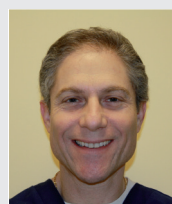


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Biologic therapies for psoriasis: do we use them enough?

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“The development of biologic drugs to treat autoimmune diseases has been a major advance in our ability to modify disease.”

Psoriasis vulgaris is a common, chronic immune-mediated disease manifesting as thick scaling plaques on the skin. It is found in approximately 3% of the US population, and is equally prevalent in males and females. The lesions are commonly found in typical areas of koebnerization, such as the knees, elbows, scalp, hands and feet. Less common variants include flexural, pustular and erythrodermic forms. It is estimated that approximately 30% of patients will develop a form of psoriatic arthritis, usually presenting up to 10 years after the skin lesions appear.

A dramatic breakthrough in our understanding of the disease came after the observation that transplant patients treated with cyclosporine A underwent dramatic clearance of their skin disease. This led investigators to study the underlying immunology behind this, a work still in progress. Over the years, this research has resulted in a remarkable breakthrough in our understanding of psoriasis as a systemic inflammatory disease.

This research has identified an inflammatory dendritic cell that stimulates, via IL-23 and other cytokines, the production of a discrete T cell helper (Th)-17 cell, which is independent of Th-1 cells. These activated T cells produce a variety of cytokines, such as IL-17, IL-20, IL-22 and IL-23, which are important in the pathophysiology of the disease [1]. An

important unknown is the autoantigen that these dendritic cells present to the Th-17 cell.

The development of biologic drugs to treat autoimmune diseases has been a major advance in our ability to modify disease. Biologic drugs are simplistically defined as biologically active molecules that are capable of modifying an immune response. As these are large proteins, they must be administered by subcutaneous, intramuscular or intravenous routes. TNF- α antagonists are now commonly used to not only treat psoriasis, but have efficacy for multiple clinical indications. TNF- α is produced by activated monocytes, and induces changes in gene-expression patterns of adipose and liver cells. This results in a proatherogenic lipid profile. Humans with a *TNF- α Nco1* polymorphism have increased serum TNF- α and insulin resistance [2]. In animal studies, TNF- α administration also induces insulin resistance. The Nurses Health study has shown that obesity predisposes to psoriasis [3]. Adipocytes produce adipokines, such as TNF- α , IL-6, IL-8 and leptin [4], which are proinflammatory and may predispose to metabolic syndrome and dyslipidemia.

We have sufficient data to show psoriasis can affect quality of life and job performance. Surveys show that the impact of psoriasis on physical functioning can be similar to other serious diseases such as

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diabetes, myocardial infarction and arthritis [5]. Patients with psoriasis have an increased risk of depression and selective serotonin reuptake inhibitor drug use. There is some data to show that there are increased serum levels of TNF- α in patients with depression [6]. Studies show that Dermatology Quality Of Life scores correlate with severity. In addition, these scores improve with clearance of the disease [7].

A National Psoriasis Foundation survey in the USA, performed in 2007, concluded that psoriatic patients with moderate-to-severe disease were not adequately treated. Greater than a third did not receive therapy, and even less received systemic therapy [8].

Comorbidities

Recent data has shown psoriasis is associated with several comorbidities. As already stated, approximately a third develop a form of psoriatic arthritis. One study demonstrated that patients with psoriasis have a 4.2% increased risk of metabolic syndrome, versus 1.1% in controls, with an odds ratio risk of 5.92. Diabetes was found in 11.7% of psoriatics versus 5.8% of controls, with an odds ratio risk of 2.48 [9]. Using a General Practice Database in the UK, patients with severe psoriasis had approximately a sevenfold adjusted relative risk of MI versus the control population. This risk was particularly evident in the younger psoriatic population [10]. Gelfand *et al.* demonstrated patients with severe psoriasis had an increased overall mortality risk. Male and female patients with severe disease died 3.5 and 4.4 years sooner than controls [11].

Can biologic therapy decrease comorbidity risk?

We have some short-term data that suggest this may be the case. Etanercept has been shown to lower proinflammatory markers, C-reactive protein and IL-6 levels [12]. Infliximab has been shown to improve endothelial function and lower insulin levels in rheumatoid arthritis patients. Two large studies have shown that TNF- α antagonists are associated with a lower incidence of first cardiovascular events in the rheumatoid arthritis population [13]. In the British study, the improvement was limited only to responders [14]. Burmester *et al.* recently looked at 19,041 patients from 36 clinical trials on adalimumab, across

all six indications, over a 9-year period. They found a decreased overall mortality in treated patients compared with an age- and sex-matched population [15].

Psoriatic arthritis is a progressive disease that can lead to permanent deformity and disability. TNF- α inhibitors have been proven to be preventative. Infliximab significantly inhibited radiographic progression in patients with psoriatic arthritis as early as 6 months after starting treatment [16]. In the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), the clinical and radiographic efficacy of adalimumab was sustainable during long-term treatment, with a favorable risk-benefit profile [17].

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Conclusion

The biologic drugs have dramatically improved our ability to treat and control the symptoms of moderate-to-severe psoriasis and psoriatic arthritis. Along with unquestionable efficacy scientists have come concerns regarding safety. With time and experience, medical providers have become more adept at monitoring and identifying these safety risks. As we continue to accumulate long-term safety data, we will better understand these risks. Over time, we also need to monitor for the reduction of these comorbidity risks. Ideally, we will have the ability and knowledge to not only treat severe skin disease, but to improve the patients' overall health and reduce comorbidity risk factors.

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