

WHITE PAPER PRESENTED BY PREMIER RESEARCH

The Changing Landscape of Psoriasis Treatment



ABSTRACT

Over the past two decades, biologic therapies have revolutionized the treatment of psoriasis, with more than half of treated patients now able to achieve essentially complete clearing of their disease. In this white paper, we will explore the history of psoriasis treatment – including topical and oral therapies – and the evolution of biologics.

DERMATOLOGY



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.

Introduction

Psoriasis is a common, chronic skin disorder, affecting as many as 7.5 million people in the U.S.¹ and at least 100 million worldwide.² Although psoriasis itself often does not affect survival, it is associated with a variety of comorbidities, including psoriatic arthritis, metabolic syndrome, cardiovascular disease, type 2 diabetes, inflammatory bowel disease, and depression.^{3,4} It can also cause significant detriment to quality of life.⁵ 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.⁶

Prior to 1955, psoriasis was treated with a wide variety of therapeutic agents ranging from arsenic and ammoniated mercury to chrysarobin, anthralin, and tars. Topical

corticosteroids have been widely used in psoriasis and other skin conditions since 1951, and have been the standard therapy for inflammatory skin diseases. Usage of methotrexate as a treatment for psoriasis became more common in the 1970s.⁷

Over the past 60 years, the landscape of psoriasis treatment has changed dramatically. Advances in psoriasis therapy have accelerated over the past two decades, and have been life changing for those who are severely afflicted with the condition. In this white paper, we explore the history of psoriasis treatment, including the recent evolution of biologics.

Pathogenesis of psoriasis

Psoriasis is clinically heterogeneous disease characterized by excessive growth and aberrant differentiation of keratinocytes.

The pathogenesis of the disease is complex and multifactorial, involving genetic, immunological, and environmental factors.

Psoriasis has a genetic basis, although the mechanisms of its inheritance are complex and involve at least nine different genes. Genome-wide association studies have identified approximately 50 genetic loci associated with psoriasis risk.⁸ Of note, the single nucleotide polymorphisms in many of these loci are also associated with other autoimmune diseases, including inflammatory bowel disease and ankylosing spondylitis.⁹

From an immunological standpoint, psoriasis arises as a result of dysregulated interactions of the innate and adaptive immune systems in the context of skin epithelium and connective tissue.¹⁰ The genetic loci associated with psoriasis risk highlight fundamental immunological processes and pathways that appear crucial for disease susceptibility, including nuclear factor kappa B (NF-κB) signaling, the interleukin (IL)-23/IL-17 axis, innate immune signaling, and the type I interferon pathway.

One example of an important immunogenetic association is gene variants in the IL-23 receptor (IL-23R) that appear to confer protection against psoriasis.¹¹

The trigger of the keratinocyte response in psoriasis is thought to be 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.

The newest therapies for psoriasis target its immune components, and may predict potential treatments for other inflammatory diseases.¹²

Evaluating the efficacy of psoriasis therapies

Generally, clinical studies of psoriasis treatments 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 the most common clinical study endpoint for almost all dermatology indications, including psoriasis, acne, and atopic dermatitis.¹³ IGA is typically the primary endpoint in clinical studies of topical psoriasis treatments.

The IGA scale preferred by the Dermatology Division at the FDA is a five-point scale ranging from 0 (clear) to 4 (severe).

Figure 1. Example of a five-point Investigator’s Global Assessment (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

In the context of a clinical trial, IGA success is defined as an end-of-study designation of ‘clear’ or ‘almost clear’, along with a two-point improvement from baseline. Of note, patients who enter a study with severe disease must still reach ‘almost clear’ – a three-point improvement – in order to qualify for IGA success.

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

PASI is a complex assessment which divides the body into four regions: head/neck, upper extremities, lower extremities, and trunk. Each body region is assessed for:

- + Percentage area of disease involvement (based upon a 0-6 grading system)
- + Severity of the pathognomonic signs of psoriasis: erythema, scaling, and induration (lesion thickness), each rated 0-4 (see Figure 3)

The body regions are weighted for their respective percentage of total body surface area. PASI scores range from 0-72. A common benchmark in clinical trials of psoriasis is PASI 75, or a 75 percent reduction in the PASI score.

Figure 2. Psoriasis Area and Severity Index

Area	Head						Arms										
	<input type="checkbox"/> 0%	<input type="checkbox"/> <10%	<input type="checkbox"/> 10-29%	<input type="checkbox"/> 30-49%	<input type="checkbox"/> 50-69%	<input type="checkbox"/> 70-89%	<input type="checkbox"/> 90-100%	<input type="checkbox"/> 0%	<input type="checkbox"/> <10%	<input type="checkbox"/> 10-29%	<input type="checkbox"/> 30-49%	<input type="checkbox"/> 50-69%	<input type="checkbox"/> 70-89%	<input type="checkbox"/> 90-100%			
Erythema (redness)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Induration (thickness)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Desquamation (scaling)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Area	Trunk						Legs										
	<input type="checkbox"/> 0%	<input type="checkbox"/> <10%	<input type="checkbox"/> 10-29%	<input type="checkbox"/> 30-49%	<input type="checkbox"/> 50-69%	<input type="checkbox"/> 70-89%	<input type="checkbox"/> 90-100%	<input type="checkbox"/> 0%	<input type="checkbox"/> <10%	<input type="checkbox"/> 10-29%	<input type="checkbox"/> 30-49%	<input type="checkbox"/> 50-69%	<input type="checkbox"/> 70-89%	<input type="checkbox"/> 90-100%			
Erythema (redness)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Induration (thickness)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Desquamation (scaling)	<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4		<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

