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Psoriasis: pathogenesis, progression, and treatment

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Thesis

PSORIASIS: PATHOGENESIS, PROGRESSION, AND TREATMENT

by

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PSORIASIS: PATHOGENESIS, PROGRESSION, AND TREATMENT

SPENCER SHIN

ABSTRACT

Psoriasis (PsO) is a chronic, immune-mediated skin disease that arises from a complex interplay of genetic predisposition, environmental triggers, and immune dysregulation. Early-onset PsO is associated with familial inheritance and specific loci such as HLA-Cw6, along with polymorphisms in genes linked to the IL-23/Th17 axis. Environmental factors that take the form of infections, physical trauma, air pollution and stress can trigger or exacerbate flares. A dysregulated immune system, including abnormal keratinocytes and dendritic cell and T cell interactions, drives psoriatic inflammation via cytokines and intracellular pathways such as NF- κ B. Treatment approaches can look like traditional topicals to targeted biologics and novel delivery systems. First-line topical agents like vitamin D analogs, corticosteroids, retinoids, calcineurin inhibitors, and emollients effectively address mild to moderate PsO, often as combination therapies. Phototherapy, specifically narrowband UVB, has shown to be an important adjunct or alternative. Systemic treatments like methotrexate and cyclosporine have spurred the development of biologics: TNF- α inhibitors and IL-12/23, IL-17, and IL-23 inhibitors. These induce better skin clearance with lower toxicity. Nanofiber formulations and microneedle patches are additional new developments that seek to enhance drug penetration and minimize side effects. Attention has also turned to modifiable lifestyle factors, as weight management and anti-inflammatory diets may mitigate PsO symptoms. Additionally, treating gut and skin dysbiosis with probiotics or

fecal microbiota transplantation is continually being explored. By integrating pharmacologic treatments, innovative drug delivery, and holistic care, PsO treatment can become individualized with patients seeing sustained remission and improved quality of life.

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LIST OF ABBREVIATIONS

BB.....	Broad Band
CNI.....	Calcineurin Inhibitor
FMT.....	Fecal Microbiota Transplantation
GR.....	Glucocorticoid receptor
IFN.....	Interferon
IL.....	Interleukin
NB.....	Narrow Band
PARPs.....	Poly (ADP-ribose) polymerases
PASI.....	Psoriasis Area and Severity Index
PASI(#).....	# % or greater reduction (sign of improvement) of PASI score
PED.....	Prescription Emollient Device
PsO.....	Psoriasis
SCH.....	Stratum Corneum Hydration
sPGA.....	Static Physician's Global Assessment
TEWL.....	Trans epidermal water loss
TNF- α	Tumor necrosis factor-alpha
TNFR.....	TNF-Receptor
TRIM.....	Tripartite motif protein
UV.....	Ultraviolet

INTRODUCTION

Psoriasis is a chronic autoimmune skin disorder characterized by inflammation driven primarily by immune cells such as dendritic cells, T-cells, and inflammatory cytokines including tumor necrosis factor alpha (TNF- α)¹. Clinically, psoriasis is characterized by clearly defined red plaques covered by silvery scales and thickening of the epidermis (acanthosis)¹. The disease is known to have negative impacts on patients' quality of life and additional associations have been noted between the disease and other systemic inflammatory conditions like cardiovascular and kidney diseases, arthritis, colon, lung, breast, and skin cancers^{2,10}. While the direct cause of psoriasis remains under investigation, the increasing prevalence of psoriasis in the U.S. and other countries has sparked interest in identifying novel, effective treatment and diagnosis methods^{3,4,6,7}. On average, the onset of psoriasis in males occurs at 20-39 years and in females at 40-49 years of age⁹.

The clinical presentation of psoriasis can be made more complex by the existence of different types of the disease, each with their own set of manifestations. These include plaque psoriasis, the most common form, which is characterized by red patches covered in silver scales; guttate psoriasis, which manifests as small, drop-shaped lesions; pustular psoriasis, which is distinguished by white pustules surrounded by redness; and erythrodermic psoriasis, a rare severe form that is characterized by systemic redness and peeling⁵. The disease can also be named based on anatomical location, namely scalp, inverse/flexural, palmoplantar, genital, and nail psoriasis⁵. For 30% of patients, psoriasis may also develop into an inflammatory arthritis, with various presentations and

symptoms¹¹. Currently, diagnosis and classification criteria are based on various clinical phenotypes, on the age of onset, disease severity, and disease morphology¹¹.

To date, the treatment for psoriasis depends on the severity and type of psoriasis and on the response to previous treatments. In general, topical therapies are prescribed for mild psoriasis, and more aggressive interventions such as immunotherapy / biologics that inhibit TNF- α , IL-12/23, IL-17, and IL-23 are prescribed for moderate to severe psoriasis⁸. Despite having several topical and systemic therapies, the chronic and likelihood of relapse of the disease places a major burden on affected individuals and clinicians.

SPECIFIC AIMS

1. Review of literature to characterize the nature of psoriasis, target markers of progression, and modalities of treatment.
2. Investigate the different therapeutic strategies available to patients by focusing on their mechanisms, and what their outcomes are.
3. Propose future direction regarding the research and treatment for psoriasis.

PATHOGENESIS OF PSORIASIS

I. Genetic Factors

PsO pathogenesis is multifaceted. Studies have found that genetic factors, environmental triggers, lifestyle factors, and immune dysregulation all contribute to the pathogenesis of PsO. For individuals who specifically experience an early onset of PsO, family history and certain genetic loci may play a part. This reveals the role that genetic predisposition plays in PsO pathogenesis.

A multicenter observation study done by Ohata et al. demonstrated that patients with PsO that had a family history of the disease exhibited a 34.7% higher chance of experiencing an earlier disease onset and longer disease duration than those without¹². This finding confirms the importance of genetic factors, suggesting that specific genetic variations may and can be inherited which predisposes the people affected to earlier or more severe outbreaks of PsO.

One of the most notable genetic factors that is correlated with PsO pathogenesis is *HLA-Cw6*. Chen was able to demonstrate that *HLA-Cw6* correlates strongly with guttate PsO and confers distinct responses to therapeutics, saying that the drugs methotrexate and Ustekinumab had better efficacy over other drugs¹³. When it comes to different ethnicities, there has been some variability in the results which suggests the need for more research to clarify how *HLA-Cw6*, or its disequilibrium with other genetic loci differs across population groups.

IL-23/Th17 Axis and Genes: One of the main immunopathological axes associated with PsO pathogenesis is the IL-23/Th17 axis. A study by Nair associated

IL12B and *IL23R* polymorphisms with PsO in Caucasian participants, which prompts questions about how these associations might apply to other ethnicities¹⁴. Another study conducted by Boca found that the protective alleles, or the existence of at least one C allele in either the *IL12B* and *IL6* SNPs, is linked to lower PsO risk¹⁵. They also noted that the absence of *HLA-Cw6* mitigated PsO risk. Taken together, these findings suggest that the genes involved in the IL-23/Th17 axis is plays a significant role in PsO pathogenesis and susceptibility, and can be effective points to target for therapeutic drugs. Additionally, a study by Ellinghaus et al. and Tsoi et al. compiled GWAS data that identified *TRAF3IP2* and several other novel loci that converge on the IL-17 signaling and innate immunity pathways. Their findings reinforced the concept that both the innate and adaptive immune systems actively take part in PsO pathogenesis^{16,17}.

CARD14 and NF- κ B Activation: Jordan et al. discovered that mutations in *CARD14* (aka PSORS2 locus) can drive PsO pathogenesis through a gain-of-function mechanism that accentuates NF- κ B activity¹⁸. *CARD14* is normally expressed in basal keratinocytes in healthy individuals but can be abnormally upregulated in supra-basal layers in psoriatic lesions. This aberrant expression and subsequent activation of downstream cascades promotes an excessive production of inflammatory mediators like IL-8 and CCL20. This creates a local environment that leads to the recruitment of T-cells and inflammation.

Epigenetics: Although some focus has been on heritable single-nucleotide polymorphisms (SNPs), recent research has also highlighted epigenetics. Zhang S. demonstrated how modifications such as DNA methylation, histone acetylation, and non-

coding RNAs regulated gene expression without altering the DNA sequence itself¹⁹. These modifications either exacerbated or dampened the inflammatory processes that drive PsO, linking the interplay between genetic predisposition and epigenetic modulation.

Genes and the Environment: PsO is not purely genetic. External triggers like infections, obesity, and stress are common factors that may precipitate or worsen flares. A study by Harris T. found that in the case of monozygotic twins, though disease onset and severity may be similar, concordance between the twins is not 100%²⁰. This underscores the pivotal role environmental factors play in not only the pathogenesis of PsO, but other diseases as well.

Multi-Ancestry Genome-Wide Meta-Analysis Building upon these genetic discoveries, a multi-ancestry genome-wide meta-analysis done by Zhang M. identified 74 genome-wide significant loci, including 32 novel risk loci specifically for psoriasis²¹. These findings corroborate earlier findings of overlapping genetic predispositions for other autoimmune diseases like inflammatory bowel disease (IBD), Crohn's disease, and ulcerative colitis, expanding possible therapeutic targets. The illumination of these shared immune pathways across diseases can encourage the development of broader anti-inflammatory strategies that may benefit multiple autoimmune conditions.

II. Environmental Factors

While the genetic basis of PsO is well established, increasing evidence suggests that environmental triggers also play a role in disease onset and development. Historically, a lot of the focus was on microbial infections and physical trauma as

catalysts for PsO pathogenesis. However, additional research has broadened this view, implicating factors such as air pollution, weather, psychological stress, and lifestyle choices to be just as involved.

Infections: Infections which are particularly caused by streptococcal pharyngitis have been implicated in the onset and development of PsO. Streptococcal infections are strongly associated with guttate psoriasis, a subtype characterized by sudden onset and widespread small lesions. A study done in 1995 suggests that a streptococcal superantigen-driven process may explain this correlation, which leads to an aberrant immune response and subsequent PsO lesions²². Furthermore, infections are known to disrupt immune homeostasis which can trigger disease manifestation²³. Other than bacterial infections, viral and fungal pathogens are also involved in PsO pathogenesis. The Rig-I antiviral signaling pathway has been shown to drive IL-23 production, a critical cytokine in psoriasis pathogenesis²⁴. This sheds light on the role of viral infections in triggering inflammatory responses that contribute to PsO onset and progression.

Trauma and the Koebner Phenomenon: Trauma is another known trigger of PsO. Trauma often leads to the Koebner phenomenon which means that new psoriatic lesions develop at sites of skin injury. This phenomenon can also be defined as the appearance of lesions with the same clinical and histopathological characteristics as the primary lesions after trauma or stimulation (mechanical, chemical, or infectious). It exemplifies how external physical insults can exacerbate PsO²⁵. Additionally, keratinocytes also play a role in mediating the Koebner phenomenon through mechano-

induced signaling pathways . This may explain the high frequency of psoriasis lesions on areas prone to mechanical stress, such as the extensor side of the elbows and knees^{25,26}.

