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Paid supplement to

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Psoriasis is a chronic immunologic disease that manifests as a severe skin condition (Pariser 2007). It often presents as raised red patches or lesions accompanied by a silvery white buildup called scale (NPF 2010a). Psoriasis often is considered a variable and diverse disease because of its different forms and subsequent characteristics (NPF 2010a). The most common form, plaque psoriasis, accounts for approximately 80 to 90 percent of the reported cases of psoriasis in the United States and is estimated to affect as many as 7.5 million Americans (Pariser 2007, NPF 2009b).

The biology of psoriasis

Four significant histological changes can be seen in psoriatic skin lesions: Hyperproliferation of keratinocytes, hyperkeratosis, angiogenesis, and immunocyte infiltration (Schön 2005). Epithelial cells in psoriatic skin multiply at a rate as much as 50 times greater than non-psoriatic skin, and this drastic increase in mitotic activity diminishes the typical cycle necessary for keratinocyte movement to the stratum corneum (Schön 2005). In addition, the keratinization process is intensified, resulting in hyperkeratosis or marked thickening of the cornified layer (Schön 2005). The scaling frequently seen in psoriasis plaques stems from the failure of terminally differentiated keratinocytes to stack normally, secrete lipids, and adhere to each other. This functional failure ultimately breaks the protective barrier these cells provide (Lowes 2007).

Angiogenesis and dilatation also are apparent in psoriatic lesions and are evident by the significant increase in the number and size of blood vessels present in the epidermal layer (Schön 2005). The elongated, hyperplastic, dilated blood vessels become contorted and reach underneath the epidermis and dermal papillar regions, resulting in the characteristic redness often seen in many psoriatic lesions (Lowes 2007, Schön 2005). On a molecular level, vascular endothelial cells in psoriatic lesions have shown an increased expression of intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and other activation markers (Krueger 2002).

Another histological feature common to psoriatic lesions is the presence of a leukocytic infiltrate within the dermis (Schön 2005). In psoriasis, cytokines released from T cells act primarily in a proinflammatory fashion, causing the traditional pathological histology changes seen in psoriasis (Walsh 2004). Tumor necrosis factor (TNF) is produced by T cells and induces keratinocytes to produce vascular endothelial growth factor (VEGF) and interleukin 8 (IL-8). TNF expression leads to the proliferation of endothelial cells, enhanced expression of ICAM on the endothelial surface, increased expression of VCAMs on the endothelial surface, and inten-

TABLE Sampling of cytokines overexpressed in psoriatic lesions

Cytokine	Secreting cell	Action
Interferon	T cells and natural killer cells	• Immunomodulatory • Influence cell mediated mechanisms of cytotoxicity • Modulates T cell growth and differentiation
Interleukin 2	T cells	• Proliferation of T cells • Promotes the proliferation of activated B cells
Interleukin 8	Keratinocyte, monocytes, endothelial cells	• Activates neutrophils • Attract neutrophils to location (Walsh 2004)
Interleukin 12	B and T cells	• Induces the synthesis of interferon gamma, interleukin 2, and TNF • Co-stimulator for TNF production
Interleukin 23	Activated dendritic cells	• Induces proliferation of T cells • Stimulates production of interferon gamma
TNF alpha	Macrophage, monocytes, neutrophils, T cells	• Angiogenesis • Enhances neutrophil phagocytosis and cytotoxicity • Potent chemoattractant for neutrophils
VEGF	Macrophages	• Mitogen for vascular endothelial cells

TNF=tumor necrosis factor; VEGF=vascular endothelial growth factor
Source: COPE 2010

sified recruitment of activated T cells to the area (Walsh 2004).

The overabundance of proinflammatory cytokines at the cutaneous site leads to the significant tissue damage typically seen in the psoriatic skin (Walsh 2004). For example, the interferon secreted by activated T cells induces keratinocytes to enhance their secretion of proinflammatory cytokines and encourages a regenerative response, which results in the excess proliferation and inadequate maturation of keratinocytes (Walsh 2004). The Table shows a sampling of cytokines that are overexpressed in psoriatic lesions.

Therapeutic targets

Having a clearer understanding of some of the immunologic pathways involved allows for the fundamental rationale of targeted treatment strategies, including biologic agents. These agents can be described as proteins or antibodies that target specific molecules involved in a pathogenic process (Lowes 2007). Biologic therapies for the treatment of psoriasis are subdivided into three targeted categories: T cells, TNF, and the interleukin (IL)-12 and -23 inhibitors.

T-cell targeted biologic agents. T cells and antigen-presenting cells collaborate to stimulate and enhance cell-mediated immune responses. Viable targets to inhibit activation, costimulation, proliferation, and T-cell destruction to modify the immune response of T cells have been investigated (Walsh 2004). Biologic agents that use T cells as a target often focus on specific cell surface receptors. The CD2 marker participates in cell-mediated immune responses by increasing the expression of T-cell growth factor IL-2 and its receptors (COPE 2010). For example, one biologic agent binds to the CD2 surface receptor of T cells to limit immune activation (Amevive 2006). The subsequent binding of the CD2 receptor blocks the costimulatory signals necessary for T-cell activation (Walsh 2004). This particular biologic also has the capacity to bind to natural killer cells that form a bridge with differentiated T cells, which eventually causes apoptosis of the activated T cells (Amevive 2006). This particular biologic has a dual mechanism of action that is specific to the CD2 surface marker and natural killer cells. As a result, the biologic does not appear to garner as much concern regarding global immunosuppression compared with other systemic immunosuppressive drugs (Walsh 2004).