Figure 3. 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

Treatments for psoriasis

Topical treatments

For patients with mild to moderate psoriasis, topical corticosteroids and vitamin D derivatives remain the mainstays of treatment. Other topical treatments include anthralin, coal tar, emollients, salicylic acid, and tazarotene. These topical medications may be used alone, or in combination with other medications.

Topical corticosteroids. Available in a variety of strengths and formulations, these powerful anti-inflammatory drugs are the most frequently prescribed medications for mild to moderate psoriasis. They slow cell turnover by suppressing the immune system, reducing inflammation, and relieving associated pruritus. Unfortunately, topical corticosteroids do not tend to be effective or practical for treating moderate to severe psoriasis.

Vitamin D analogues. Synthetic forms of vitamin D, such as calcipotriene and calcitriol, are cell differentiators, which help to slow down and correct the hyperproliferative state in psoriasis. They can be used chronically, but are often irritating.

Phototherapy

Moderate to severe psoriasis often necessitates treatment with phototherapy, the use of ultraviolet light to slow the growth of new skin cells. Phototherapy treatment includes narrow-band and broad-band ultraviolet B (UVB) and UVA (UVA) treatment. UVB light may be used alone, or in combination with topical tar or anthralin products. UVA penetrates more deeply into the skin than UVB, and it is often used in combination with psoralen drugs (i.e., PUVA).

Oral Medications

Methotrexate. Methotrexate (MTX) has been used to treat psoriasis for over half a century. And yet, clinical data characterizing its efficacy and safety are sparse. Recent meta-analyses of the efficacy and safety of MTX found that over 45 percent of treated patients achieve PASI 75 after 12-16 weeks, but adverse events may be treatment limiting in approximately seven percent of patients treated for six months. Methotrexate can infrequently produce irreversible liver damage and bone marrow suppression, even in the low doses used for psoriasis. Neither the efficacy nor the risk-to-benefit ratio in psoriasis compare to the critical role MTX plays in the treatment of rheumatoid arthritis.¹⁴

Cyclosporine. First used to help prevent rejection in organ transplant patients, cyclosporine was approved for use in patients with severe psoriasis and otherwise normal immune systems in 1997. Cyclosporine has a quick onset of effect in psoriasis, but relapse after the drug is withdrawn is almost universal.¹⁵ Individuals previously treated with phototherapy, methotrexate, other immunosuppressive agents, or radiation therapy are at increased risk of developing skin cancer or lymphoma when taking cyclosporine. Treatment with cyclosporine may also lead to nephropathy and hypertension. As such, cyclosporine should only be used as short-term therapy when no other reasonable treatment choices exist.¹⁶

Acitretin. A synthetic form of vitamin A, acitretin is the only oral retinoid approved by the FDA specifically for treating psoriasis. Unlike methotrexate and cyclosporine, acitretin is not immunosuppressive. Retinoids help control cell multiplication, including the speed at which skin cells grow and shed, but their exact mechanism in psoriasis is unknown. If monotherapy with acitretin is inadequate, it can be used in combination with other treatments, particularly UVB phototherapy.¹⁷

Apremilast. In March 2014, the FDA approved apremilast (brand name Otezla®), an oral phosphodiesterase (PDE)-4

inhibitor, for the treatment of active psoriatic arthritis.¹⁸ The dominant phosphodiesterase expressed in immune cells, PDE-4 degrades cyclic AMP (cAMP) into AMP. PDE-4 inhibition elevates intracellular cAMP, which can downregulate inflammatory responses through mechanisms such as partial inhibition of the expression of inflammatory cytokines and increased expression of anti-inflammatory mediators, such as IL-10.¹⁹

The safety and efficacy of apremilast were evaluated in three clinical trials involving 1,493 patients with active psoriatic arthritis.^{20,21} These studies found the apremilast effective in improving the signs and symptoms of psoriatic arthritis, as well as physical function, for up to 52 weeks. In September 2014, apremilast was also approved for patients with moderate to severe plaque psoriasis for whom systemic therapy or phototherapy is appropriate.²² Apremilast's efficacy is less than methotrexate, with only 33 percent of patients achieving PASI 75 after 16 weeks of treatment, but it is safe with common side effects limited to the gastrointestinal tract.²³

Biologics

The revolution in psoriasis treatment has come in the biologics arena. Advances in our understanding of disease pathogenesis had led to targeted immunomodulatory, or biologic, therapies that act on the cytokine pathways that are upregulated in psoriasis.

