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Psoriasis: An Introduction

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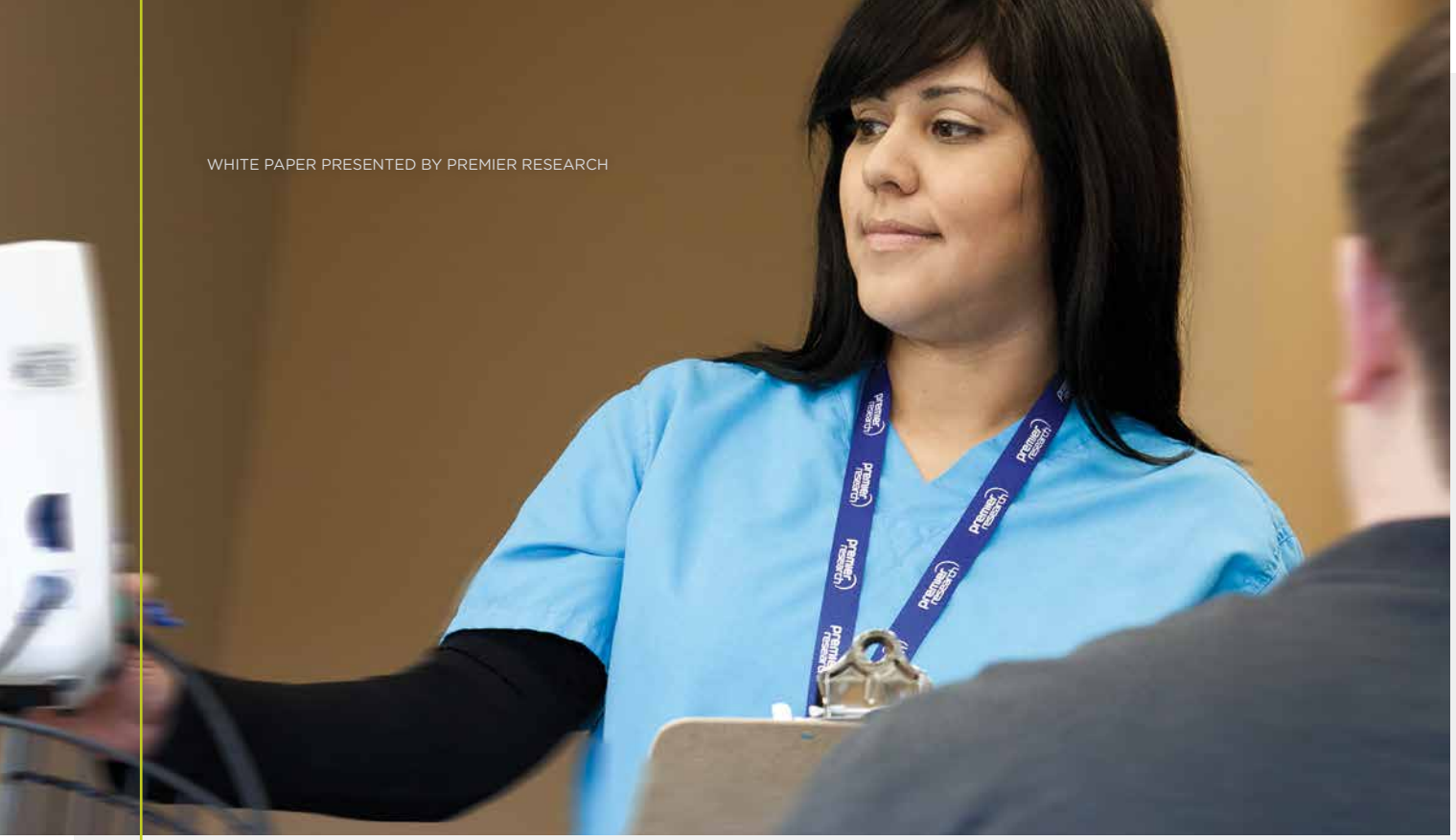
ABSTRACT

A systemic disease with a variety of comorbidities, psoriasis is a common condition with several clinical subtypes. In this white paper, we discuss the pathogenetic and clinical aspects of psoriasis, as well as the nuances of designing and conducting psoriasis clinical trials.

