

Biologic Therapies For Psoriasis in 2013: Do We Use Them Enough?

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Psoriasis is a chronic autoimmune disease affecting approximately three percent of the US population. A better understanding of its underlying pathophysiology has led to breakthrough biologic therapies that have revolutionized our treatment algorithms.

Biologic drugs are biologically active large proteins that are capable of modifying an immune response. These drugs can no longer be considered new, as TNF-alpha antagonists have been used to treat patients for more than 10 years. More than two million patients worldwide, with a variety of autoimmune diseases, have been dosed with these drugs. Therefore, psoriasis patients benefit not only from their efficacy, but also from the accumulation of long-term safety data. A newer treatment blocks the p40 subunits of interleukins (IL) 12 and 23, also resulting in impressive efficacy with five-year safety data now published.¹

PSORIASIS AS A SYSTEMIC DISEASE

Over the last decade we have begun to understand that psoriasis is not just a disease of epidermal hyperproliferation, but also a systemic autoimmune disease. When clinicians see a patient with a characteristic butterfly facial eruption of systemic lupus, we immediately think about treating the skin eruption and everything else is going on systemically. We now feel the same is true with our psoriasis patients, and we need to have the same thought process when evaluating them. In addition to ascertaining severity of disease and quality of life, we must also look for associated comorbidities.

Psoriasis is partially mediated by Th-1 helper cells. This results in elevated pro-inflammatory cytokines such as TNF-alpha, IL-6, IL-12, interferon-gamma, and leptin. A more recent discovery was the identification of an activated Th-17 helper cell, which causes an increase in IL-17, IL-20, IL-22 and IL-23. These immune mediators result in a systemic autoimmune disease. Elevated TNF-alpha increases leptin and decreases adiponectin (an insulin sensitizer), which could influence insulin resistance, metabolic syndrome, and the appearance of nonalcoholic fatty liver disease.² Metabolic syndrome is three times more prevalent in the psoriasis versus the general population.

Although several expert groups have proposed different diagnostic criteria for metabolic syndrome, they all include the same core components. It is defined by central obesity along with any two of the following five criteria: elevated

THE METABOLIC SYNDROME

Defined by central obesity along with any two of the following five criteria:

- elevated blood pressure
- elevated fasting plasma glucose
- previous diagnosis of type 2 diabetes
- elevated triglycerides
- low HDL.

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blood pressure, elevated fasting plasma glucose, previous diagnosis of type 2 diabetes, elevated triglycerides, or low HDL. Non-alcoholic fatty liver disease in psoriasis patients is associated with obesity and metabolic syndrome. In a UK population-based cohort observational study, patients with severe psoriasis had a hazard risk of 1.46 for type 2 diabetes and were more likely to need treatment with oral medications.³ The Nurses Health Study, during a 14-year follow-up, confirmed that increased adiposity and weight gain are strong risk factors for incident psoriasis in women.⁴

Psoriasis itself is a risk factor for cardiovascular disease, even after adjusting for other risk factors such as smoking, diabetes, hypertension, lipid abnormalities, age, and sex. In a UK general practice database, there was a 6.2 percent increase in major adverse cardiac events (MACE) over 10 years in the severe psoriasis population compared to the general population.⁵ The risk of myocardial infarction (MI) associated with psoriasis is greatest in young patients with severe disease.⁶ Elevated plasma osteopontin levels are also associated with psoriasis and is another unfavorable cardiovascular risk factor.⁷

Other known comorbidities associated with psoriasis include depression in 15 to 25 percent of patients, sleep disorders, and ocular diseases, such as anterior uveitis which occurs in seven to 20 percent of patients with psoriasis. Psoriasis patients are at increased risk for other autoimmune diseases, such as inflammatory bowel disease with an odds ratio (OR) of 2, and celiac disease (OR 2.7).⁸ Other diseases such as vitiligo, pernicious anemia, and Hashimoto's thyroiditis are also seen more frequently. A retrospective cohort study showed psoriasis patients have an OR risk of 1.6 to develop one other and OR 1.9 to develop two other autoimmune diseases.⁹

WHAT EVIDENCE DO WE HAVE BIOLOGICS CAN IMPROVE COMORBIDITIES?

