



Psoriasis pathogenesis and current treatment: A Review

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ABSTRACT

Psoriasis is a multi-factorial skin disease with a complex pathogenesis. Various factors which have been suggested to play a key role in the pathogenesis are T cells, antigen presenting cells (APC's), keratinocytes, Langerhans' cells, macrophages, natural killer cells, an array of Th1 type cytokines. The age of onset, chronicity, physical, and psychosocial consequences of the disease cause psoriasis to have a significant impact on patient quality of life. Scalp psoriasis is no different, and effective treatment results in an improvement in quality of life. Successful management of scalp psoriasis includes topical therapies that are acceptable to the patient for mild-to-moderate disease, and systemic therapies for recalcitrant or moderate-to-severe disease. The factors influencing psoriasis severity, the indications for systemic treatments, the overall parameters to be considered in the treatment choice, life style interventions, and the recommendations for the use, screening, and monitoring of systemic therapies available including acitretin, cyclosporine, methotrexate, apremilast, adalimumab, etanercept, infliximab.

Keywords: Psoriasis, pathogenesis, systemic therapies

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease with a strong genetic predisposition and autoimmune pathogenic traits. The worldwide prevalence is about 2%, but varies according to regions ¹. It shows a lower prevalence in Asian and some African populations, and up to 11% in Caucasian and Scandinavian populations. The dermatologic manifestations of psoriasis are varied; psoriasis vulgaris is also called plaque-type psoriasis, and is the most prevalent type. The terms psoriasis and psoriasis vulgaris are used interchangeably in the scientific literature; nonetheless, there are important distinctions among the different clinical subtypes. About 90% of psoriasis cases correspond to chronic plaque-type psoriasis. The classical clinical manifestations are sharply demarcated, erythematous, pruritic plaques covered in silvery scales. The plaques can coalesce and cover large areas of skin. Common locations include the trunk, the extensor surfaces of the limbs, and the scalp ^{2,3}.

Also called flexural psoriasis, inverse psoriasis affects intertriginous locations, and is characterized clinically by slightly erosive erythematous plaques and patches. Guttate psoriasis is a variant with an acute onset of small erythematous plaques ⁴. It usually affects children or adolescents, and is often triggered by group-A streptococcal infections of tonsils. Pustular psoriasis is characterized by multiple, coalescing sterile pustules. Pustular psoriasis can be localized or generalized. Two distinct localized phenotypes have been described: psoriasis pustulosa palmoplantaris (PPP) and acrodermatitis continua of Hallopeau. Both of them affect the hands and feet; PPP is restricted to the palms and soles, and ACS is more distally located at the tips of fingers and toes, and affects the nail apparatus.⁵

Pathogenesis:

The hallmark of psoriasis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. The histology of the psoriatic plaque shows acanthosis (epidermal hyperplasia), which overlies inflammatory infiltrates composed of dermal dendritic cells, macrophages, T cells, and neutrophils. Neovascularization is also a prominent feature. The inflammatory pathways active in plaque psoriasis and the rest of the clinical variants overlap, but also display discrete differences that account for the different phenotype and treatment outcomes. Disturbances in the innate and adaptive cutaneous immune responses are responsible for the development and sustainment of psoriatic inflammation ⁶. An activation of the innate immune system driven by endogenous danger signals and cytokines characteristically coexists with an auto inflammatory perpetuation in some patients, and T cell-driven autoimmune reactions in others ⁷. Thus, psoriasis shows traits of an autoimmune disease on an (auto) inflammatory

background ⁸, with both mechanisms overlapping and even potentiating one another. The main clinical findings in psoriasis are evident at the outermost layer of the skin, which is made up of keratinocytes. However, the development of the psoriatic plaque is not restricted to inflammation in the epidermal layer, but rather is shaped by the interaction of keratinocytes with many different cell types (innate and adaptive immune cells, vasculature) spanning the dermal layer of the skin. The pathogenesis of psoriasis can be conceptualized into an initiation phase possibly triggered by trauma (Koebner phenomenon), infection, or drugs ⁶ and a maintenance phase characterized by a chronic clinical progression.