DERMATOLOGY



Introduction

Psoriasis is a chronic skin disorder and the most prevalent autoimmune disease in the U.S., affecting as many as 7.5 million people.[1] A recent study on the economic burden of psoriasis found that the estimated annual direct and indirect costs of psoriasis can be as high as $25,796 per person, or approximately $135 billion per year.[2]

Psoriasis is characterized by exaggerated and disordered epidermal cell proliferation and keratinization. Despite advances in our understanding of the disease, the chain of events that culminates in this aberrant keratinization has not yet been elucidated.[3] In this white paper, we explore the pathogenetic and clinical aspects of psoriasis and discuss nuances of designing psoriasis clinical trials for topical treatments.

Epidemiology of psoriasis

About two percent of the American population is afflicted with psoriasis. Psoriasis is primarily seen in adults, but approximately 10-15 percent of psoriasis presents in childhood. Approximately 80 percent of those affected with psoriasis have mild to moderate disease, while 20 percent have moderate to severe psoriasis that affects more than five percent of their body surface area.[4]

Up to 40 percent of people with psoriasis – generally the more severely affected – have a concomitant destructive arthritis, called psoriatic arthritis.[1] For these patients, skin and joint symptoms tend to flare and remit synchronously.

Despite advances in our understanding of the disease, the chain of events that culminates in this aberrant keratinization has not yet been elucidated.

Pathophysiology of psoriasis

Psoriasis is a complex multifactorial condition related to a combination of genetic, immunological, and environmental factors.

Psoriasis is a genetic disease, although the mechanisms of its inheritance are complex and involve at least nine different genes. The genetic basis of psoriasis is supported by the increased incidence of the disease observed in first- and second-degree relatives of patients with psoriasis, as well as the two- to threefold increased risk in monozygotic twins compared to dizygotic twins.[5] If both parents have psoriasis, their offspring have an 80 percent chance of developing psoriasis. Genome wide association studies have identified approximately 50 genetic loci associated with psoriasis risk.[6] However, the interactions between these genes and the phenotypic traits remain poorly understood at present.[7]

Psoriasis arises as a result of dysregulated interactions of the innate and adaptive immune system in the context of skin epithelium and connective tissue.[8] The pathophysiology of psoriasis involves the activation and proliferation of T helper cells, in particular Th-17 cells. These activated Th-17 cells produce the clinical hallmarks of psoriatic lesions:

+ **Erythema**, from inflammation
+ **Scaling**, from abnormal epidermal differentiation, histologically called parakeratosis
+ **Induration**, from epidermal hyperproliferation

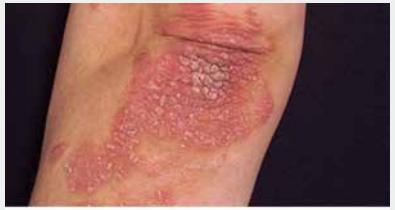
There are several environmental triggers which are known to exacerbate psoriasis. Among them are emotional stress, injury to the skin (Koebner phenomenon), some types of infection (e.g., streptococcus), and reactions to certain drugs, including lithium, beta-blockers, anti-malarials, non-steroidal anti-inflammatory drugs, and tetracyclines. These triggers are likely most relevant in individuals with a genetic predisposition to developing psoriasis.

