PSORIASIS

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Psoriasis is a common skin disorder that affects ~ 2% of the United States population. Psoriasis vulgaris can be characterized as a chronic inflammatory dermatosis with varying degrees of severity that seldom manifests into a debilitating condition. To gain an appreciation of the complexity of psoriasis, an overview of the causes, pathogenesis, and therapeutic options are presented.

CAUSES OF PSORIASIS

Scientific evidence indicates that both genetic transmission and environmental factors are causes of psoriasis. Epidemiologic data support the association of hereditary linkage with early onset psoriasis; however, precise loci have yet to be identified, possibly because of the heterogenic nature of the disease. Thus far, a simple Mendelian genetic transference pattern (autosomal recessive or autosomal dominant) remains elusive. In all likelihood, genetic transmission is multifactorial and only predisposes an individual to psoriasis. This predisposition renders certain individuals more responsive to environmental stimuli such as physical injury, infection, medications, photosensitivity, and dry, cold weather, any of which can initiate psoriatic disease.

PATHOGENESIS

As a broad description, psoriatic epidermis exhibits the following pathologic characteristics: erythema from increased vascular permeability and microcirculatory changes, inflammation, hyperproliferation of the epidermis, and altered differentiation of epidermal cells. This pathogenic process results in sharply demarcated plaques with massive silver-white scales that most often symmetrically involve the elbows, knees, lower back, and buttocks.[1] Within each of these stages exists a complex array of cellular communication, migration, and differentiation.

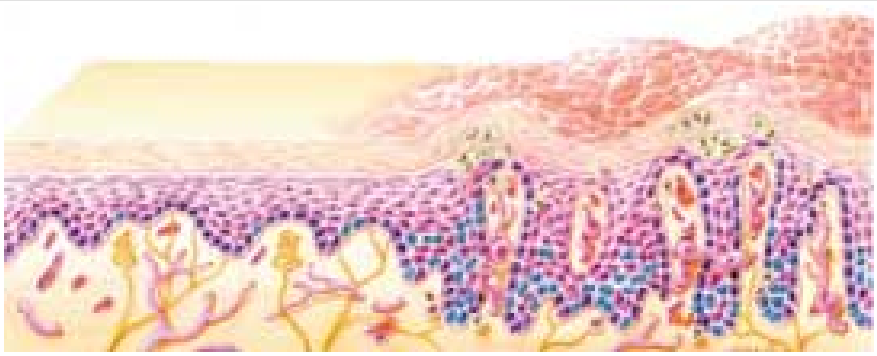
As with many disease processes, the pathogenesis of psoriasis involves numerous cell types such as polymorphonuclear leukocytes, dermal and epidermal cells, macrophages and lymphocytes (CD4+, CD8+, and T cells). In addition to the various cell types involved in pathogenesis, an equally diverse amount of regulatory mediators including cytokines (interleukins, interferon alfa), leukotrienes (LTs), and hydroxyeicosatetraenoic acids (HETEs) are produced to orchestrate the formation of psoriatic plaques.

A suggested pathogenic process of psoriasis involves the following factors: an eliciting agent (streptococci, drugs, ultraviolet B light) that stimulates the epidermis, the expression of immune-specific genes (HLA-C), the activation of leukocytes and lymphocytes, the production of cytokines and growth factors, and the formation of amplification factors (LTB4, 5-HETE, and 12-HETE) that produce upregulation of inappropriate repair mechanisms within the epidermis. The lack of appropriate downregulation at multiple steps promotes chronic disease.

The underlying offending agent implicated as the trigger for the formation of psoriatic lesions continues to be equivocal, but evidence points to a variety of antigenic stimuli. For example, a proposed mechanism for the role of streptococci as eliciting agents suggests that streptococcal toxin or proteins serve as a superantigen that binds to T-cell receptors, which results in their activation and stimulation.[2] After the provocation of T cells, additional lymphocytes and leukocytes are then recruited to the site via cytokine signaling.

