Complications of Biologic Therapy for Psoriasis: Part II

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

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Last year, biologic therapies came under the microscope for concerns over safety. After efalizumab (Raptiva, Genentech) was withdrawn from the market, the FDA issued new boxed warnings for many biologics.¹⁻⁴ In light of these warnings and heightened interest in safety data, this article series evaluates the wide-ranging complications and offers tips on how to prevent and manage these complications should they arise. In last month’s article, we reviewed a number of complications, including malignant, neurologic, and infectious. Ahead, we will examine cardiac, hepatic, hematologic, immunologic, cutaneous, and infusion/injection site complications.

Hepatic Complications
Hepatotoxicity has been reported with the use of alefacept (Amevive, Astellas), efalizumab, adalimumab (Humira, Abbott), etanercept (Enbrel, Amgen/Wyeth) and infliximab (Remicade, Centocor Ortho Biotech). Asymptomatic increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most commonly reported hepatic finding.¹⁴⁻⁶¹ These increases in liver enzymes rarely required discontinuation of the medication, however, the use of infliximab has been associated with greater liver complications than the other biologic agents listed.

The use of infliximab has been linked to acute liver failure, jaundice, hepatitis, cholestasis and autoimmune hepatitis. In some cases, elevations in the LFTs were not noted prior to recognition of liver injury.¹⁴ In studies where infliximab was used to treat psoriatic arthritis, 49 percent of patients experienced ALT elevations, compared to 16 percent on placebo. In two percent of the patients, ALT was greater than or equal to five times the upper limit of normal and in five percent of the patients, it was greater than or equal to three times the upper limit of normal.¹⁴ Patients who experience liver disease while taking the biologic agents have rarely required liver transplant and even died.

Current guidelines for monitoring liver function while taking any biologic agent include baseline chemistry screening and LFTs. Any abnormal

Take-Home Tips. Biologic agents used for psoriasis may be associated with hepatic, cardiac, hematologic, immunologic, infusion/injection site, and cutaneous complications. Successful patient management requires that clinicians understand the rates and mechanisms of these complications, identify high-risk patients, and be prepared to manage complications as they arise. Pre-screenings and regular patient monitoring are essential.
results should prompt assessment for the underlying cause. During treatment with infliximab, some experts suggest LFTs should be repeated before each infusion. If either AST or ALT rise to greater than five times the upper limit of normal, treatment should be withheld and any rise in liver enzymes should prompt repeating the test before the next infusion. A case report demonstrated that switching from one TNF inhibitor (adalimumab) to another (etanercept) because of liver dysfunction can be done safely in patients with psoriasis, however, there is not enough evidence to state that this study can be repeated safely. Close monitoring and involvement of a specialist should be considered in switching biologic agents due to liver disease.

Cardiac Complications

Patients with psoriasis have an increased risk of cardiovascular disease. Comorbidities in patients with psoriasis include higher rates of diabetes, hypertension, obesity, and dyslipidemia, which are known to increase the incidence of myocardial infarction. With these risk factors corrected for, patients continue to express a higher probability of myocardial infarction compared to controls. This is particularly true in younger patients with severe psoriasis. The increased predilection for cardiovascular disease in this patient population has caused debate over the use of potentially cardiotoxic drugs in patients with mild to severe heart failure.

Patients with congestive heart failure who were concurrently treated with TNF inhibitors were found to have worsening of heart failure in several reports. Patients with moderate to severe heart failure (NYHA Functional Class III/IV) treated with 10 mg/kg of infliximab were found to have higher rates of mortality than controls. Patients treated with 10mg/kg and those with 5 mg/kg of infliximab were both shown to have increased rates of hospitalization due to worsening heart failure. There have been post-marketing reports of worsening congestive heart failure (CHF) and new onset CHF in patients without preexisting cardiovascular disease in patients receiving infliximab or etanercept. In the patients with new onset heart failure, an alarming 50 percent had no identifiable risk factors and 26 percent were younger than 50 years of age.

Two large studies have evaluated the use of etanercept in the treatment of mild to severe heart failure in patients that did not have other serious illnesses, being dosed at 25mg once, twice, and three times weekly. Both studies were terminated prematurely, owing to lack of benefit in heart failure patients. The pooled data was analyzed in the Randomized Etanercept Worldwide Evaluation (RENEWAL) analysis, which revealed no clinically relevant effect on mortality or chronic heart failure hospitalization.

Adalimumab and golimumab (Simponi, Centocor Ortho Biotech) are two TNF inhibitors that have little data on their safety in patients with congestive heart failure. At this time, it is recommended to approach the entire class of TNF inhibitors with caution in regards to cardiac complications until more studies are conducted and patient experiences can be reported. Treatment of patients with the T-cell inhibitors alefacept and efalizumab has resulted in few cases of cardiotoxicity or worsening of heart failure that could be associated with use of these agents.