Air Pollution and Weather: More recent evidence suggests that air pollution may play a significant role in triggering PsO flares. A study by Bellinato examined short-term exposure to environmental pollutants and found a significant association between air pollution levels and PsO flare-ups²⁷. Pollutants may exacerbate PsO through oxidative stress and inflammatory pathways, implicating the role environmental toxins play in PsO pathogenesis. Higher concentrations of particulate matter in the 60 days preceding clinical assessment correlated with a higher Psoriasis Area and Severity Index (PASI) score, indicating higher severity and disease activity²⁷. Climate and seasonal changes have been observed to influence psoriasis severity. A study done by Park B.S. analyzed factors influencing psoriasis, and found that most patients reported beneficial effects from summer, sunlight exposure, and pregnancy. On the other hand, winter and stress were commonly cited as exacerbating factors²⁸. The positive effects of sunlight may be explained by ultraviolet radiation's immunosuppressive effects, which lead to a reduction in inflammatory cytokine production and improved lesion resolution. The worsening of symptoms patients experience during colder months may be due to lower humidity and reduced sunlight exposure, emphasizing the relationship between seasonal variations PsO management²⁹.

Lifestyle Factors: Lifestyle choices, including diet and body weight, have been identified as modifiable risk factors in PsO. Particularly obesity has been correlated with an increased risk of developing psoriatic arthritis for patients with PsO. A meta-analysis

by Wenhui X. demonstrated that higher body mass index significantly elevated the risk of psoriatic arthritis, suggesting that weight management either through dietary interventions and physical activity could potentially reduce PsO risk and severity³⁰. Lifestyle factors that do not have a significant association were alcohol consumption, smoking, female hormonal exposure, and psychologically traumatic events.

III. Immune System Dysregulation

While PsO has long been recognized as an immune-mediated disease, recent discoveries have unveiled new cellular and molecular players that further elucidate its complexity. In particular, the immune dysregulation that happens because of keratinocytes, dendritic cells, cytokines, T cells, and molecular players such as PARP2 and TRIM proteins, are found to play a role in pathogenesis.

Role of Keratinocytes: Keratinocytes, which are the primary skin cells, are not passively affected by inflammatory damage but actively participate in PsO pathogenesis. They interact with cytokines and immune cells which further progresses PsO. Based on a study done by Zhou, cytokines activate keratinocytes to release chemokines that end up attracting dendritic cells, macrophages, Th17 cells, and neutrophils³¹. This causes a feedback loop that induces prolonged inflammation. Additionally, the resulting structural dysfunction of keratinocytes leads to impaired skin barrier function, extracellular lipid release, and subsequent immune activation³². Recent research has also elucidated the role of environmental triggers, such as pollutants and infections, which activate pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs), exacerbating inflammation and promoting autoimmunity, worsening psoriasis³³. These findings

suggest that keratinocyte-targeted therapies could be effective in mitigating PsO pathogenesis.

Role of Dendritic Cells: Dendritic cells also play a part in initiating PsO by bridging innate and adaptive immune responses. The study by Rendon found that antimicrobial peptides (AMPs), particularly LL37, activates dendritic cells³⁴. LL37 complexes with self-DNA from damaged keratinocytes, triggering type I interferon (IFN) production, which then promotes the maturation of myeloid dendritic cells and differentiation of T-helper cells (Th1 and Th17)³⁵. Recruitment and activation of these T cells fuels the inflammatory cycle that is commonly characterized in PsO lesions. Additionally, type I, II, and III interferons have been recognized as vital mediators in psoriasis, which sustain the inflammatory environment in the skins of people with PsO³⁶. Given the role dendritic cells play in PsO pathogenesis, targeting these cells presents a potential strategy for managing PsO severity.

Cytokines and Immune Mediators: Cytokines are the messengers responsible for immune dysregulation observed in PsO. They affect keratinocyte activity and immune cell interactions, which makes them potential targets for treatment. Interleukin-1 (IL-1) induces gene expression profiles like those seen in psoriatic lesions, suggesting that it plays a key role in PsO pathogenesis³⁷. Elevated IL-1 levels also have been strongly correlated with epidermal hyperplasia and chronic inflammation, exacerbating the characteristic thickening of the psoriatic epidermis. Interleukin-36 (IL-36) is also significant because it attracts neutrophils, myeloid cells, and T cells to the skin,

sustaining inflammation³⁷. Because IL-36 has been shown to amplify immune responses, it reinforces the potential of making it a target in PsO treatment.

Another cytokine, interleukin-17A (IL-17A), is known for promoting autoimmune pathology in PsO and other inflammatory diseases³⁸. IL-17A does this by directly affecting keratinocytes, inducing them to produce pro-inflammatory molecules and antimicrobial peptides, further fueling inflammation. Therapies that inhibit IL-17A have demonstrated substantial efficacy, providing relief for patients with moderate to severe PsO.

Interleukin-23 (IL-23) is known to stabilize the transcription factor ROR γ t, which is essential for the maintenance and expansion of Th17 cells³⁸. Th17 cells secrete IL-17A, IL-21, and IL-22, which are cytokines that contribute to chronic inflammation that can exacerbate PsO symptoms. Therefore, the IL-23/IL-17 axis has been identified as a primary driver of psoriatic inflammation, making it a potent target for therapeutics.

Tumor necrosis factor-alpha (TNF- α) is another central cytokine in autoimmunity. Although TNF- α alone is limited on the effect it has on keratinocytes, it works in tandem with IL-17 to magnify an inflammatory response³⁹. One of the first biologic therapies that was approved for PsO was the TNF- α inhibitor. They continue to be a cornerstone of PsO management, demonstrating its significant efficacy in reducing its severity. Collectively, these cytokines work together to create a "cytokine storm" that drives the pathogenesis of psoriasis, underscoring the importance of cytokine inhibitors in managing and controlling PsO.

Role of T Cells: T cells, notably CD4⁺ and CD8⁺ T cells, play a key role in the pathogenesis of PsO. A study by Ghoreschi points out that CD4⁺ T cells are a critical component in the development of PsO⁴⁰. This was additionally demonstrated through skin xenograft models where the presence of CD4⁺ T cells led to psoriatic changes⁴¹. More recent studies have broadened this understanding by showing that CD8⁺ T cells also play a significant role. This was elucidated when inhibition of CD8⁺ T cells led to decreased PsO onsets, underscoring their involvement in the disease pathogenesis⁴². Moreover, gamma delta ($\gamma\delta$) T cells have now emerged as important contributors. These unconventional T cells rapidly produce IL-17A in response to IL-23 stimulation, which intensifies the inflammatory response within psoriatic lesions⁴³.

Role of PARP2: Poly (ADP-ribose) polymerases (PARPs) regulate a range of routine cellular processes that include metabolism, DNA repair, and inflammation. Within the PARP family, PARP2 has been noted for its participation in PsO pathogenesis. A study by Antal has demonstrated this fact by showing that PARP2 mRNA expression is significantly higher in psoriatic lesions⁴⁴. They further demonstrated through experimental models that the deletion of PARP2 in mice led to a reduction in psoriasis-like dermatitis, highlighting its functional relevance. In vitro, keratinocytes deficient in PARP2 exhibit suppressed NF- κ B activation, a key signaling cascade in inflammation, thereby contributing to reduced inflammation. Additionally, PARP2-deficient keratinocytes showed elevated levels of estradiol, which appears to have anti-inflammatory effects. These findings solidify the role that PARP2 plays in sustaining psoriatic inflammation.

Role of TRIM Proteins: Tripartite motif (TRIM) proteins is a family of E3 ubiquitin ligases that regulate inflammation through the NF- κ B cascade⁴⁵. Research by Yang discussed the role TRIM proteins had in the immune response for various stimuli. Specifically TRIM21 is known to promote inflammation in keratinocytes, with increased expression in the epidermis of psoriatic sites⁴⁶. Further research is needed to identify targeted approaches to mitigate TRIM proteins' inflammatory impact on PsO pathogenesis.

CURRENT TREATMENTS AND THERAPIES

A. Vitamin D Analogs

Vitamin D Analogs have been a cornerstone for PsO management because of its potent ability to induce antiproliferative, immunomodulatory, and differentiation on keratinocytes. Overall, various studies demonstrate that vitamin D analogs offer significant and sustained improvements in patients with PsO with minimal systemic adverse effects, upholding their value as a monotherapy and as a combinatorial option. The therapeutic use of vitamin D was serendipitously discovered in the 1930s when an osteoporosis patient treated with oral vitamin D showed marked improvement in their psoriatic lesions⁵². Subsequent studies have corroborated that vitamin D insufficiency is common characteristic in psoriatic patients, which has been postulated to contribute to the dysregulation of keratinocytes^{53,54,55}. This suggests a pathophysiological role beyond vitamin D's role in bone metabolism.

Biosynthesis and Activation: Vitamin D is synthesized in the skin from a precursor form, 7-dehydrocholesterol, that is located within the basal and spinous layers

of the epidermis⁴⁷. When it is exposed to UVB radiation, a photochemical reaction converts 7-dehydrocholesterol to pre-vitamin D₃ known as cholecalciferol⁴⁷.

Cholecalciferol is then hydroxylated in the liver by enzymes such as CYP27A1 and CYP2R1 to form 25-hydroxyvitamin D (25OHD)⁴⁷. The step that converts it to the active form, 1,25-dihydroxyvitamin D (calcitriol), happens in the kidney and skin via the enzyme CYP27B1⁴⁷. When this active form of vitamin D binds to the vitamin D receptor (VDR), it regulates gene transcription in various tissues, including the skin itself⁴⁷.

Vitamin D Effects: The binding of calcitriol to VDR stimulates the maintenance of homeostasis in the skin via multiple effects. . It modulates keratinocyte proliferation, differentiation and apoptosis, which is thought to restore the balance that is disrupted in psoriatic lesions. Some studies have also demonstrated that through vitamin D signaling, anti-proliferative effects on keratinocytes both in vitro and in vivo are exerted^{48,49}.

Moreover, vitamin D analogs that were created were found to modulate immune responses by reducing T-cell activation and decreasing the production of pro-inflammatory cytokines, which contributes to anti-psoriatic outcomes⁵⁰. The review by Soleymani et al. ties these processes together by clarifying that the process of epidermal differentiation is complex and tightly regulated by vitamin D and the VDR⁵¹.

There are various vitamin D analogs that differ in their chemical structure, pharmacokinetics, and side effects, yet share the ability to act upon the VDR. Multiple randomized controlled trials and meta-analyses have also validated the clinical efficacy of vitamin D analogs in PsO treatment. Highton and Kircik reported significant improvements in PASI scores with topical calcipotriene and calcitriol, respectively^{62,59}.

Comparative studies have indicated that although corticosteroids may yield rapid improvement, vitamin D analogs offer sustained benefits and reduced relapse rates. The following are some of the analogs available for PsO.

Available Analogs

Calcipotriene: Calcipotriene, also known as calcipotriol, was the first vitamin D analog introduced for PsO. A study in 1995 demonstrated a significant improvement after applying calcipotriene ointment 0.005%, with improvements observed as early as the first week ($p = 0.043$) in plaque elevation, erythema, and scaling. By week 8, 70% of patients treated with the ointment saw at least a 75% improvement, as opposed to only 19% for the control⁵⁶. Despite its efficacy, calcipotriene is known for causing local cutaneous irritation in up to 20% of patients, particularly in regions where the skin is more sensitive such as intertriginous areas and the face⁵⁷.