TNF-targeted biologic agents. Other biologic agents have been developed to target either bound or unbound TNF, as TNF has multiple functions in immune responses. TNF promotes the proliferation of T cells, mediates cell destruction and cell-to-cell contact, induces changes and the permeability of endothelial cells/layer, enhances phagocytosis and cytotoxicity of granulocytes, induces the secretion of proinflammatory cytokines, enhances leukocyte migration, and damages tissues in excessive amounts (COPE 2009, Remicade 2009).

One such TNF-targeted biologic binds to both soluble and membrane-bound forms of TNF-alpha. The antibody-bound TNF triggers a complement-mediated lysis pathway and destroys cells expressing TNF-alpha (Remicade 2009). Another biologic that also targets TNF focuses on both TNF-alpha and beta (Enbrel 2009). TNF blockade reduces the expression of leukocyte migration markers, such as E-selectin and ICAM-1, and the serum level of certain cytokines, such as IL-6 (Enbrel 2009).

One concern that has emerged in using TNF-targeted biologics is the enhanced immune suppression at the "whole cell" level or through total elimination of TNF-secreting leukocytes (Lowes 2007). TNF-blocking biologics may bind to specific surface markers on T cells, dendritic cells, and/or keratinocytes, and this action may induce such biological changes as ligation or apoptosis (Boruchov 2005, Kruger-Krasagakis 2006). The increased apoptosis of dendritic cells raises this concern. Certain dendritic cells provide protective cell-mediated immunity, and binding may limit the immune response of these cells and ultimately suppress the protection dendritic cells provide (Boruchov 2005).

Interleukin-12 and -23 targeted biologic agents. The ability of the ILs to cause and react to signals makes them attractive targets for biologic therapy. The role of two ILs, 12 and 23, has gained momentum in the targeted treatment of psoriasis. IL-12 plays a role in generating proinflammatory secreting T cells and in differentiating cytotoxic T cells (Torti 2007, Berger 2000). IL-23 functions by indirectly stimulating the formation of proinflammatory cytokines produced primarily by endothelial cells and macrophages (Torti 2007). Both ILs also share a common subunit in their structure called p40 (Torti 2007). It is the combination of these factors that make IL-12 and IL-23 optimal marks for the application of biologics therapy.

IL-23 appears to play a critical role in the development of psoriasis, with genetic studies determining that genes for IL-23 and its receptor are tied to psoriasis (Elder 2010). Recent clinical trials successfully targeting the common subunit p40 (thus, limiting the expression of both IL-12 and IL-23) confirm the role of these ILs in psoriasis (Gottlieb 2007). The administration of the anti-p40 subunit agent has subsequently downregulated the expression of IL-12 and IL-23 and other proinflammatory cytokines in psoriatic lesions resulting in remediation (Toichi 2006).

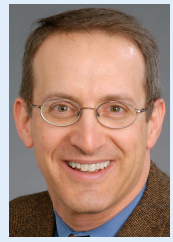
Possible future targets

Before a biologic can be developed, the pathological factors involved in psoriasis need to be discerned. Although much is known about the abnormal features of psoriasis, the initiating factors and the complicated interactions involved still remain a mystery. As new biologics are introduced into

MANAGED CARE CONSIDERATIONS

By Steven R. Feldman, MD, PhD, Professor of Dermatology, Pathology & Public Health Sciences, Wake Forest University School of Medicine, Winston Salem, N.C.

A year after joining the faculty of Wake Forest University School of Medicine in 2001, I became a psoriasis specialist. The options I had for treating psoriasis back then —topical tar, anthralin and corticosteroids, phototherapy, etretinate and methotrexate (MTX) — were rather limited. We did our best and were able to help most patients.



Steven R. Feldman, MD, PhD

Since then, numerous innovations — including vitamin D analogs, acitretin, improved formulations of cyclosporine and oxsoralen, and combination drug products — have facilitated the management of psoriasis patients. For patients with relatively localized disease, less messy vehicles and a better understanding of patients' adherence behaviors have been major advances. For patients with more extensive and severe disease, biologic drugs targeted to specific components of the immune system have been a quantum leap forward.

In particular, the tumor necrosis factor (TNF) inhibitors have been a godsend for patients with severe psoriasis. It has been wonderful helping a patient who was limping along on "traditional" systemic treatments now jumping for joy after life-changing improvement obtained by inhibiting TNF. The biologic approach provided greater efficacy than the gold-standard MTX, all the while avoiding the liver, pulmonary, renal, and hematologic toxicities that occurred with the traditional treatments.

I honestly thought that we would never again see — at least not in my lifetime — another quantum leap in psoriasis treatment like the step we took with TNF inhibitors. But I may have judged too quickly. The growing understanding of molecular mechanisms of the immune system has provided new targets for modulating immune function. Even more encouraging for the development of treatments targeted to psoriasis are the studies of the genetic properties of the disease. These studies are quickly identifying the key components of the immune system that have gone awry in psoriasis and may help identify targets that can address the disease while minimizing untoward general immunosuppressive effects.

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the market, researchers will be able to gain a better understanding of the roles and functions of inflammatory components. A greater knowledge of the mechanism of action and process will lead to a better understanding of psoriasis pathways (Lowes 2007). Some of the common pathways currently being explored in the development of new biologics involve inhibition of T-cell activation, depletion of pathogenic T cells, inhibition of leukocyte recruitment and inflammatory cytokines, and immune deviation (Schön 2005).

Conclusion

Although there has been steady and ongoing research, the initiating factors that cause psoriasis still evade detection. With the understanding that psoriasis is an immune-based disease and the development of biologic agents to treat the disease, researchers now have more options for determining and developing remediation targets. Continued research efforts into the immune pathology of psoriasis will enable scientists to discover appropriate and rational biologic targets for effective and safe psoriasis therapy.

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