A Pathogenetic Approach to Autoimmune Skin Disease Therapy: Psoriasis and Biological Drugs, Unresolved Issues, and Future Directions

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Psoriasis is a chronic inflammatory disease with a complex pathophysiology and a multigenic background. Autoimmunity and genetic hallmarks couple to confer the disease, which is characterized by chronic plaques (85-90% of all cases) and/or psoriasis arthritis (PsA), and involve the peripheral and sacro-iliac joints, nails, and skeleton. Dissecting the ethiopathogenetic mechanisms of psoriasis and PsA is a major basic research challenge. One important question is whether a single inflammatory mediator can be responsible for the interactive network that forms between immune cells and cytokines in this disease. Despite much progress, no research has yet been able to define a single model to explain the multifaceted pathogenesis of psoriasis and PsA. It is known that both the innate and adaptive immune systems are involved, antigen presenting cells and T lymphocytes play a prominent role, and that the deregulation of the T helper (Th)- 1/Th-2/Th-17/Th-23 axis is directly implicated in disease pathogenesis.

Pharmacological therapy for psoriasis has evolved with the development of human knowledge of the disease pathophysiology. Thus, the first “ethiopathogenetic” drugs (e.g., methotrexate, cyclosporin, and alefacept) inhibited T-cell activation directly or targeted coaccessory molecules implicated in T-cell activation. When the mechanism underlying psoriatic inflammation was accepted as a cytokine network disorder, more specific biologics were studied in murine models and were later used clinically. Tumor necrosis factor was the first successful target of cytokine inhibition therapy for psoriasis and PsA (e.g., infliximab, adalimumab, and etanercept). With the recently discovered role for Th-17 in autoimmunity, drugs targeting interleukin-23 (ustekinumab) have become accepted for the pharmacological treatment of psoriasis.

The expansion of pharmacological treatment options for psoriasis is not complete. As the knowledge of pathogenetic mechanisms increases, it may be possible to design therapeutic approaches that selectively target the ethiopathogenetic cells or cytokines while sparing the others. In this way, using a more targeted drug therapy may preserve the integrity of the immune system. Thus, one great struggle in treating this complex disease is the challenge to synthesize the “perfect” drug.

Keywords: IL-12/IL-23 antagonists; Psoriasis; T-helper differentiation; TNF-α antagonists; autoimmunity; biological therapy; cytokines; inflammation; keratinocyte proliferation/differentiation; psoriasis arthritis
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