Tacalcitol: Although not available in the United States, it has been successfully utilized in other countries to manage PsO effectively. Its efficacy is like that of calcipotriene with potentially different tolerability.

Calcitriol, as mentioned previously, is the naturally occurring active form of vitamin D₃ and has been studied for its anti-psoriatic properties. There were some clinical trials that successfully demonstrated that a topical calcitriol ointment (3 µg/g) is effective in reducing psoriatic plaques with an excellent safety profile^{58,59,69}. In the United States, calcitriol remains the only vitamin D analog available as an ointment, offering comparable efficacy to other analogs with minimal side effects.

Maxacalcitol: Maxacalcitol has demonstrated good efficacy compared to other vitamin D analogs. A study found that maxacalcitol ointment at a concentration of 25 µg/g was more effective than a once daily calcipotriol (50 µg/g) in reducing psoriatic lesions. However, some patients had negative experiences with burning sensations at the application site which accounts for their discontinuation in the study⁶⁰.

Paricalcitol: Evidence from randomized trials indicates that paricalcitol is another option for patients who may be intolerant to other vitamin D analogs. Durakovic reported significant improvements in psoriatic lesions with a lower incidence of side effects, suggesting a potential role for this agent in the therapeutic armamentarium⁶¹.

Long-term studies have shown that vitamin D analogs can be used safely over long periods without increasing systemic toxicity⁶³. It also demonstrated sustained clinical improvement and a low incidence of adverse events with prolonged use⁶⁴.

The most common adverse effects because of vitamin D analog administration are localized skin irritation and erythema⁶⁵. Hypercalcemia is also a potential concern with vitamin D analogs due to its role in calcium metabolism, but it remains a rare occurrence when proper dosing is adhered⁶⁵. Moreover, while vitamin D supplementation has been explored as an adjunct treatment in PsO, conflicting results indicate that further research is needed to identify optimal dosing strategies and target populations⁶⁶.

More recently, there therapies are trending towards using analogs in combination with other therapies like corticosteroids. This combinatorial approach over monotherapy has been a pivotal advancement in PsO management. Fixed-dose formulations, such as the calcipotriene/betamethasone dipropionate aerosol foam (Enstilar®), are now

considered first-line therapies in both the United State and Europe. These combination regimens leverage complementary mechanisms of both treatments. Calcipotriene targets epidermal dysregulation while betamethasone targets pro-inflammatory cytokines while enhancing keratinocyte differentiation^{67,68}.

Topical calcipotriene was also tested in conjunction with narrow-band UVB phototherapy and has shown a positive synergistic effect, which led to the reduction of treatment duration and minimization of UV exposure from phototherapy⁶⁴. This approach not only enhances clinical efficacy but also helps mitigate some of the side effects associated with high-dose phototherapy.

The ongoing development of new vitamin D analogs, including paricalcitol and maxacalcitol, reflects an effort to expand treatment options for patients who are intolerant to conventional agents or who need alternatives. Early clinical trials of these novel compounds have shown promising results, but there is still a need for confirmation via long-term studies^{60,61}.

B. Retinoids

Retinoids, particularly tazarotene, have been studied for their efficacy in managing PsO. Tazarotene is a synthetic acetylenic retinoid introduced in 1997, with a chemical structure that is different than other retinoids⁷⁰. It is a topical treatment that is FDA approved not only for PsO, but also for acne and photodamaged skin. The therapeutic effects of tazarotene are via its action on retinoic acid receptors (RARs) that are present in the epidermis. According to Duvic, tazarotene mitigates PsO pathogenesis through three primary pathways: downregulation of differentiation markers in

keratinocytes which normalizes epidermal turnover, inhibition of keratinocyte proliferation, and reduction in inflammatory marker expression via gene regulation⁷¹.

These mechanisms contribute to the improvement of PsO and alleviate disease severity.

The efficacy of tazarotene in treating PsO has been demonstrated in a study done by Weinstein. They conducted two multicenter, double-blind, randomized vehicle-controlled studies evaluating the efficacy of tazarotene cream (0.05% and 0.1%) in patients with plaque PsO⁷². They discovered that both concentrations significantly reduced the severity of PsO compared to the placebo, but the 0.1% concentration exhibited the most clinical improvement. The therapeutic effects of the treatments persisted for up to 12 weeks after ceasing administration. Furthermore, these formulations were well-tolerated among participants, with minimal adverse effects. These findings support tazarotene's continued use in PsO management.

A more recent review by Tanghetti et al. reaffirmed tazarotene's efficacy in reducing PsO plaque elevation and scaling after 12 weeks of treatment⁷³. Going back to combinatorial approaches, the study also suggested that combining tazarotene with topical corticosteroids enhances efficacy and reduces local irritation, demonstrating a synergistic effect. Similarly, Sugarman et al. conducted a phase II clinical trial assessing a fixed combination of halobetasol propionate and tazarotene in plaque psoriasis⁷⁴. Their findings indicate that this combination provided rapid and sustained efficacy, with a positive safety profile.

In addition to tazarotene, retinoids such as acitretin, alitretinoin, and bexarotene have been studied for PsO treatment⁷⁹. However, a 2023 registry-based study found that

acitretin was lower in efficacy when compared to other systemic treatments like ciclosporin and methotrexate⁷⁵. Such variability in efficacy may imply that retinoid therapy may not be best for PsO. Another study found contrasting results, saying that low-dose acitretin (25 mg/day) led to fewer adverse effects while maintaining clinical efficacy, supporting its use at lower doses for better patient tolerability⁷⁶.

Alitretinoin, which is normally used for hand dermatitis, has also been explored as a potential option for treating PsO. A randomized controlled trial in 2021 evaluated the combination of low-dose oral alitretinoin (10 mg daily) with narrowband ultraviolet B (NB-UVB) therapy. They found that doing this combination provided higher skin clearance and less adverse effects when compared to a higher dose of oral alitretinoin (30 mg daily) in patients⁷⁷. Acitretin, although effective, has unwanted side effects such as elevated cholesterol levels and teratogenicity. This warrants the need for strict contraception guidelines for female patients⁸⁰. Similarly, alitretinoin's teratogenic tendency also limits its use for some patients.

A study by Patel 2024 outlined that the main side effects of tazarotene include skin irritation and increased sensitivity to light⁷⁸. Some limitations of the compound include poor stability, and suboptimal solubility⁷⁸. Additionally, ineffective controlled drug release poses challenges in optimizing therapeutic outcomes⁷⁸. However, combination treatments with corticosteroids have been promising in mitigating these limitations⁷³.

C. Corticosteroids

Corticosteroids have been widely utilized for PsO treatment for over 50 years because of their immunosuppressive, anti-inflammatory, and antiproliferative properties⁸¹. According to the Psoriasis Expert Group (PEG), corticosteroid treatments are often selected by physicians due to their rapid relief and effectiveness, with minimal immediate adverse effects⁸². However, long-term use becomes unsustainable by cutaneous side effects that lead to atrophy, striae, and telangiectasia. Different approaches like pulse therapy and combination therapies aim to optimize long-term application by balancing safety and effectiveness. Despite its drawbacks, corticosteroids are still considered first-line treatments for various forms of PsO and severities. They can exist in gel, cream, ointment, foam, lotion, oil, and spray formulations.

Corticosteroids exert their effects through genomic and nongenomic pathways^{81,83}. The genomic pathway starts with corticosteroids binding to glucocorticoid receptors (GR) located in the cytoplasm. The receptor complex then translocates to the nucleus where gene transcription becomes modulated. The result is the increased expression of anti-inflammatory genes such as IL-10 and DUSP-1, and the simultaneous downregulation of pro-inflammatory genes that regulate cytokines and growth factors. Moreover, corticosteroids also suppress the transcription factors NF- κ B and AP-1, enhance the production of annexin A1 to inhibit phospholipase A2, and induce MAPK phosphatase 1, which culminates in the inactivation of inflammatory kinases c-Jun and p38. However, if there is mutation on the GR or any disruption in these pathways, it can cause glucocorticoid resistance, rendering corticosteroid treatments ineffective.

The nongenomic pathway induces rapid anti-inflammatory effects that do not exert its effects via gene transcription. Rather, it acts via membrane-bound receptors and second messengers. This pathway quickly affects the activity of monocytes, T cells, and platelets, which provides immediate relief from PsO symptoms.

With regards to PsO, corticosteroids exhibit several biological effects. Because they have anti-inflammatory properties by reducing cytokines like IL-1, IL-6, and TNF- α and exhibit antiproliferative actions by decreasing keratinocyte overgrowth, PsO flares can be kept under control. Corticosteroids are also shown to regulate apoptosis by promoting programmed cell death in eosinophils and lymphocytes while prolonging the survival of neutrophils. They can also reduce blood flow via vasoconstriction, all of which leads to decreased inflammation⁸⁴. Additionally, corticosteroids exert immunosuppressive effects by switching the state of the immune response from a Th1-dominant that is pro-inflammatory, to a Th2-dominant response that is anti-inflammatory. And finally, they can inhibit inducible nitric oxide synthase (iNOS), thereby reducing nitric oxide levels that contribute to inflammation, and they regulate mast cell activity by lowering mast cell numbers and decreasing histamine release^{85,86}.

The long-term use of corticosteroids is known to have significant side effects that may start to outweigh the benefits, including adrenal insufficiency, Cushing's Syndrome, and osteoporosis. These downsides remind us of the importance of monitoring dosage and frequency of usage, and to be considerate of each patients' circumstances⁸⁷.

Combinatorial therapy and formulations of lower concentrations have been made to mitigate the unwanted effects. Clobetasol propionate (CP) 0.05% foam is notable for

its effectiveness and for the positive reviews it receives from patients, especially when treatment is implemented with penetration modifiers⁸⁸. Fixed-dose combinations that use calcipotriol with betamethasone dipropionate also provide patients with great results and assurance of safety over monotherapy of corticosteroids alone, which has shown significant improvement of psoriatic lesions⁸³.

D. Emollients

A study by Sorokina highlighted the important role emollients play in PsO⁸⁹. They particularly noted that when they are used with pharmacological therapies, like when combining it with betamethasone and calcipotriol, can lead to better outcomes⁸⁹. Specifically, patients who included emollients as part of their treatment regimens experienced significant reductions in their PASI scores and general improvements in skin condition, as opposed to those receiving pharmacological treatments as monotherapy⁸⁹. These findings highlight the ability of emollients to enhance the efficacy of established therapies by optimizing skin hydration and barrier function.

A review done by Fluhr discussed how emollients, moisturizers, and keratolytic agents are essential compounds to incorporate in treating PsO that can serve as adjuvants to pharmacological treatments⁹⁰. They mainly function by reducing scaling of the skin, normalizing keratinocyte hyperproliferation and differentiation, and promote an anti-inflammatory environment via replenishing physiological lipids. The summation of these contributes to strengthened barrier integrity and increased hydration of the stratum corneum. This conveniently decreases the probability of triggering the Koebner phenomenon, a factor in PsO pathogenesis.