Based on clinical trials, post-marketing experience and the FDA, TNF alpha inhibitors should not be used in patients with psoriasis who have moderate to severe heart failure (NYHA Class III/IV). In patients with well-compensated mild heart failure (NYHA Class I/II), data is not sufficient to determine the safety of TNF inhibitors. In this setting, physicians should obtain a baseline echocardiogram and those patients with an ejection fraction less than 50 percent should avoid treatment with TNF alpha inhibitors. If the ejection fraction is normal, then an informed discussion with the patient and close monitoring for signs or symptoms of worsening heart failure is appropriate. Any of these biologic treatments should be stopped immediately in the setting of new symptoms or worsening of heart failure.
Hematological Complications
Alefacept is a recombinant fusion protein that works by binding to the T-cell lymphocyte antigen CD2. It is known to inhibit T lymphocyte activation and reduce the number of circulating CD4+ and CD8+ T-cells in a dose-dependent relationship. It is also contraindicated for use in patients with human immunodeficiency virus (HIV). In patients treated with alefacept, a baseline complete blood cell count should be obtained and CD4+ T-cell counts monitored every two weeks throughout the 12 week course of dosing. In the intramuscular study conducted, lymphocytopenia was more common after six to eight weeks of therapy. During this study, 28 percent of patients had abnormally low CD4+ T-cell counts. If the CD4+ count falls below 250 cells/μL, dosing should be withheld and weekly monitoring initiated. Alefacept treatment should be discontinued if the CD4+ count does not normalize within a month.

The anti-TNF alpha agents have been rarely associated with anemia, leukopenia, neutropenia, thrombocytopenia, pancytopenia and aplastic anemia. In some cases, the patients were also being treated with other medications and it is difficult to determine the causality of the hematologic disturbance. One recent study in rheumatoid arthritis patients actually showed a significant improvement in hemoglobin level while being treated with infliximab and methotrexate. Due to the current lack of evidence and possibly related fatalities following hematologic complications while being treated with TNF inhibitors, caution is advised. Patients who develop easy bruising, prolonged bleeding, pallor or fever should be evaluated for a hematologic cause. Patients should have complete blood cell counts, including platelet counts, before starting therapy with these biologic agents and be appropriately monitored.

Immunologic Complications
The use of TNF alpha blocking agents has been associated with the development of auto-antibodies. Antinuclear antibodies (ANA) and anti-dsDNA antibodies were found at different prevalence rates among the various agents. Infliximab is associated with the highest occurrence rate of ANA with approximately 50 percent of patients treated testing positive. In comparison, only 12 percent and 11 percent of patients tested ANA positive that were treated with adalimumab and etanercept, respectively. All three medications, incidence of ANA or anti-dsDNA antibodies did not correlate with development of Lupus-like syndromes.

A retrospective review of all TNF inhibitor use in French hospitals found an incidence of lupus-like syndrome in a group of about 10,700 patients to be 0.19 percent for infliximab and 0.18 percent for etanercept. In these patients all systemic lupus erythematosus symptoms resolved within 16 weeks of discontinuation of the drug. These patients most commonly present with rash, purpura, myalgia, serositis, and pneumonitis.

The monitoring of patients for ANA, anti-dsDNA antibodies and anticardiolipin antibodies while being treated with TNF inhibitors is not necessary. The correlation between development of auto-antibodies to signs and symptoms of lupus has not been shown, therefore, these nonspecific antibodies are not a contraindication to therapy with TNF inhibitors, nor do they necessitate discontinuation of therapy, should they develop. If a patient develops signs or symptoms of lupus, the biologic agent should be withheld, and resolution of symptoms most often occurs.

Development of antibodies to alefacept has been reported to occur in 2.4 to three percent of patients treated and usually found at low titers. The development of antibodies to etanercept was approximately six percent in clinical trials. The formation of antibodies to either of these medications has not been found to correlate with clinical response or adverse events. The long-term immunogenicity of these antibodies is currently unknown.
Clinical studies have shown that patients with psoriasis who are treated with infliximab are more likely to develop antibodies against infliximab at lower doses. One study showed that over a year 36 percent of patients receiving 5mg/kg compared to 51 percent of patients receiving 3mg/kg developed antibodies to infliximab. It has also been demonstrated that low dose methotrexate can lower the percentage of patients who develop these antibodies. Patients who develop antibodies to infliximab were more likely to have increased clearance rates, reduced efficacy and more infusion reactions. Approximately one percent of patients treated with infliximab will experience a serum sickness reaction that can occur as early as the second infusion and will recur if treatment is reinitiated. Clinical findings include fever, rash, myalgia, arthralgia, headache, facial edema, and/or dysphagia. Prior to treatment, antihistamines, corticosteroids, and epinephrine should be available and used promptly, if a reaction occurs. Use of infliximab should not be continued in that patient.