TNF Inhibitors. The revolution began with the tumor necrosis factor (TNF) inhibitors:

- + **Etanercept** (brand name Enbrel®). In a Phase III study, nearly half of patients treated with etanercept achieved PASI 75 after 12 weeks, as compared with four percent in the placebo group.²⁴ Etanercept is self-injected once or twice weekly.
- + **Infliximab** (brand name Remicade®). In a Phase III study, nearly 80 percent of patients randomized to infliximab achieved PASI 75 through 23 weeks of therapy.²⁵ Infliximab's use is limited by an intravenous route of administration.



Further characterization of the pathways that underlie the disease will help to identify novel disease mechanisms and, potentially, new therapeutic targets.

- + **Adalimumab** (brand name Humira®). In a Phase III trial comparing adalimumab, MTX and placebo, adalimumab provided significantly greater efficacy, with 80 percent of patients achieving PASI 75 after 16 weeks.²⁶ Adalimumab is self-administered by subcutaneous injection every other week.

While the anti-TNF biologics are also very helpful in the treatment of rheumatoid arthritis, they only produce a 20 percent improvement in signs and symptoms of RA (ACR 20) in about 25-30 percent of patients, compared to placebo, and a 50 percent improvement in (ACR 50) in about 15 percent of patients.

IL-12/23 inhibitors. The TNF inhibitors were followed by ustekinumab (brand name Stelara®), a monoclonal antibody that targets the p40 subunit shared by IL-12 and IL-23 (IL-12/23).²⁷ The importance of the IL-23/Th17 axis in the development of psoriasis is underscored by the relatively superior efficacy of ustekinumab compared to the TNF inhibitors. A PASI 75 response is achieved in about 70 percent of treated subjects after 12 weeks of dosing. An important advantage of ustekinumab is that maintenance therapy only requires injections every three months.

IL-17 Inhibitors. More recently, the psoriasis treatment landscape has been changed by the IL-17A inhibitors:

- + **Secukinumab** (brand name Cosentyx®). Secukinumab is approved for adults with moderate to severe plaque psoriasis that involves large areas or many areas of the body, and who may benefit from taking systemic therapy or phototherapy (alone or with systemic therapy). It is also approved for active psoriatic arthritis and active ankylosing spondylitis.²⁸ Secukinumab acts on the Th17 pathway by blocking cytokine IL-17A. PASI 75 responses approaching 80 percent are observed after 12 weeks of treatment and PASI 90 improvements of 70 percent are reported after 16 weeks of treatment. Maintenance therapy is every four weeks.

- + **Ixekizumab** (brand name Taltz®). Ixekizumab is a humanized anti-IL-17 monoclonal antibody. It is approved for adults with moderate to severe plaque psoriasis who may benefit from taking systemic therapy or phototherapy. In a Phase II study, treatment with ixekizumab resulted in a higher likelihood of IGA success than placebo, as well as significant improvements in Dermatology Life Quality Index (DLQI) scores, with no serious adverse events. Notably, ixekizumab showed efficacy in difficult-to-treat areas, such as the scalp and nails.²⁹ Two Phase III studies of ixekizumab compared with either placebo or etanercept showed that ixekizumab had greater efficacy over 12 weeks, with nearly 90 percent of patients achieving PASI 75 and over 83 percent experiencing IGA success when ixekizumab was given every two weeks.³⁰

Brodalumab (brand name Siliq®). Approved by the FDA in February 2017, brodalumab is a human monoclonal antibody directed against IL-17RA, the receptor of IL-17A.³¹ Brodalumab is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. Findings from a Phase III trial of brodalumab showed that, after three months of treatment, up to 83 percent of people achieved PASI 75 and up to 76 percent experienced IGA success.³² There were four completed suicides in the psoriasis clinical trials of brodalumab and this drug carries a black box warning for suicidal ideation and behavior. Brodalumab is only available through a restricted program under a Risk Evaluation and Mitigation Strategy.³³

Figure 4. Biologic and small molecule inhibitors for the treatment of moderate to severe psoriasis

Drug	Target	Formulation
Apremilast	Phosphodiesterase 4 (PDE-4)	Small molecule inhibitor (oral)
Etanercept	TNF-receptor	Human p75 Fc fusion protein
Infliximab	TNF-alpha	Chimeric monoclonal (IgG1)
Adalimumab	TNF-alpha	Human monoclonal (IgG1)
Ustekinumab	Anti-IL12/IL-23	Human monoclonal (IgG1)
Secukinumab	IL-17 receptor	Human monoclonal (IgG1)
Ixekizumab	IL-17A	Human monoclonal (IgG4)
Brodalumab	IL-17A	Human monoclonal (IgG2)

Conclusion

Advances in our understanding of the genetic, immunological, and environmental factors that contribute to the pathogenesis of psoriasis have led to the development of targeted, precision therapies that alleviate patient morbidity and improve quality of life, especially for patients with moderate to severe disease. However, considerable variability has been seen in individual response to biologics, and studies are needed to characterize patient- and disease-specific immune and molecular features that help to predict response to therapy. In addition, further characterization of the pathways that underlie the disease will help to identify novel disease mechanisms and, potentially, new therapeutic targets.

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