Because emollients can act as an occlusive film to prevent water loss from the skin, they are effective at providing comfort and reducing scaling and fissuring when reapplied regularly⁹¹. On the other hand, keratolytic agents like salicylic acid and high-concentration urea are actually preferred over emollients in the early stages of PsO treatment to promote descaling⁹¹. Depending on the phase of PsO treatment, adjusting the approach like this with topical therapy maximizes the effects of emollients, allowing the skin barrier to be restored quickly and maintained throughout the healing process.

The study by Maroto-Morales delved deeper into the effects emollients have on the skin barrier in patients with PsO⁹². To do this, they measured transepidermal water loss (TEWL) and stratum corneum hydration (SCH) to rate barrier integrity and effectiveness of different emollient formulations. TEWL was found to be elevated and SCH was found to be lower in psoriatic plaques compared to healthy skin, demonstrating the compromised state of hydration of psoriatic skin. After the application of Vaseline jelly, the measurements for TEWL significantly decreased by $5.59 \text{ g}\cdot\text{m}^{-2}\cdot\text{h}^{-1}$ ($p = 0.001$), reflecting improved barrier status after emollient application. Similarly, a water-based formula emollient increased SCH by 9.44 arbitrary units ($p = 0.003$), signifying a high hydrating effect. Ultimately these findings suggest that regardless of the emollient type, they all can provide improvements to skin barrier function and improve PsO symptoms. They can do this through either occlusive formulations that reduce water loss, or through hydrating formulations that increase water content.

Prescription emollient devices (PEDs) is an example of a recent advancement in emollient formulations. Such improvements offer benefits specifically for difficult-to-

treat or sensitive areas. Dall'Oglio assessed a PED that worked in combination with furfuryl palmitate (an antioxidant and anti-inflammatory compound), tocopherol, and dimethicone in patients with PsO on sensitive areas and folds⁹³. Eight weeks post-treatment, participants showed a significant decrease in erythema, scaling, infiltration, and itching without adverse effects. This trial illustrates the potential for specifically formulated emollients that can be used in place of potent pharmacologic therapies and be used as a less intoxicating monotherapy option, or even as adjuncts when treating PsO.

E. Calcineurin Inhibitors (CNI)

Calcineurin inhibitors like cyclosporine A (CsA) and tacrolimus induce immunosuppressive effects by inhibiting the calcium-dependent phosphatase calcineurin. Doing this blocks dephosphorylation and nuclear translocation of nuclear factor of activated T cells (NFAT), which ultimately inhibits the transcription of the pro-inflammatory cytokines IFN- γ , IL-4, and IL-17⁹⁴. As mentioned previously, these cytokines are known to play a role in the differentiation and function of Th1, Th2, and Th17 cells, which are also involved in PsO pathogenesis. Tsuda's study confirms calcineurin inhibitors like CsA and Tac suppress cytokine production and inhibit naïve T cell differentiation into cytokine-disseminating cells. This finding underscores the rationale for their use in treating diseases that are driven by immune dysregulation like PsO.

Topical CNIs, notably tacrolimus and pimecrolimus, have been studied for off-label use in PsO, specifically for sensitive areas around the face, genitals, and intertriginous zones. Wang conveniently reviewed the outcomes of several studies⁹⁵.

They found that tacrolimus, which was corroborated by nine double-blind and 13 open studies, is effective on these areas on the body. Pimecrolimus also generally had positive outcomes, but this was not as widely demonstrated as tacrolimus. Because these areas are more prone to cutaneous atrophy with prolonged topical corticosteroids, CNIs are an attractive alternative for their low atrophogenic potential.

A study by Silvestri supported these findings through a systematic review, describing the considerable efficacy tacrolimus and pimecrolimus had on inverse PsO, which commonly affects areas of flexion, which are prone to irritation⁹⁶. These benefits were again verified in Luger's study, which reiterated the advantage of CNIs in areas of the body where the side effects of corticosteroids particularly undesirable⁹⁷.

A recent review done by Amiri provided additional evidence of the efficacy and safety of topical CNIs on facial and genital areas affected by PsO⁹⁸. After reviewing 24 studies, including randomized controlled trials and case reports, all reached a positive consensus. The common adverse effects that were reported were localized stinging, burning, and itching, with no other systemic side effects. However, Amiri was careful to point out the limitations in the literature, including inconsistent severity ratings, differing safety self-reports, and low number of long-term studies. Although percutaneous absorption in sensitive areas being higher than other areas raises concerns about systemic exposure, there currently is no existing data that has documented clinically relevant systemic concentrations of tacrolimus or pimecrolimus when used for PsO.

CsA and Tacrolimus: Systemic CNIs like CsA have been used for many years for treating severe PsO because of their potent immunosuppressive activity. Recently,

tacrolimus has been studied for treatment-refractory PsO and in patients with cardiovascular disease or inflammatory bowel disease comorbidities. For these individuals CsA may pose additional risks⁹⁹. Despite the risk, there are not enough studies regarding the systemic impact of tacrolimus, with a dearth of standardized methodologies and outcomes which impedes the writing of clinical guidelines.

Voclosporin was in a trial for treating PsO that seemed promising at first but was not deemed superior to CsA in clinical trials⁹⁹. Even though voclosporin's main target is for treating lupus nephritis, its expanding scope in dermatology implies its potential for future applications in PsO management, particularly for patients wanting other options to systemic therapies.

Although CNIs can serve as alternatives to corticosteroids, especially when considering more sensitive and delicate areas on the body, there are gaps in the literature. In their studies, both Amiri and Silvestri proposed the need for long-term randomized controlled trials with standardized measures to better outline the safety and efficacy of CNIs, particularly its systemic absorption and effects after prolonged use^{96,98}. On top of that, more studies that compare CNIs to other therapies, including biologics, could be useful to clarify where they stand in the options available for PsO treatment.

F. Phototherapy

Ultraviolet (UV) radiation can treat PsO because it is capable of modulating the immune response and reducing epidermal hyperplasia. UVB radiation is when the wavelengths lie between 280–320 nm, and it is absorbed in the epidermis where it causes DNA damage by creating cyclobutyl pyrimidine dimers and (6-4)-photoproducts¹⁰⁰. This

damage triggers apoptosis in keratinocytes and T lymphocytes, which slows down the progression of pathogenesis PsO¹⁰⁰. Additionally, UVB exposure increases the level of reactive oxygen species, increasing oxidative stress, which further promotes apoptosis and immunosuppression¹⁰⁰. Another key molecule involved in phototherapy is urocanic acid (UCA). UCA goes from trans- to cis-UCA through photoisomerization when exposed to UVB. It is the Cis-UCA form that suppresses the immune response and inflammation¹⁰⁰. Phototherapy also alters cytokine production, decreasing the pro-inflammatory cytokines IFN- γ and IL-12 while increasing the anti-inflammatory cytokines IL-4 and IL-10¹⁰⁰. These changes allow the immune response to change from a more Th1/Th17-dominated response towards a more anti-inflammatory response, minimizing PsO progression.

Types of UVB: Broadband UVB (BB-UVB) phototherapy, meaning wavelengths between 280–320 nm, has been used in PsO treatment since the 1970s¹⁰⁰. Later narrowband UVB (NB-UVB) in the late 1980s came about, which uses wavelengths in the 311–313 nm range, has replaced BB-UVB because it had better efficacy and safety profile^{100,101}. The reason why is because NB-UVB's spectrum has a reduced tendency to cause erythema while maximizing therapeutic outcomes. NB-UVB has shown to stimulate keratinocyte and T-cell apoptosis, decrease epidermal hyperplasia, and suppress the Th17 pathway¹⁰⁰. As opposed to BB-UVB, treatment with NB-UVB resulted in a greater decrease in epidermal and dermal T-cell populations, with a preferential depletion of activated T cells via the FasL pathway for apoptosis¹⁰⁰. These characteristics has led to its widespread adoption as a first-line phototherapy treatment for PsO.

Psoralen + UVA (PUVA): Treatments that combine psoralen, a photoactive compound that is naturally found in certain plants like parsley and celery, with UVA exposure (wavelengths of 320–400 nm), remains one of more effective phototherapy treatments for PsO, having response rates that range from 74% to 100%¹⁰⁰. The way PUVA works is that the psoralen compound intercalates into the DNA in cells, and the UVA exposure encourages covalent cross-linking, which inhibits cellular proliferation and altering gene expression¹⁰¹. When we consider PUVA holistically, it is associated unfortunately associated with higher risks when used long-term, including photoaging and an increased incidence of cutaneous malignancies, which have led to being more cautious around its usage relative to NB-UVB¹⁰⁰.

Excimer Laser: Some advances in targeted phototherapy have led to the development of devices such as the 308 nm excimer laser and lamps, delivering high-intensity, localized UVB therapy for localized or treatment-resistant plaques¹⁰¹. This allows focused treatment of affected areas, preserving surrounding healthy skin and reducing cumulative UV exposure.

Other recent innovations include ultraviolet light-emitting diode (UV-LED) and flat-type fluorescent UVB (F-UVB) lamps, which also are able to emit high-intensity emissions in narrow wavelength ranges (wavelengths of 300–313 nm), being more precise in its delivery and improving safety for targeting PsO¹⁰¹.

Combinatorial therapy that incorporates phototherapy has also gained popularity to prioritize efficacy and lower adverse effects¹⁰². Because phototherapy lacks potency in its ability to suppress the immune system on a systemic level, it makes it an ideal

candidate for combining it with different topical agents, systemic drugs, and more recent nanotechnologies.

Nanoparticle-based delivery tactics are a more recent development that have been tried to augment phototherapy's effectiveness. In particular, photodynamic therapy (PDT), which involves a photosensitizer activated by visible light, has demonstrated promise. For instance, chitosan/alginate nanoparticles encapsulating curcumin, combined with blue light irradiation (400–480 nm), have shown significant antiproliferative effects on TNF- α -induced keratinocyte hyperproliferation in vitro¹⁰². These findings give good reason for integrating nanotechnology with phototherapy to control and treat PsO.

While phototherapy is generally tolerated well, some side effects include erythema, pruritus, and xerosis. Long-term UV exposure also increases the risk of photoaging and carcinogenesis¹⁰². Regardless, studies reassure that NB-UVB, if given at clinically monitored doses, does not pose a higher risk for cancer¹⁰⁰.

G. Diet and Lifestyle Remedies

Because PsO is associated with systemic inflammation, patients can also often present with comorbid obesity, cardiovascular disease, and insulin resistance. With time, dietary and nutritional strategies have gained popularity to treat and manage PsO. Studies have also supported that dietary patterns, specific nutrients, and lifestyle interventions can influence PsO severity, and general health of those affected.

Dietary Patterns: Recent research has connected dietary habits with systemic inflammation. They have found that psoriatic individuals tend to consume fewer anti-inflammatory foods and more pro-inflammatory options as opposed to healthy controls.

As an example, patients with PsO were found to consume less olive oil, berries, fish, seafood, and nuts but consumed more dairy products, sugary drinks, and processed meats more regularly¹⁰³. Additionally, red meat, high-glycemic index foods, and saturated fats have also been correlated with higher PASI scores.