Subtypes of psoriasis

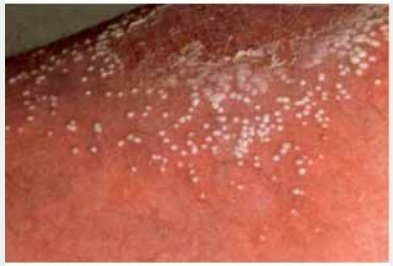
Psoriasis is a clinically heterogenous disease with several clearly-defined subtypes:

+ **Chronic plaque psoriasis** is by far the most common, comprising 80-90 percent of cases. Chronic plaque psoriasis is characterized by erythema, scaling and induration of silvery plaques, which are often bilateral and have a predilection for the extensor surfaces of the body, such as the elbows and knees.
+ **Inverse psoriasis**, also known as flexural psoriasis, is concentrated in the flexural folds, including the axillae, groin, inframammary areas, gluteal cleft, and skin folds. Inverse psoriasis frequently lacks the scale seen in chronic plaque psoriasis.
+ **Pustular psoriasis** is characterized by small pus-filled vesicles that are surrounded by erythema, and can be either generalized or localized to the hands and feet. In some cases, pustular psoriasis is precipitated by withdrawal of systemic or potent topical corticosteroids or by infection.[9]
+ **Guttate psoriasis** typically presents with small, coin-shaped lesions diffusely distributed on the trunk and extremities, and is often preceded by streptococcus infection.
+ **Erythrodermic psoriasis** most often represents a severe exacerbation of chronic plaque psoriasis, with total body erythema and scaling.
+ **Palmo-plantar psoriasis** is limited to the hands and feet and occurs without pustules. Its relationship to the other subtypes of psoriasis has been questioned.

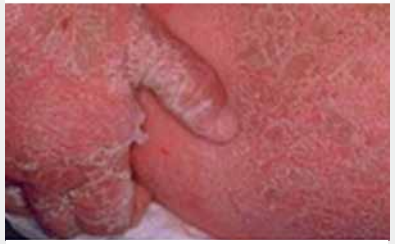
Figure 1. Sub-types of psoriasis



Chronic Plaque Psoriasis



Pustular Psoriasis



Erythrodermic Psoriasis

Quality of life and psychological aspects of psoriasis

Although psoriasis itself often does not affect survival, it can cause significant detriment to quality of life.[10] In fact, patients with psoriasis have a reduction in their quality of life similar to, or worse than, patients with other chronic diseases, such as heart disease and diabetes.[11] Up to 60 percent of patients with psoriasis describe stress as a key trigger or exacerbator of their disease.[12] Despite this, most clinical trials of new psoriasis treatment focus on objective physical measures for the primary endpoint of efficacy.

Comorbidities of psoriasis

Many of the comorbidities of psoriasis, other than psoriatic arthritis, have only been discovered in the past decade, but have changed perceptions of the disease.

Metabolic syndrome. This is the name for a cluster of conditions – increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels – that occur together, increasing the risk of heart disease, stroke, and diabetes.[13] Metabolic syndrome is found in 40 percent of patients with psoriasis, compared to 23 percent of the general population.

Cardiovascular disease. Patients with severe psoriasis are 58 percent more likely to have a major cardiac event and 43 percent more likely to have a stroke.

Type 2 diabetes. Patients with severe psoriasis are 30 percent more likely to have type 2 diabetes.

Inflammatory bowel disease. Ten percent of women with psoriasis develop some form of inflammatory bowel disease, such as Crohn's disease or ulcerative colitis. In fact, the incidence of Crohn's disease and ulcerative colitis is 3.8 to 7.5 times greater in patients with psoriasis than in the general population.[14]

Uveitis. Approximately 7 percent of people with psoriatic arthritis will develop uveitis. Uveitis also tends to develop more frequently in patients with pustular psoriasis.[15]

Depression. The prevalence of depression in patients with psoriasis may be as high as 50 percent.[16]

Designing and conducting psoriasis clinical trials

In clinical practice, broad global assessments of psoriasis disease activity and its effect on quality of life are used to assess the severity of a patient's disease and their response to treatment. In clinical trials, more objective, validated instruments are required as clinically meaningful measures of disease severity.

Tools for evaluating treatment efficacy

Generally, psoriasis clinical studies involve two major efficacy endpoints: the Investigator's Global Assessment (IGA) scale and the Psoriasis Area and Severity Index (PASI).