Within the inflammatory process there is a genetic correlation between the specific HLA-Cw6 allele and psoriasis. This relationship is particularly evident in early onset psoriasis in contrast to late-onset psoriasis, in which a lucid HLA expression is absent. A possible pathogenic explanation for individuals who manifest the HLA-Cw6 allele is that of amino acid substitution within the epitope-binding pocket sequence.[2] This alteration in the HLA binding pocket could lead to miscommunication between the antigen-presenting cell such as a macrophage and T cells (primarily the CD4+ cells). The consequence of this miscommunication is the deleterious activation of T cells, which inevitably causes inflammation. In addition to the HLA-Cw6 allele, other class I and class II HLA antigens (including B13, Bw57, and DR7) demonstrate a connection to the development of early onset psoriasis.

Because most of the cells connected to psoriatic lesion formation can produce cytokines, their individual contribution remains unclear. Despite the inability to identify the cell type responsible for the cytokines in psoriasis, several cytokines have been isolated in connection with the initiation and persistence of psoriatic lesions.[2] Most notable are interferon gamma and interleukin 2, which have been reported to elicit or exacerbate psoriatic lesions. Additional cytokines, including in-



Psoriatic lesions develop in healthy skin as microscopic pathology is initiated by the inflammatory cascade.

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terleukin 1, interleukin 6, transforming growth factor β, interleukin 5, and many others have been detected in affected epidermis, depending on the method of detection. Although the precise cytokines implicated remain obscure, the chief function of cytokines is to regulate inflammatory events: endothelial cell adhesion, migration toward an inflammatory site, and functional activities at those sites.[2]

The subsequent formation of amplification factors is also a critical component in inflammation and has been traditionally a site for drug intervention. LTB_4 and 12-HETE emerge as the most important molecules in the amplification of an impending psoriatic lesion.[3] 12-HETE can cause skin inflammation and stimulate epidermal keratinocyte proliferation,[4] and LTB_4 is a chemoattractant for polymorphonuclear cells that cause intraepidermal neutrophil microabscesses.[5] Inhibition of the enzymes responsible for the production of those molecules has been reported to resolve psoriatic lesions. Although the application of LTB_4 and 12-HETE to the epidermis incites a response that is characteristic of psoriasis, a psoriatic lesion could not be elicited. Those findings suggest that LTB_4 and 12-HETE are probably instrumental in lesion formation but that other chemoattractants are required.[3]

Chronic psoriasis can be the result of a genetically determined susceptibility to triggers, environmental antigens, or autoantigens in addition to a defect in downregulation of the acute inflammatory regulators. Hence the intent of treatment consists of decreasing exposure to trigger agents, selectively inhibiting the immune system initiation process, and limiting production of amplification factors.

THERAPEUTICS

Historically, therapy has targeted cell proliferation, the role of arachidonic acid and its metabolites in the inflammatory pathways, and recently, focal immunosuppression. Given the extensive immunologic involvement in patients with psoriasis, immunosuppression seems a powerful approach to treatment. The macrolide tacrolimus is an effective systemic therapy. It is also effective when used topically after the lesions have been descaled and the skin has been occluded.[6,7] Other reports[8] refute the efficacy of tacrolimus. The more commonly known polypeptide cyclosporine has long been used systemically with good results, but evidence of its efficacy when used topically is noticeably lacking in the literature. To a lesser degree, mycophenolate mofetil has been used in the treatment of psoriasis. All 3 of those agents alter (at various levels) T-cell functions including humoral and cellular immunity, which is consistent with their role as immunosuppressive agents.