Moreover, a 2024 review by Hawkins et al. found that PsO patients exhibited increased dietary fat and lower fiber intake than normal controls, with higher fiber intake specifically linked with reduced PsO severity¹⁰⁴. These findings deepen the significance of establishing dietary patterns that reduce systemic inflammation and improve gut health for PsO patients.

Plant-Based and Mediterranean Diets: Plant-based and Mediterranean diets were observed as potentially beneficial treatments for PsO¹¹³. These diets are known for centering around fruits, vegetables, legumes, whole grains, and healthy fats, which are known to improve gut microbiome diversity, reduce oxidative stress, and lower glycemic load, reducing systemic inflammation^{105,106}.

Observational studies consistently demonstrated that a greater adherence to the Mediterranean diet lowers PASI scores and improved clinical outcomes¹⁰⁷. The abundant consumption of omega-3 polyunsaturated fatty acids (PUFAs), polyphenols, and fiber obtained from this diet may be the source of its anti-inflammatory effects. Vegan and vegetarian diets may also exert anti-inflammatory and protective effects by limiting the amount of pro-inflammatory animal products, but larger, randomized-controlled trials are needed to solidify these benefits¹⁰⁶. The study by Musumeci et al. further buttressed the

use of low-calorie, Mediterranean, and protein-restricted or vegetarian diets as options to reduce inflammation and improve PsO symptoms¹⁰⁸.

Weight: Obesity is a well known risk factor for PsO, and reducing weight when needed has been shown to improve symptoms. The reduction of adipose tissue will decrease the induction of systemic inflammation because there will be less adipose tissue that can release adipokines and cytokines. In a randomized controlled trial conducted by Naldi et al, it was demonstrated that PsO patients who were comorbidly obese experienced a median PASI reduction of 48% after implementing a 20-week dietary and physical exercise regime, compared to a 25.5% reduction in the control group that received only basic dietary counseling¹⁰⁹. In the same vein, Garbicz et al. recommended limiting saturated fat intake and replacing it with omega-3 PUFAs when overweight PsO patients partake of low-energy diets, to encourage weight loss to improve symptoms¹¹⁰. Intermittent fasting, like Ramadan fasting, has also shown decreased PASI scores by reducing postprandial inflammation and improving metabolic health¹⁰⁷.

Supplements: Taking nutritional supplements is another viable approach for PsO treatment. As of late, omega-3 fatty acids from fish oil have garnered the strongest evidence that supports their role in reducing inflammation and improving PsO severity¹¹¹. Other supplements like vitamin D, vitamin B12, selenium, and antioxidant carotenoids and isoflavones have potential benefits, albeit the need for larger studies to more fully establish their efficacy¹¹². Functional foods, such as 9-cis-rich beta-carotene extracted from alga *Dunaliella*, have also improved the severity of plaque PsO in randomized controlled trials¹¹².

Lifestyle Factors and Patient Education: Lifestyle factors such as smoking, alcohol consumption, physical activity, and stress management are also important to consider holistically when trying to optimize PsO treatment¹⁰⁸. These factors can contribute to systemic inflammation and exacerbate disease burden.

Despite the growing interest in using diet as a means for treatment, patients and providers need to be wary of the misinformation about PsO diets is online. Hawkins et al. observed that PsO patients often view diet as an important aspect in managing their disease and frequently self-directed some dietary implementations and restrictions without professional help¹⁰⁴. The result of such independent measures, if derived from the dietary information found on social media and other platforms, can sometimes be misleading or potentially harmful¹⁰⁸. Though it is favorable when patients are taking initiative regarding their health, the responsibility of providers and professionals to offer accurate advice regarding diet is more important than ever.

H. Immunotherapy

A recent study by Floris provided evidence that biological treatment for PsO may also reduce the risk of psoriatic arthritis (PsA)¹¹⁴. 1023 PsO participants received rheumatologic assessments that also collected clinical and therapeutic data. Chi-square tests and multivariate regression analyses were adjusted for known PsA risk factors, and they observed a distinctly lower incidence of PsA (8.9%) in patients who had received at least one biologic treatment compared to those who had never received one (26.1%). They reached a similar conclusion after doing a multivariate analysis, with those who did biologic treatment having lower rates of PsA for the entire cohort. They then evaluated

each biologic class and found that the TNF- α , IL-17, and IL-23 or IL-12/23 inhibitors all resulted in significant protective effects, significantly reducing various forms and severities of PsA.

A study done by Brownstone found that the biologics of the classes that target TNF- α , IL-17, and IL-23, have transformed PsO and PsA treatment for the better¹¹⁵. Before biologics came about, systemic therapies like methotrexate, oral retinoids, and cyclosporine were commonplace but were not enthusiastically received because of multiple black box warnings and other safety concerns. But if we look at the benefits biologics bring to the table like being able to precisely modulate the immune system by acting on specific cytokines, this not only improves accurate outcomes but also has fewer systemic side effects. Furthermore, the frequency at which patients need to take biologics can be as few as four injections per year, making treatment more manageable and convenient. Additionally, these targeted therapies stem from knowing that PsO pathogenesis stemming from immune dysregulation. As the number of available biologics continues to grow, however, clinicians may face challenges in determining the most appropriate one for each patient.

Table 1. Biologic Treatments for Psoriasis

Medication, Year of FDA Approval	Brand Name	FDA Approved for	Dosing Regimen	Alternative Dosing Regimen	Key Merit
TNF-alpha inhibitors					
Adalimumab, 2002	Humira®	RA, PsO, PsA, AS, CD, Pediatric CD, UC, HS (age>12), uveitis, polyarticular JIA	80mg SC at week 0, 40 mg at week 1, then 40mg SC q2w		One of the most efficacious for psoriatic arthritis with FDA approval for inhibition of joint destruction
Etanercept, 2004	Enbrel®	RA, PsO, PsA, AS, JIA, pediatric PsO	50mg SC twice weekly for first 12 weeks, then 50mg SC weekly		Safe for use in geriatric patients with severe psoriasis
Infliximab, 2006	Remicade®	RA, CD, PsO, PsA, AS, UC, Pediatric CD, Pediatric UC	5 mg/kg IV at weeks 0, 2 and 6 and thereafter every 8 weeks		N/A
Certolizumab pegol, 2008	Cimzia®	RA, CD, PsO, PsA, AS, nr-axSpA	Patient weight > 90kg: 400 mg SC at weeks 0, 2 and 4, then 200mg SC q2w		Safe for use in pregnant and nursing patients
IL-17 inhibitors					
Secukinumab, 2015	Cosentyx®	PsO, PsA, AS, nr-axSpA	300mg SC at weeks 0,1,2,3,4,	Low body weight and minimal disease	Dedicated studies for treatment of scalp

			then 300mg SC q4w	severity: 150 mg maintenance q4w	psoriasis, nail psoriasis, palmoplantar psoriasis and axial psoriatic arthritis
Brodalumab, 2017	Siliq®	PsO	210mg SC at weeks 0, 1, and 2, then 210mg SC q2w		Frequently succeeds among patients who failed other biologics including other IL-17 agents
Ixekizumab, 2017	Taltz®	PsO, PsA, AS, nr-axSpA, Pediatric PsO	160mg SC at week 0, 80mg at weeks 2,4,6,8,10,12, then 80mg SC q4w	Maintain treatment response: 80mg SC q2w	Only biologic agent FDA approved for treatment of genital psoriasis
Bimkizumab	N/A				Pending FDA Approval
IL-23 inhibitors					
Guselkumab, 2017	Tremfya®	PsO, PsA	100mg SC at week 0 and 4, then 100mg q8w		Only IL-23 agent FDA approved for PsA
Tildrakizumab, 2018	Ilumya®	PsO	100mg at week 0 and 4, then 100mg SC q12w		Only biologic for PsO covered by Medicare part B
Risankizumab, 2019	Skyrizi®		100mg at week 0 and 4, then 100mg SC q12w		Very high efficacy, durability and rapid

					onset of action
Mirikizumab	N/A				Pending FDA approval
IL-12/23 inhibitor					
Ustekinumab, 2009	Stelara®	PsO, PsA, CD, UC, Pediatric PsO	Patient weight <100kg: 45mg SC at week 0 and 4, then 45mg SC q12w. Patient weight >100kg, 90mg SC at week 0 and 4, then 90mg SC q12w	Pediatric patient weight <60kg: weight-based dose of 0.75mg/kg. Patient weight 60-100kg, 45mg SC. Patient weight >100kg, 90mg SC	Higher dose FDA approved for patients with larger weight

Abbreviations: RA, rheumatoid arthritis; PsO, plaque psoriasis; PsA, psoriatic arthritis; AS, ankylosing spondylitis; CD, Crohn's disease; UC, ulcerative colitis; HS, hidradenitis suppurativa; JIA, juvenile idiopathic arthritis; nr-axSpA, non-radiographic axial spondylarthritis

TNF- α Inhibitors

TNF- α is a pro-inflammatory cytokine, and it exerts its effects by binding to two separate receptors: TNFR1 (p55 or CD120a) and TNFR2 (p75 or CD120b). The binding initiates a cascade within the cell that activates the NF- κ B, mitogen-activated protein kinase, and apoptotic pathways mediated by caspase-3 and caspase-8. It should be noted that when the NF- κ B pathway is activated, it rapidly influences the production of various inflammatory cytokines, chemokines, and adhesion molecules¹¹⁶. Therefore, TNF- α is an attractive target for inhibition, the act of which is characterized by two approaches. The first is using the monoclonal antibodies infliximab, adalimumab, and certolizumab pegol. These sequester TNF- α , preventing further pro-inflammatory signaling to occur. The second is using soluble receptor construct called etanercept, and it works by competitively inhibiting the interaction between TNF- α and the receptors¹¹⁶.

Etanercept (Enbrel[®]) is made up of a human IgG1 Fc fragment that is fused to the extracellular domain of the p75 TNF- α receptor. This forms a soluble TNFR2 dimer. This structure has higher affinity for TNF- α than the naturally occurring forms of TNFR1 and TNFR2¹¹⁷. This allows for it to bind to TNF- α , preventing it from interacting with TNFRs on the surfaces of cells, ultimately inhibiting inflammatory cascades. Unlike other TNF- α inhibitors, etanercept can also bind to another pro-inflammatory cytokine called lymphotoxin- α that is also involved in the NF- κ B pathway¹⁷. This enables etanercept to block TNF- α on two fronts, making it a useful biologic that can mitigate the irregular immune activity associated with PsO.

Earlier trials were able to establish etanercept's efficacy as a monotherapy for moderate to severe PsO. Leonardi et al conducted a 24 week, randomized double-blind study that evaluated 652 patients who received a placebo or etanercept in varying doses (25 mg once weekly, 25 mg twice weekly, or 50 mg twice weekly)¹¹⁸. At week 12, PASI 75 (or improvement of at least 75% in the PASI score) was achieved by only 4% of placebo-treated patients, but the etanercept group had a 14%, 34%, and 49% improvement of the low-, medium-, and high-dose etanercept groups, respectively. By week 24, these rates increased to 25% for the low dose, 44% for medium, and 59% for the high dose groups, highlighting dose-dependent efficacy of etanercept.