The formation of antibodies to adalimumab has also been shown to result in neutralization of the medication and likely decreased efficacy. In contrast to infliximab, there have been no adverse reactions associated with these antibodies. In the three controlled trials reviewed, antibodies against adalimumab were detected in 12 percent of patients treated for rheumatoid arthritis. The use of methotrexate concomitantly with adalimumab resulted in only one percent of patients developing antibodies to adalimumab. The studies revealed that more frequent dosing was associated with fewer patients developing these antibodies, as well.

Infusion/Injection Site Complications
The most common adverse events associated with infliximab are infusion reactions. Approximately 20 percent of patients in clinical studies experienced an infusion reaction. Patients had various presentations such as chills, fevers, pruritus, urticaria, irregularities in blood pressure and changes in heart rate. Serious infusion reactions occurred in less than one percent of patients and included anaphylaxis, convulsions and erythematous rash. Interestingly, patients who developed antibodies to infliximab were two to three times more likely to develop an infusion reaction than those who did not. During the event of an infusion reaction, the symptoms should be treated appropriately and the infusion rate should be decreased or stopped based on the severity of the reaction. Various pre-treatment regimens including corticosteroids and antihistamines have inconsistently been shown to reduce the risk of infusion reactions. It has also been reported that maintaining a regular dosing regimen may result in fewer infusion reactions. Most importantly, patients who experience a severe infusion reaction should discontinue therapy with infliximab indefinitely, as future reactions may occur if treatment is resumed.

Adalimumab, etanercept, and golimumab have all been associated with injection site reactions. The most common reactions are mild to moderate in severity and include erythema, itching, hemorrhage, pain or swelling at the injection site. These adverse events rarely necessitate discontinuing the TNF inhibitor, and they often decrease in severity and frequency following the first month of therapy. In order to decrease the likelihood of injection site reactions, one should vary the site of injection.

Etanercept treatment for plaque psoriasis was associated with 14 percent of patients developing injection site reactions compared to 37 percent of all patients treated for a rheumatologic disease in clinical trials. The increased frequency of injection site reactions during treatment of rheumatologic diseases other than psoriasis was seen with all the TNF inhibitors. In clinical trials, adalimumab was associated with 20 percent of patients experiencing injection site reactions. There was also a one percent incidence of hypersensitivity reactions, including allergic rash, anaphylactoid reactions, fixed drug reaction or urticaria. Treatment should be discontinu-
ued in patients who experience serious allergic reactions. Clinical trial data indicates that golimumab may have the lowest rate of injection site reactions among the TNF inhibitors at six percent of patients.27

Alefacept is associated with injection site reactions as well. These reactions occurred in 16 percent of patients during clinical trials and remained constant throughout all courses of treatment. The most common injection site reactions include inflammation, bleeding, edema, and non-specific reactions.26

Cutaneous Complications
The TNF alpha inhibitors approved for treatment of psoriasis have paradoxically been reported in numerous case studies to be associated with new onset or exacerbation of cutaneous psoriasis. The T-cell inhibitor alefacept has not been associated with these same complications. The FDA reviewed 69 cases in which patients receiving TNF inhibitor therapy for various rheumatologic conditions developed new onset psoriasis.17 The overall prevalence of induced psoriasiform lesions is estimated by several authors to be about 1.0-5.3 percent in various rheumatologic diseases.84-86 The most common presentations have been development of pustular and palmoplantar forms of psoriasis. In a large review of 120 cases, there were 25 patients whose psoriasis worsened and several other cases in which psoriasis shifted in type during treatment with a TNF inhibitor.87 The time from induction of therapy to exacerbation or new onset of psoriasis varied considerably, but occurred at a mean 9.5 months in these cases.87 After discontinuation of the TNF inhibitor alone or in association with other psoriatic therapy, the majority of patients experience complete or partial improvement.17,87 Prior to treatment, patients should be counseled on these risks and advised to report any changes or new onset of lesions as hospitalization has been necessary in some cases.17

An association between TNF inhibitors and vasculitis has been established during the post-market-
in 18 of 33 patients in one study.20 The remaining 14 required high-dose glucocorticoids and/or immunosuppressants for symptom resolution over several weeks.

Dr. Bechtel is on the Speaker’s Bureau for Centocor, Amgen, and AbbV. Mr. R. Bauer has no conflicts.

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