Agents directed at the arachidonate cascade include nutritionals (essential fatty acids, fish oils, and other oils), 5-lipoxygenase inhibiting drugs, and the glucocorticoids. With regard to the lipoxygenase-inhibiting drugs, only vitamin E might be considered as available for use by the compounder. The incorporation of vitamin E into topical products for psoriasis as an active agent, as an emollient, and as an antioxidant may prove useful when it is combined with other therapies. We affect the arachidonate cascade primarily via the glucocorticoids, which decrease arachidonate mobilization from tissue phosphatidyl stores. The effect of these agents is as significant as that of any other group of therapeutic agents but will be overlooked in deference to less well-known therapies. Consistent with glucocorticoid activity and in the area of "natural" medicine, sarsaparilla and glycyrrhetinic acid have probably never assumed their full scientific potential. Glycyrrhetinic acid has been shown to potentiate hydrocortisone activity by inhibiting 11-ß hydroxysteroid dehydrogenase (the enzyme by which cortisol is inactivated).[9] Sarsaparilla, another saponin-containing herb, has been shown in poorly controlled trials to treat psoriasis effectively.[10]

From coal tar, salicylic acid, psoralens, and anthralin to the use of vitamins A and D and their analogues, most therapies target psoriasis via the keratinizing process occurring in the dermal-epidermal space. Despite the consistent historic use of coal tar, its active component has been elucidated only recently. In 1985, quinoline and isoquinoline proved to be active coal tar extracts that are useful in normalizing keratosis.[11] Today, coal tar extracts are rarely used alone, but rather in combinations in which other agents might predominate therapeutically. In 1987, Schulze et al.[12] demonstrated that although coal tar did not add to the effectiveness of anthralin, it made short contact therapy significantly less irritating and more acceptable. Those authors report plaque clearance or near clearance in 92.7% of patients. Anthralin acts by reducing the mitotic rate of the rapidly reproducing keratinocytes.

Psoralens (methoxsalen, trioxsalen), which are usually used in combination with ultraviolet radiation, decrease cell proliferation via cell injury. Psoralens covalently bind deoxyribonucleic acid (DNA) on photoactivation. Methoxsalen, when used as a topical solution to decrease systemic side effects, provides good results.[13] In addition, an attempt to decrease the volume of bathing solution to decrease cost has been successful.[14]

Vitamin D_3 (1,25 dihydroxy D_3) and its analogues tacalcitol (1,24 dihydroxy D_3) and calcipotriene are safe and effective therapies for the treatment of psoriasis.[15-18] Vitamin D_3 (1,25 dihydroxy D_3) is significantly decreased in psoriatic patients.[19] As probable therapeutic targets, keratinocytes exhibit the lack of differentiation and hyperproliferation that is consistent with vitamin D deficiency while immune mediators proliferate in the surrounding tissues. Holick[15] recognized that defects of vitamin D metabolism are an effect rather than a cause of psoriasis. As a result, his treatment of psoriasis showed the efficacy of a 3-µg/gm 1,25 dihydroxy vitamin D_3 ointment. In a later double-blind study, more than 90% of patients showed significant improvement when treated with a concentration of 15 µg/gm. Tacalcitol produces the same effects with similar efficacy.[17,20] It is administered at 2 or 4 µg/gm as an ointment, and the chemical may soon be available in the United States; it was patented in 1976. Calcipotriene is currently available as Dovonex.®

Other psoriatic agents include fumaric acid and capsaicin. Fumaric acid and its

esters have been well studied in Europe.[21,22] Therapy consists of dimethyl fumaric acid ester and monoethyl fumaric acid ester, sometimes in combination with topical fumaric acid. Although this therapy is promising, questions about its effects on the gastrointestinal tract, the liver, and the kidneys remain. In a double-blind study,[23] capsaicin was used to treat pruritic psoriasis effectively, and appropriate neurogenic pathways have been implicated.

Psoriasis therapeutics might seem the domain of compounding pharmacy. The tools available to treat diseases such as psoriasis are more comprehensive than those available to the average ambulatory pharmacist. The disseminated knowledge of how to use each and every agent in the compounding armamentarium promotes the quality of life of the psoriatic patient.

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