Long-term trials were also able to verify the efficacy and sustainability of etanercept. After Kivelevitch reviewed various clinical trials, they concluded that etanercept remains a highly effective monotherapy, or as an effective biologic when combined with other PsO treatments¹¹⁹. Together these findings make etanercept an important and reliable option to consider when managing and treating moderate to severe PsO, with a more than a decade of use.

Like other TNF- α inhibitors, etanercept needs to be prescribed with caution, especially when we consider its immunosuppressive properties, and the risks that it implies for recipients. Complications can include increased susceptibility to more serious infections like tuberculosis and hepatitis B, and the risk of contracting diseases like lymphoma and non-melanoma skin cancer¹¹⁹. Despite these negative possibilities, the reported instances of such adverse effects are similar in rate to the general population,

especially when patients undergo correct screening and monitoring. As such, the benefits of etanercept generally outweigh the risks.

Adalimumab (Humira®) is a human immunoglobulin G1 monoclonal antibody that can neutralize TNF- α when it binds to the soluble and membrane bound forms of TNF- α . This prevents it from interacting with p55 and p75, the cell-surface receptors¹²⁰. Adalimumab's ability to interrupt TNF- α signaling will result in a decreased expression of inflammatory cytokines, inhibition of the recruitment of neutrophils, and a decrease in the amount of reactive oxygen species in psoriatic lesions.

Various randomized, controlled, and long-term trials have provided sufficient clinical evidence to verify the efficacy and safety of using adalimumab for PsO. The study by Gordon (2006) was a randomized, double-blind, placebo-controlled trial that had 147 participants who either received adalimumab (40 mg every other week or 40 mg weekly) or a placebo over 12 weeks¹²¹. At week 12, they noted that 53% of patients in the adalimumab group that took 40 mg every other week, and 80% of those in the adalimumab group that took 40 mg weekly, reported a 75% improvement or greater in their PASI scores. In contrast, only 4% of the placebo group even obtained an improvement of 75% for their PASI. They additionally did an extension phase that revealed that these improvements remained the same 60 weeks post-trial. Moreover, there were no safety issues that emerged which makes adalimumab a favorable option for PsO treatment.

Longer-term efficacy was also demonstrated in phase III trials. In the REVEAL study, participants who had moderate to severe plaque PsO were treated with

adalimumab for 52 weeks. Those who completed this trial became eligible for an open-label extension, granting them up to three additional years of treatment¹²². If the participant got improved their PASI score by at least 75% at week 16 and at week 33, they were defined as sustained responders. These individuals were found to have maintained high response rates for more than three years. For these sustained responders, at week 100 of continued adalimumab treatment, 83% of them still had a 75% improved PASI, 59% of them achieved a 90% improvement in PASI, and 33% even had a 100% improved PASI. There was a slight decrease in PASI scores for the three categories at week 160, however. Furthermore, there were patients who fell short of a PASI 75 during the earlier stages of the REVEAL study, but they eventually got a PASI 75 after a longer duration of treatment. This outcome suggests that late responders can benefit from a longer treatment duration. The occurrence of adverse effects was consistent with what was reported in shorter trials, and no new safety issues were observed in the extended trial.

Side effects of adalimumab often look like injection-site reactions and infections. Additionally, because any biologic can predispose individuals to more severe infections, screening for tuberculosis and being extra cautious about opportunistic infections is critical before starting treatment. Nevertheless, for most patients, such risks are well tolerated and manageable.

Certolizumab Pegol (Cimzia®) is a PEGylated, Fc-free, TNF- α inhibitor that has garnered attention for being an effective treatment for moderate to severe plaque PsO. Similar to other TNF- α inhibitors, it neutralizes TNF- α inhibiting inflammation thereby

mitigating PsO pathogenesis¹²³. On a molecular level, Certolizumab pegol can be characterized by the absence of the Fc region, minimizing cytotoxicity that is caused by antibodies and complement. This feature can also decrease immunogenicity and risk of adverse effects that commonly come with TNF- α inhibitors.

Long-term studies had encouraging results. After analyzing three phase III randomized studies that spanned the course of three years, no new risks were found, and the overall risk of adverse effects did not increase after prolonged treatment or with higher doses¹²⁴. Common side effects that were reported were upper respiratory tract and urinary tract infections and rashes. Because serious infections like tuberculosis have also been reported, it is highly recommended to screen for latent tuberculosis before treatment. The CRADLE study also verified long-term safety, which tested certolizumab pegol in breastfeeding mothers¹²⁵. They found that certolizumab pegol was either undetectable or at levels below 1% of maternal plasma concentrations in breast milk, and the dose received by the infant was only 0.15% of the maternal dose. Notably, oral absorption by infants is unlikely thanks to its low bioavailability and non-Fc containing design. These results suggest that receiving certolizumab pegol even when breastfeeding is plausible with minimal risk.

Infliximab (Remicade[®]) is another TNF- α monoclonal antibody and has been used for moderate to severe PsO for about two decades. It acts by binding to soluble and membrane-bound TNF- α , which inhibits the pathways that cause epidermal hyperplasia and immune cell infiltration in psoriatic plaques¹²⁶. This leads to decreased activation of

CD4+ and CD8+ T cells, decreased dendritic cell function, normalization of keratinocytes, and a decreased plaque thickness.

One study investigated a group of patients that were undergoing five or more years of infliximab treatment for chronic plaque PsO. Researchers found that overweight or obese participants had better long-term remission rates than those who were normal weight¹²⁷. It seemed that a higher body mass index (BMI) correlated with a better maintained response to treatment, suggesting that dosages based on weight may be beneficial for patients with higher BMIs. Another study analyzed the sustained effect of infliximab for PsO patients that were treated with it for more than six years. Most participants received 4–6 mg/kg infusions every eight to ten weeks¹²⁸. In that study they found that 70% of the participants chose to stay on infliximab after six years, implying good drug survival rate. However, a some eventually stopped treatment, mostly because infliximab became no longer effective. These variabilities in efficacy stress the importance of monitoring throughout treatment.

Despite infliximab's effectiveness for many, there are some safety concerns. Like other TNF- α inhibitors, infliximab can predispose recipients to infections like tuberculosis, and there is a risk of malignancy with longer treatment durations¹²⁸. If it is administered intravenously, there is also a risk of acute or delayed infusion reactions¹²⁹. These events can present as mild erythema and urticaria or more severely as hypotension, bronchospasms, and chest pain. A review by Lichtenstein et al. suggests that scheduled dosing and using immunomodulators in combination may decrease the rate of infusion reactions by lowering the formation of antibodies against infliximab¹³⁰. Even after doing

this infusion reactions may still occur, so premedication, infusion protocols, or desensitization may be done if necessary. There is still a need for standardized guidelines for preventing and managing such reactions.

IL-12/23 Inhibitors

Ustekinumab (Stelara) is a human monoclonal antibody that binds with specificity and high affinity for the p40 subunit on the IL-12 and IL-23 cytokines¹³¹. This act inhibits these cytokines, thus modulating the Th1 and Th17-mediated inflammation cascades. Because IL-12 drives Th1 responses, while IL-23 supports the expansion and maintenance of Th17 cells, inhibiting these cytokines will decrease proinflammatory cascades that contribute to the pathogenesis of PsO¹³².

Clinical trials in the early phases established the ustekinumab's efficacy against plaque PsO. In a phase I trial, researchers found that ustekinumab improved PASI scores in patients with moderate to severe PsO¹³¹. An additional randomized control trial known as the PHOENIX 1 study also reported similar, reassuring results. At 76 weeks, patients had a improvement of at least 75% in their PASI¹³³.

A few years ago, a 9-year retrospective observational study by Babuna conducted in Turkey evaluated what the long-term outcomes were for 52 patients treated with ustekinumab for up to 105 months¹³⁴. They observed PASI 50, PASI 75, PASI 90, and PASI 100 responses over the course of many years. Specifically, during the first year, 97.8% of participants had a PASI 50, 88.9% had a PASI 75, 53.3% had a PASI 90, and 35.5% had a PASI 100 response. At the fifth year, they found that 100% had achieved a PASI 50, 80.0% for PASI 75, 60.0% for PASI 90, and 40.0% for PASI 100. These

improvements to PASI scores over long term use illustrates ustekinumab's effectiveness for treating and maintaining remission in chronic plaque psoriasis. Additionally, they found that having a healthy weight and biologic-naïvety lead to better long-term responses, specifically for achieving PASI 90.

Within the same cohort, nine patients were chosen to receive adjuvant therapies, and another nine received dose escalation therapy (dose frequency or amount)¹³⁴. These combination and dose-modulating options were found to be successful in recapturing clinical responses for those who had a partial loss of the effects of treatment over time.

The commonly reported side effects after use are upper respiratory tract infections and nasopharyngitis¹³³. Hypersensitivity reactions, headaches, fatigue, and diarrhea have been reported to be mild or moderate in severity. The probability of experiencing these and other side effects rises from the inhibition of IL-12/23. People who are deficient in these cytokines are generally more susceptible to infections contracted from mycobacteria, salmonella, and bacillus Calmette-Guérin vaccinations¹³². Despite this, large-scale clinical trials and post-marketing surveillance have not observed significant increase in serious infections as of late. Going back to the study by Babuna, no dose-related or toxicity was reported over a mean treatment duration of 33.5 ± 21.1 months¹³⁴. The main reason for any account of discontinuation was secondary loss of efficacy as well as not being able to follow-up with the participant, not for safety concerns. Regardless of having a good safety profile, caution and proper screening should still be exercised with any biologic.

IL-17 Inhibitors

One arm in PsO pathogenesis is contributed by the interaction between Th17 cells and keratinocytes. Th17 cells activate in response to IL-23 from myeloid dendritic cells, signaling them to produce IL-17A, a key effector cytokine in PsO. IL-17A eventually binds to IL-17RA/RC receptor complexes on cells in the skin, promoting more inflammatory cytokines like IL-6 and IL-8 that induce keratinocyte hyperplasia and a recycling of inflammation¹³⁵. IL-17F, also interacts with the same receptor as IL-17A, so both cytokines have been posed as good targets for therapeutics¹³⁶.

Secukinumab (Cosentyx®) was the first FDA approved therapeutic in this category of biologics. It is a human IgG1 monoclonal antibody that neutralizes IL-17A. This mode of inhibition has been demonstrated to decrease signs and symptoms of PsO, which was notably seen in the ERASURE and FIXTURE trials. For both studies, over 80% of the participants taking 300 mg of secukinumab achieved a PASI 75 response at week 12, with clear or almost clear skin¹³⁷. These results show the impressive efficacy secukinumab has and confirms IL-17A as an effective target for PsO.

Ixekizumab (Taltz®), a humanized IgG4 monoclonal antibody that also binds to IL-17A, inhibiting it from interacting with the IL-17 receptor. The UNCOVER 1, 2, and 3 trials have been able to establish ixekizumab's efficacy in treating PsO. Here, 80% of the participants treated with ixekizumab achieved significant improvements to their skin (specifically erythema, thickness, and scaling) when using guidelines from the static Physician's Global Assessment (sPGA) and obtained a PASI 75 response at week 12. Moreover, these responses were still stable and sustained for 60 weeks during long-term studies¹³⁸.

