antiviral therapy is often recommended as reactivation flares of HBV can occur rapidly.<sup>37,55</sup> Any patient with active HBV or HCV should not be started on biologic therapy until their disease is well controlled.

## Conclusion

This article has evaluated a number of complications associated with the use of biologics in the treatment of psoriasis. Importantly, we have provided useful strategies for addressing and preventing these complications whenever possible. Next month's article will examine more complications, such as cardiac, hepatic, hematologic, immunologic, cutaneous, and injection/infusion site complications. ■

*Dr. Bechtel is on the Speaker's Bureau for Centocor, Amgen, and Abbott. Mr. Bauer has no conflicts.*

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