Investigator's Global Assessment (IGA) scale. Developed with input from regulatory authorities and clinical trial investigators, IGA is a highly valued endpoint by the FDA for almost all dermatology clinical study indications, including psoriasis, acne, and atopic dermatitis.[17] IGA is typically the primary endpoint in clinical studies of topical psoriasis treatments.

Figure 2. A five-point IGA scale for psoriasis

Score	Category	Description
0	Clear	No erythema, induration, or scale
1	Almost clear	Faint (pink) erythema, minimal plaque elevation, occasional fine scale
2	Mild	Light red color, mild plaque elevation, fine scale dominates
3	Moderate	Definite red color, moderate plaque elevation, coarse scale dominates
4	Severe	Bright red coloration, marked plaque elevation, thick non-tenacious scale dominates

The IGA scale preferred by the Dermatology Division at the FDA is a five-point scale ranging from 0 (clear) to 4 (severe). (See Figure 2) To have IGA success, one must have an end-of-study designation of 'clear' or 'almost clear', and also exhibit a two-point improvement from baseline. Hence, if a patient has 'mild' disease at baseline, he/she must reach 'clear' at the end-of-study. If a patient has 'moderate' disease at baseline, he/she must reach 'almost clear'. And, if a patient is classified as 'severe' at baseline, he/she must still reach 'almost clear', even though that requires a three-point improvement.

Psoriasis Area and Severity Index (PASI-75). PASI is the other major psoriasis endpoint, and is especially important for systemic therapies. Psoriasis clinical trials involving oral or biologic therapies typically use IGA and PASI as co-primary endpoints of response rate.

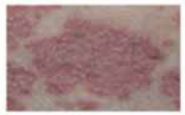
Figure 3. Psoriasis Area and Severity Index

Area	Head	Arms
	☐0% ☐<10% ☐10-29% ☐30-49% ☐50-69% ☐70-89% ☐90-100%	☐0% ☐<10% ☐10-29% ☐30-49% ☐50-69% ☐70-89% ☐90-100%
Erythema (redness)	☐0 ☐1 ☐2 ☐3 ☐4	☐0 ☐1 ☐2 ☐3 ☐4
Induration (thickness)	☐0 ☐1 ☐2 ☐3 ☐4	☐0 ☐1 ☐2 ☐3 ☐4
Desquamation (scaling)	☐0 ☐1 ☐2 ☐3 ☐4	☐0 ☐1 ☐2 ☐3 ☐4

Area	Trunk	Legs
	☐0% ☐<10% ☐10-29% ☐30-49% ☐50-69% ☐70-89% ☐90-100%	☐0% ☐<10% ☐10-29% ☐30-49% ☐50-69% ☐70-89% ☐90-100%
Erythema (redness)	☐0 ☐1 ☐2 ☐3 ☐4	☐0 ☐1 ☐2 ☐3 ☐4
Induration (thickness)	☐0 ☐1 ☐2 ☐3 ☐4	☐0 ☐1 ☐2 ☐3 ☐4
Desquamation (scaling)	☐0 ☐1 ☐2 ☐3 ☐4	☐0 ☐1 ☐2 ☐3 ☐4

PASI is a relatively complex assessment which divides the body into four regions: head/neck, upper extremities, lower extremities, and trunk. Each body region is assessed for extent (area) of disease involvement (based upon a 0-6 grading system) and severity of the clinical signs erythema, scaling, and induration, each rated 0-4. (See Figures 3 and 4) The body regions are weighted for their respective percentage of total body surface area. PASI scores range from 0-72.

Figure 4. PASI severity scoring

Intensity	Absent	Mild	Moderate	Severe	Very severe
Erythema	 Score 0	 Score 1	 Score 2	 Score 3	 Score 4
Scaling	 Score 0	 Score 1	 Score 2	 Score 3	 Score 4
Induration	 Score 0	 Score 1	 Score 2	 Score 3	 Score 4

Of note, the PASI concept of a disease 'Area and Severity Index' has been extended to atopic dermatitis (eczema), where it is called the Eczema Area and Severity Index (EASI). EASI has different clinical signs but also uses a 0-72 scale. In the case of vitiligo, a related scale called the Vitiligo Area Scoring Index (VASI) has been developed, with a 0-100 scale.