Brodalumab (Siliq[®]) has a different mechanism than the other IL-17 inhibitors because it targets the IL-17 receptor A (IL-17RA), not the cytokine. Inhibiting the receptor inhibits downstream cascades of other IL-17 family cytokines, which include IL-17A, IL-17F, IL-17C, IL-17E/IL-25, and IL-17A/F heterodimer. Analysis of the AMAGINE 2 and AMAGINE 3 studies found that when brodalumab was administered at 210 mg every 2 weeks, participants experienced high rates of skin clearance, with up to 86% of them achieving a PASI 90 response, and 74% of them achieving a PASI 100 response at week 120. This clearly shows brodalumab's long-term efficacy in treating PsO symptoms with sustained remission¹³⁹.

Bimekizumab is a more novel biologic that dually inhibits the cytokines IL-17A and IL-17F. The reasoning behind targeting two cytokines instead of one stems from knowing that IL-17A is the main cytokine driving PsO, but IL-17F also promotes a lot of the inflammation that exacerbates it. Bimekizumab is a humanized IgG1 monoclonal antibody that has high affinity for IL-17A and IL-17F. Clinical studies have found that dually neutralizing the cytokines in this way can result in a deeper, more rapid response than targeting IL-17A alone, making bimekizumab a favorable option¹³⁶.

A common side effects present in all IL-17 biologics is increased susceptibility to infections, upper respiratory tract infections and mucocutaneous candidiasis. It makes sense that such infections arise because IL-17 plays an essential role in mucocutaneous immunity and defense against fungal pathogens^{137,138}. Injection site reactions and hypersensitivity have also been observed. Though these effects are manageable, like any other biologic they should be used with caution.

IL-23 Inhibitors

IL-23 inhibitors are different than Ustekinumab which targets both the IL-12 and IL-23 cytokines. IL-23 inhibitors only block the p19 subunit of IL-23, which keeps IL-12-mediated immune responses intact¹⁴⁰. This property allows it to be effective without serious side effects.

Tildrakizumab (Ilumya®) is a humanized IgG1 κ monoclonal antibody that binds to the p19 subunit of IL-23. A retrospective study in Italy had 237 patients with chronic plaque PsO that were treated with tildrakizumab for 52 weeks. By the end of the study, 90.91% of the participants reported a PASI 75 response, and 73.55% and 58.68% reported a PASI 90 and PASI 100 responses, respectively. An absolute PASI ≤ 2 , which means that patients had mild or almost clear PsO, was achieved in 85.95% of patients, with even higher rates of clearance compared to Phase III clinical trials. It was noted that even patients who had not much success with biologics in the past, or those who had cardio-metabolic comorbidities saw significant improvements with treatment with no new safety concerns^{140,141}.

Risankizumab (Skyrizi®) is another humanized IgG1 monoclonal antibody with sequence alterations (L234A and L235A) that decrease unnecessary Fc γ receptor interactions. The LImMitless is a major study that demonstrated Risankizumab's long term efficacy and safety. Participants received continuous Risankizumab treatment for up to 5 years. On week 256, they found that 85.1% of the participants obtained a PASI 90 and 52.3% obtained a PASI 100 response. 85.8% of all participants reported attaining clear or almost clear skin according to the sPGA rubric. Patients also reported

improvements in their quality of life, as outlined by the Dermatology Life Quality Index (DLQI), and there were not many reports of adverse side effects^{140,142}.

Guselkumab (Tremfya®) is the first approved human IgG1 λ monoclonal antibody that targets the p19 subunit of IL-23 that inhibits its binding to the IL-23 receptor. It was found to be specifically beneficial for patients who previously did not find success with IL17 inhibitors. In a two-year study with 61 participants, Guselkumab treatment resulted in 60.7% those participants achieving a PASI 90 response at week 16, and by week 104, 73.8% of them achieved a PASI 90 response. PASI 100 responses were also recorded: 37.7% of participants experienced this at week 16, and then 59.0% of participants achieved a PASI 100 at week 104. It was observed that difficult-to-treat areas such as the fingernails and palmoplantar regions were slower to show signs of improvement, but by week 28, responses in these areas were comparable to other areas on the body. There were minimal to no reports of severe adverse events in the study^{143,144}.

Mirikizumab is a humanized IgG4 monoclonal antibody that targets the IL-23 p19 subunit. In a phase III trial called OASIS-1, Mirikizumab demonstrated significant efficacy at week 16 of treatment. Then, 69.3% of the participants were found to have a sPGA score of 0 or 1 (indicating an appearance of mild or clear skin), and 64.3% achieved a PASI 90 response. These improvements were stayed that way until week 52 even under different dose administrations. The safety profile was comparable to placebo, with low rates of reported side effects^{145,146}.

Despite having low incidences of adverse effects, the most common are upper respiratory tract infections (approximately 8.5%), nasopharyngitis (12.2%), and injection

site reactions (4.0%). These adverse events are generally mild and manageable when treated IL-17 inhibitors¹⁴⁷.

I. Microbiome

More recently, research has turned more attention towards the skin and gut microbiomes, and various studies suggest that they are possible contributors to PsO pathogenesis. Studies have demonstrated that dysbiosis, or a decrease in microbial diversity, may not only influence PsO severity but also increase the rate of metabolic disorders and immune dysfunction. Thus, microbiome-based interventions like fecal microbiota transplantation (FMT), probiotics, and prebiotics, seem to be promising avenues for further exploration.

Some studies have observed that there are differences in the skin microbiome of PsO patients compared to those without it. A study by Olejniczak-Staruch showed that psoriatic lesions had decreased alpha- and beta-diversity compared to healthy skin¹⁴⁹. Specifically, beneficial *Cutibacterium*, *Burkholderia spp.*, and Lactobacilli were lower, while other taxa like *Corynebacterium kroppenstedii*, *Corynebacterium simulans*, *Neisseria spp.*, and *Finegoldia spp.* were more abundant. However, a study by Chen warned that such recorded differences may be due to imperfect sampling techniques, environmental factors, and intrinsic host factors¹⁵⁰. These unfortunately can create inconsistencies in the literature regarding skin microbiome in PsO.

The gut microbiome in PsO and psoriatic arthritis patients has also garnered attention because multiple studies have seen a dysbiotic pattern for these individuals. Studies by Olejniczak-Staruch and Myers found that PsO was associated with the less of

a presence of beneficial bacteria, specifically *Faecalibacterium prausnitzii*, *Bifidobacterium spp.*, and *Lactobacillus spp.*. On the other hand there was an increase in less beneficial bacteria like *Escherichia coli*, *Campylobacter sp.*, and other inflammatory species^{149,151}. Scher et al. additionally found supporting evidence of decreased bacterial diversity in psoriatic arthritis patients, an observation that is corroborated the study by Codoñer et al., who noted increased bacterial diversity in certain PsO cohorts, illustrating the complex and heterogenous nature of the changes to gut microbiota^{152,153}.

A finding that has been consistent across many studies is an increased Firmicutes-to-Bacteroidetes ratio in PsO patients. This imbalanced ratio is suggested to have a role in local gut inflammation as well as obesity and type 2 diabetes, comorbidities that are commonly seen with PsO. The loss of such butyrate-producing bacteria leads to a decreased ability to maintain regulatory T cell numbers and suppression of inflammatory Th17 responses. These consequences imply a relationship between the disruption of the gut epithelial barrier and systemic inflammation^{150,151,152}.

Amidst these findings, a study Koper pointed out that the gut microbiota for people with PsO may benefit from prebiotics, which are rich in polysaccharides, because it may help restore beneficial microbial populations and improve the intestinal barrier¹⁵⁵. Doing so will decrease inflammation by decreasing additional exposure to microbial antigens that can trigger or make inflammation worse.

Although relatively new, FMT has emerged as a potential intervention that hopefully restores healthy gut microbes. The historical use of FMT has been dated as far back as 1,700 years ago with ancient Chinese practices that have laid some of the

foundations for its uses today¹⁵⁶. Recent studies by Almeida et al. and Karimi talked about some of the more updated measures for preparing and storing fecal matter for FMT, but challenges still remain^{157,158}. Variables like being exposed to oxygen during sample processing disrupts the viability of obligate anaerobes, leading to disparate results. For instance, a study by Kragnaes et al. investigated patients with active peripheral psoriatic arthritis being treated with FMT. While FMT was deemed generally safe, it did not exhibit significant benefits compared with the placebo that underwent a sham procedure¹⁵⁹. On the flip side, a study by Yin demonstrated significant improvement in a patient with severe plaque PsO and irritable bowel syndrome after two administrations of FMT¹⁶¹. In another study done by Kragnaes et al., they set up a protocol for a double-blind, placebo-controlled trial was outlined to aim to test if FMT combined with methotrexate could reduce disease activity¹⁶⁰. They hoped that by creating such a protocol it would help standardize the administration and measurements of FMT and eliminate disparities for future FMT studies.

Probiotics have also been explored as a means to improve gut microbiota and ameliorate PsO symptoms. A study by Navarro-Lopez did a randomized, double-blind, placebo-controlled trial where the administration of a probiotic mixture significantly improved PASI scores and sPGA in patients with PsO¹⁶². Similarly, a meta-analysis by Kebo Wei confirmed the benefits of probiotic supplementation which clearly outperformed placebo controls, with consistent improvements to PASI scores and Dermatology Life Quality Index scores¹⁶³.

It is not just probiotics that have been seen to be beneficial. Formulations that combine probiotics with precision prebiotics are thought to target immunological pathways more effectively. A study by Buhas confirmed this theory in a 12-week treatment of using a probiotic/prebiotic combination, after which patients had improved clinical scores and their gut microbiota changed to exhibit more anti-inflammatory properties¹⁶⁴. Another study by Choy similarly replicated these results on Southern Chinese PsO patients by using an innovative E3 probiotics formula and found that it beneficially remodeled the gut microbiota and eliminated dysbiosis¹⁶⁵.

Studies using animal models have shed light on the mechanism of treatments regarding the microbiome. Chen was able to demonstrate that supplementation with *Lactobacillus reuteri* increased the expression of the anti-inflammatory cytokine IL-10, rebalanced Th17/Treg ratios, and protected against imiquimod-induced psoriasis-like inflammation in mice¹⁶⁶. Additionally, another study reported that *Bifidobacterium breve* CCFM683 ameliorated psoriasis in a dose-dependent manner by restoring the gut flora and preserving the intestinal barrier¹⁶⁷. However, a study by Suriano concluded that treatment with *Lactobacillus rhamnosus* did not exhibit significant improvements in skin lesion scores. This finding shows that selecting the type of strain and dosing are critical components to consider when modulating the microbiome for treatment, and indicates the need for further investigation before widespread use¹⁶⁸.