It is well known that dendritic cells play a major role in the initial stages of disease. Dendritic cells are professional antigen-presenting cells. However, their activation in psoriasis is not entirely clear. One of the proposed mechanisms involves the recognition of antimicrobial peptides (AMPs), which are secreted by keratinocytes in response to injury and are characteristically overexpressed in psoriatic skin. Among the most studied psoriasis-associated AMPs are LL37, β -defensins, and S100 proteins ⁹. LL37 or cathelicidin has been attributed a pathogenic role in psoriasis. It is released by damaged keratinocytes, and subsequently forms complexes with self-genetic material from other damaged cells. LL37 bound to DNA stimulates toll-like receptor (TLR) 9 in plasmacytoid dendritic cells (pDCs) ¹⁰. The activation of pDC is key in starting the development of the psoriatic plaque, and is characterized by the production of type I IFN (IFN- α and IFN- β). Type I IFN signaling promotes myeloid dendritic cells (mDC) phenotypic maturation, and has been implicated in Th1 and Th17 differentiation and function, including IFN- γ and interleukin (IL)-17 production, respectively

Treatment

Psoriasis is a chronic relapsing disease, which often necessitates a long-term therapy. The choice of therapy for psoriasis is determined by disease severity, comorbidities, and access to health care. Psoriatic patients are frequently categorized into two groups: mild or moderate to severe psoriasis, depending on the clinical severity of the lesions, the percentage of affected body surface area, and patient quality of life ¹¹. Clinical disease severity and response to treatment can be graded through a number of different scores. The PASI score has been extensively used in clinical trials, especially those pertaining to the development of the biologic drugs, and will be used throughout review. Mild to moderate psoriasis can be treated topically with a combination of glucocorticoids, vitamin D analogues, and phototherapy. Moderate to severe psoriasis often requires systemic treatment. The presence of comorbidities such as psoriasis arthritis is also highly relevant in treatment selection. Cyclosporine is a T cell-inhibiting immunosuppressant from the group of the calcineurin

inhibitors. Cyclosporine is effective as a remission inducer in psoriasis and as maintenance therapy for up to two years¹². Hypertension, renal toxicity, and non-melanoma skin cancer are significant potential side effects. Nephrotoxicity is related to the duration of treatment and the dose. Retinoids are natural or synthetic vitamin A-related molecules. Acitretin is the retinoid used in the treatment of psoriasis. It affects transcriptional processes by acting through nuclear receptors and normalizes keratinocyte proliferation and differentiation. Apremilast, a phosphodiesterase-4 inhibitor, inhibits the hydrolyzation of the second messenger cAMP. This leads to the reduced expression of pro-inflammatory cytokines TNF- α , IFN γ , and IL-12, and increased levels of IL-10. Apremilast was shown to have broad anti-inflammatory effects on keratinocytes, fibroblasts, and endothelial cells. The traditional systemic drugs are immunomodulators, which except for apremilast require close clinical monitoring due to the common side effects involving mainly the kidney and the liver. Methotrexate and cyclosporine are the only systemic therapies for psoriasis included in the World Health Organization (WHO) Model List of Essential Medicines, albeit for the indications of joint disease for the former and immunosuppression for the latter. The potential side effects of FAE and apremilast are usually not life-threatening, but might be sufficient to warrant discontinuation.

CONCLUSION

Psoriasis is a complex multifactorial disease for which various novel therapies have arisen in the past years. In spite of the refinement of the targeted therapies, psoriasis remains a treatable but so far not curable disease. The targeted therapies show high clinical efficacy for the inhibition of IL-23 and IL-17. Some degree of a persistent antipsoriatic effect by these therapies could be demonstrated after drug discontinuation, and argue for disease modification concept. This important finding will be followed up in ongoing and future studies. However, in other cases, an initial clinical response is only short lived, requiring treatment with a different biologic

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