Instruments for evaluating quality of life

Psoriasis clinical trials may also incorporate quality-of-life metrics, such as the Dermatology Life Quality Index (DLQI). Developed in 1994, the DLQI was the first dermatology-specific quality-of-life instrument. It is a simple, validated, 10-question questionnaire that has been used in over 40 different skin conditions in over 80 countries. Today, the DLQI is the most widely used quality-of-life metric in psoriasis clinical trials. Interestingly, the correlation between PASI and DLQI is not always high. However, a recent systematic review found that mean PASI and DLQI correlate predictably in patients with chronic, moderate-to-severe plaque psoriasis who are undergoing treatment with biologic agents.[18]

Studying topical treatments in psoriasis

The outermost layer of the skin – the stratum corneum – is an excellent barrier to penetration of foreign materials. Only one to five percent of even highly penetrable topical drugs actually enter the epidermis. Nevertheless, topical drugs offer the opportunity for local efficacy without the side effects of systemic exposure. Although psoriatic lesions are thick, psoriatic skin is more permeable than normal skin per unit area, making the overall permeability of topical treatments in psoriasis often roughly equivalent to the permeability in normal patients.

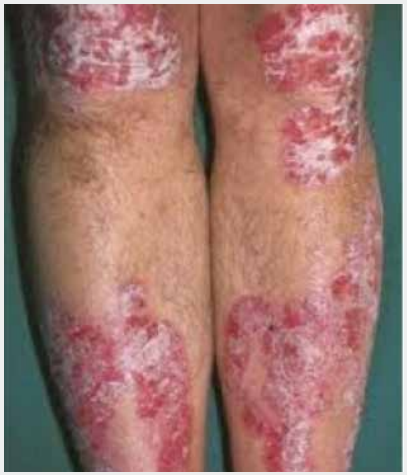
Clinical studies of psoriasis can take advantage of the ease of visual assessment, as well as the multiplicity and frequent symmetry of lesions. Since the efficacy endpoints in psoriasis clinical studies (e.g., IGA and PASI) rely completely on visual assessment, 'left/right' studies can be an efficient mechanism to achieve proof of concept (POC) in early development.

In a left/right study, also known as a self-control study, the investigative drug is applied to one arm or leg, while the opposite arm or leg receives the vehicle. The side that receives the investigative drug is randomly assigned. One of the main advantages of a left/right study is that it eliminates inter-individual variability. Thus, less than half the number of subjects is required for statistical power as compared to an inter-individual study, where a patient receives either active drug or vehicle, but not both.

Potential disadvantages of a left/right study are occasional patient confusion over left versus right application, or deliberate use of only one material on both sides if that material appears to be more efficacious.

Sponsors should be aware that the FDA will only allow the intra-individual left/right study design in early Phase II studies. All Phase IIb and Phase III topical studies must utilize an inter-individual design.

Figure 5. Symmetry of psoriasis



Conclusion

A chronic disease with high comorbidity, psoriasis is a common and complex disease that remains the focus of many clinical studies. The World Health Organization estimates that at least 100 million individuals are affected by psoriasis worldwide, and many suffer due to incorrect or delayed diagnosis, inadequate treatment options, insufficient access to care, and social stigmatization.[19] Currently, there is no cure for psoriasis, but advances in treatment – particularly biologics – are bringing new hope to patients living with this disabling condition.

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Dr. Welgus has extensive experience in pharmaceutical R&D and in academia. He supported the development efforts of several companies through his own consultancy company and previously was Chief Medical Officer at Nycomed US and Vice President and Head of Dermatology and Inflammation at Pfizer Global R&D in Ann Arbor, Michigan.

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