Patients with autoimmune diseases such as psoriasis are known to live about four years less than the general popu-

lation. As stated previously, this is related to an increase in MACE events. But if we can reduce systemic inflammation with biologic drugs, it makes intuitive sense that the associated comorbidities should also decrease. Studies also indicate that biologics reduce these risks. Two large studies in RA show TNF-alpha inhibitors do reduce first CV events.^{10,11}

Etanercept (Enbrel, Amgen/Pfizer) has been shown to lower pro-inflammatory markers such as CRP and IL-6 and increase adiponectin in patients with psoriasis, psoriatic arthritis (PsA), and metabolic syndrome.¹² Leptin is a protein made by fat cells that tells the brain “you're full” so you stop eating. Leptin levels are elevated in overweight people due to leptin resistance. The brain does not get this signal, so the person eats even more, which becomes a vicious cycle leading towards obesity. Leptin levels however, are decreased with adalimumab (Humira, AbbVie) or infliximab (Remicade, Janssen).¹³ In obese patients with metabolic syndrome, etanercept over a six-month period improved fasting glucose and increased the ratio of high molecular weight to total adiponectin.¹⁴

Solomon, et al. showed that in RA or psoriasis, TNF-alpha antagonists and hydroxychloroquine, but not methotrexate or other non-biologic disease modifying anti-rheumatic drugs (DMARDs), decreased the incidence of diabetes.¹⁵ In a Danish database over a three-year period, the incidence rates of MACE events in severe psoriasis patients were reduced with use of biologic drugs, with hazard ratio (HR) of 0.28 versus 0.65 with methotrexate. In this group 80 percent of the patients were treated with TNF-alpha antagonists and 20 percent with IL-12/23 inhibitors.¹⁶

Wu, et al. published a retrospective cohort of Kaiser patients with psoriasis and PsA. The HR of MI was 0.5 compared to the topical cohort. Therefore, half the number of patients in the TNF-alpha treated groups had cardiac events compared to the number treated only with topical agents.¹⁷ Burmester, et al. published a long-term safety analysis of over 23,000 patients on adalimumab from global clinical trials with six different autoimmune diseases. Patients were treated for up to 12 years. For treated subjects with rheumatoid arthritis (RA), ankylosing spondylitis, and psoriasis, the observed number of deaths was less than expected in an age- and sex matched population. However, in PsA and Crohn's disease studies, the observed number of deaths was similar to the number expected in the reference general population.¹⁸ This improvement in mortality rates for the psoriasis population is likely related to the overall reduction in inflammation resulting in reduced MACE events. Although several studies show a clear effect on lipids is not evident with the TNF-antagonists, these

BIOLOGICS' POSSIBLE BENEFITS

In addition to improvement of cutaneous symptoms, data suggest that use of biologic therapies in patients with psoriasis may be associated with:

- Reduction in cardiovascular events
- Decrease in leptin levels
- Improvement in fasting glucose levels
- Reduction in incidence of diabetes
- Prevention of joint destruction of PsA

drugs may improve cardiometabolic risk through its net anti-inflammatory effect.¹⁹

Depending on the study, PsA can occur in up to 40 percent of psoriasis patients. TNF-alpha antagonists significantly improve the symptoms of disease and can prevent irreversible joint destruction.²⁰ Ustekinumab (Stelara, Janssen) also has a moderate clinical effect in reducing ACR scores in early studies. In the Phase 3, multicenter PSUMMIT I study, ustekinumab significantly reduced signs and symptoms of PsA at week 24.²¹

CONCLUSION

A National Psoriasis Foundation survey concluded that more than one third of psoriasis patients with moderate-severe disease were not adequately treated. Biologic drugs have dramatically improved our ability to treat this systemic disease and should therefore be considered more widely for patients with moderate to severe disease. We have seen mounting evidence that these therapies also improve quality of life and reduce associated comorbidities.

The combined effect of improved insulin sensitivity along with a reduction of pro-inflammatory mediators likely has the net effect of interrupting the inflammatory cascade linking psoriasis with metabolic syndrome and MACE events. Although these drugs have potential side effects, numerous studies prove both efficacy and lack of cumulative toxicity.

Importantly, biologics should only be used in conjunction with educating our psoriasis patients about the known cardiovascular risk factors. Patients should also be encouraged to address modifiable behavioral changes, such as avoiding smoking or excessive alcohol consumption, in addition to maintaining a healthy diet and sufficient exercise. Not only can we now improve quality of life in our

psoriasis patients with biologic therapy, but we can also possibly increase longevity by reducing systemic inflammation and cardiac risk factors. ■

Dr. Prussick has served as a consultant, speaker, trainer or investigator for Abbott, Allergan, Amgen, Gene Logic, Janssen, Leo, L'Oreal, Pharmaderm, Medicis and Medimetriks.

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