Probiotic interventions have been seen as generally safe. It was shown that the rate of adverse effects for those treated with probiotics were similar to or lower than the placebo, gastrointestinal symptoms being the most common side effect¹⁶⁹. A review by

Rawal further highlighted that prebiotics and postbiotics can maintain and improve skin health by producing antimicrobial compounds that discourages the colonization of pathogenic bacteria, a property that can be potentially taken advantage of for treating psoriatic lesions which are prone to infections¹⁷⁰.

J. New Drug Delivery Systems

Ineffective drug delivery remains a challenge for pharmaceutical treatments. Thus, new mechanisms for delivering current medications have been explored as potential improvements for treatment.

Aerosol Foam: A study by Lind found that incorporating already established drugs into an aerosol formulation significantly improved drug penetration through the skin¹⁷¹. Specifically, supersaturating calcipotriene and betamethasone dipropionate in the aerosol foam made them more bioavailable. They theorize the mechanism relies on the foam's ability to alter the stratum corneum of the skin which allows for rapid intracellular delivery. This is significantly more efficient than the hydration-dependent penetration seen with the more common creams, gels, and ointments.

Nanofibers: Advances in nanotechnology have made nanofibers a possible carrier for drugs used for PsO. A study by Thakur investigated the effects of combining tazarotene and calcipotriol and co-loading them onto polyvinyl alcohol/polyvinylpyrrolidone nanofibers that were interweaved into a hydrogel film¹⁷². This novel set up not only increased drug penetration and exhibited a controlled release, but as a plus also promoted skin regeneration, cell adhesion, and proliferation because of

the regenerative capacity nanofibers have. The benefits of better drug penetration and skin recovery make nanofibers a very promising avenue for topical PsO treatment.

Nanogels are three-dimensional, cross-linked polymeric networks that are made to encapsulate therapeutics. In a review by Maddiboyina, nanogels were praised for their biocompatibility, adjustable mechanical strength and controlled release, and excellent skin penetration ability¹⁷³. A study by Pawan Patel reinforced these claims by incorporating tazarotene on a nanogel¹⁷⁴. They saw that this method resolved tazarotene's poor solubility and stability in aqueous environments and increased its bioavailability and efficacy on the skin. Additionally, nanogels' ability to control drug release can effectively maintain effective drug concentrations in affected psoriatic skin layers only, decreasing systemic toxicity.

Liposomal Gels: Another potential delivery method uses liposomes. A study by Saka investigated the effectiveness of a topical liposomal gel that had bexarotene in an imiquimod-induced psoriatic plaque mice model¹⁷⁵. They observed improved penetration and retention of bexarotene in psoriatic skin, which decreased inflammation and improved outcomes. They speculate that because liposomal formulations can merge with cellular membranes, they can be a solution for drugs that have low bioavailability when used through traditional delivery methods like bexarotene.

AI and Nanotechnology: Optimizing treatments for PsO not only depends on what method drugs are delivered, but also on selecting the right drugs. A review by Tarek detailed drug repurposing by using nanotechnology and machine learning¹⁷⁶. In it they noted that traditional treatments face issues like systemic toxicity and poor localization.

So, turning to alternatives like repurposing FDA-approved drugs for topical application, and incorporating them with nanocarrier systems are potential solutions. They also indicated that machine learning can help predict optimal drug combinations, which can eliminate unnecessary time and cost that comes with drug discovery. Though still in development, the use of AI in drug delivery and discoveries has the potential to personalize and increase the efficacy of PsO treatment.

Microneedle Patch: A study by Li Huang discussed how microneedle patches target the inflammatory and relapse processes of PsO¹⁷⁷. The patch that was made combined a macrophage membrane, which can target multiple inflammatory cytokines, with etomoxir, a compound that targets CD8⁺ tissue resident memory T cells that are involved in PsO relapse. They found that using polydopamine in combination with the microneedle set up further increased drug retention and skin penetration. This new delivery method not only improved psoriatic symptoms, but it exhibits better potency by targeting underlying mediators involved not only in inflammation but also relapse.

K. Novel Approaches

Combining Topicals: A study by Heim combined topical treatments like emollients and steroids with the vitamin D analogue calcipotriol, and observed how this affected PsO patients¹⁷⁸. They tested betamethasone foam alone, a combination of calcipotriol/betamethasone foam, a clobetasol propionate ointment, and a placebo. They found that the calcipotriol/betamethasone combination treatment was better at eliminating both the epidermal and dermal number of CD8⁺ T cells. This combination also decreased CD8⁺ IFN γ ⁺ cells and IL-17⁺ MPO⁺ neutrophils, which are markers of inflammation in

PsO. These results show the potential combination therapy has by its ability to target multiple pathways and its effectiveness compared monotherapy.

Biologics and Phototherapy: A review by Farahnik added to this by looking at the efficacy and safety of combining biologics with phototherapy¹⁷⁹. This review took data from randomized controlled trials and other studies that used biologics like etanercept, ustekinumab, adalimumab, and infliximab that were combined with NB-UVB therapy. They concluded that the evidence suggested that combination therapy not only led to better clinical outcomes, but it also was relatively safe, with less than 3% of patients reporting any safety concerns. Even though the long-term effects of combination therapy are not well known, what is certain is that phototherapy used with biologics is a promising option for patients who do not obtain adequate results with monotherapy or traditional treatment methods.

Nanotechnology Combination: Building on the concept of combining different therapies, a study by Asad investigated a nanotechnological approach that used methotrexate and tacrolimus¹⁸⁰. They used an imiquimod-induced PsO model and tested Eudragit E100 nanoparticles embedded in a chitosan hydrogel matrix. The optimized nanoparticles were the appropriate particle size and exhibited high drug entrapment efficiency that led to increased penetration and sustained drug release into deeper layers of the skin. They noted significant decreases in TNF- α and IL-6, as well as improvements in histopathological features and a decrease in systemic inflammation. These findings show the potential benefits of using nanotechnology in treating PsO.

Targeting T-Cell Signaling: Another promising approach is by inhibiting interleukin-2-inducible T-cell kinase (ITK) which is involved in T-cell activation and differentiation. Previous studies have shown that ITK inhibitors not only reduced inflammatory markers like ear and back skin thickness, myeloperoxidase activity, and immune cell infiltration, but it also decreased Th17 cells and increased regulatory T-cells¹⁸¹. These findings offer a potential new target for ameliorating psoriatic inflammation.

New Topicals: Tapinarof cream is a topical aryl hydrocarbon receptor–modulating agent that has been effective in phase III clinical trials. It improved sPGA and PASI scores, as well as decreased pruritus sensations on the skin, though some local reactions were reported¹⁸². Another new topical is roflumilast cream which is a phosphodiesterase-4 inhibitor. It was recently approved for plaque PsO because it was found to be relatively safe and convenient with its once-a-day application. Phase III trials have also seen significant clearing of the skin and reduced itch severity¹⁸³.

Natural Compounds and Barrier Restoration: Natural products have also gained popularity, with studies exploring compounds like amygdalin and avocado-based treatments. Amygdalin has demonstrated its anti-inflammatory and immune-modulating properties by decreasing epidermal thickness and inflammatory cytokines, while simultaneously increasing the skin barrier and integrity proteins filaggrin, involucrin, and keratin¹⁸⁴. On a similar note, avocado-based topical treatments take advantage of the avocado extract's antioxidant and moisturizing properties, the application of which has led to better skin elasticity and moisture retention with a decrease in inflammatory symptoms, all of which are pluses for managing PsO symptoms¹⁸⁵.

Systemic and Repurposed Therapy: Brepocitinib is a systemic, novel TYK2/JAK1 inhibitor that had promising results in patients with psoriatic arthritis. Brepocitinib achieved very positive American College of Rheumatology response rates and improvements to PASI scores, as well as maintained its efficacy for 52 weeks with a good safety profile¹⁸⁶. The repurposing of drugs like talazoparib, a PARP inhibitor used in tumor therapy, has also been investigated in mice induced with PsO. There, they found that talazoparib promotes terminal differentiation of keratinocytes, which is good for restoring normal skin architecture, but it also ended up increasing pro-inflammatory chemokines¹⁸⁷. Because of these dual effects, there is a need for further research regarding the repurposing of drugs.

Antioxidants: Lastly, the antioxidant ergothioneine has been studied for its role in modulating macrophage polarization and inflammation. Ergothioneine is known to promote anti-inflammatory M2 macrophages over the pro-inflammatory M1 macrophage, and it can also decrease the production of IL-1 β , COX-2, and TNF- α . Ergothioneine has also been found to modulate the NF- κ B/JAK-STAT3 pathway, which ameliorated PsO symptoms in experimental models¹⁸⁸. The mechanism by which it decreases inflammation suggests that antioxidants could be potentially integrated as a therapeutic agent for treating PsO.

DISCUSSION AND CONCLUSION

PsO management employs a variety of therapeutic. These include topical agents like vitamin D analogs (calcipotriene, calcitriol), retinoids (tazarotene, acitretin, alitretinoin), corticosteroids, calcineurin inhibitors (tacrolimus, pimecrolimus), and emollients. Phototherapy, systemic treatments (biologics), and nanotechnology-based delivery, microbiome manipulation, and combination treatments are newer avenues. Each approach has pros and cons regarding their potency, safety, convenience, and long-term effects.

Topical therapies are mainly considered as first-line for mild to moderate PsO, or as adjuncts with vitamin D analogs because they are good keratinocyte modulators, but they can cause irritation or rare hypercalcemia with long-term use. Retinoids also effectively regulate keratinocyte differentiation, but the cons it brings are mucocutaneous dryness and hyperlipidemia. Corticosteroids are great for rapid management but cutaneous atrophy and systemic toxicity are valid concerns with long-term use. Calcineurin inhibitors are great for sensitive or hard to reach areas due to their lower risk of thinning the skin. Emollients do not decrease inflammation per se, but they significantly improve the skin's hydration and barrier, so they are best used as complements to other therapies.

Phototherapy that specifically uses NB-UVB is a great option with better safety than broadband UVB or PUVA, though those can be very effective despite the higher risks of photoaging and malignancy.

Diets that contain more anti-inflammatory nutrients like Mediterranean or plant-based diets, combined with weight management can help PsO symptoms and improve comorbidities, highlighting the multifactorial nature of PsO and the benefit of holistic care. Still, more long-term randomized controlled trials are needed before solidifying dietary approaches.

TNF- α inhibitors (etanercept, adalimumab, infliximab, certolizumab pegol) offer consistently high clearance rates but require careful screening for infection risks and malignancy. Notably, infliximab's weight-based dosing has prompted questions about whether higher doses yield more sustained remission in overweight and obese patients, possibly reflecting the greater inflammatory burden in such individuals. Elsewhere, the IL-12/23 inhibitor ustekinumab demonstrates enduring efficacy by modulating Th1 and Th17 pathways through blocking the p40 subunit, though some patients require combinatorial therapy or dose-escalation. IL-17 inhibitors (secukinumab, ixekizumab, brodalumab, bimekizumab) also exhibit high skin clearance but carry a risk of mucocutaneous candidiasis and are contraindicated for patients prone to inflammatory bowel disease or certain psychiatric conditions. IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab, mirikizumab) can selectively target IL-23's p19 subunit, leading to excellent PASI 90/100 response rates with minimal adverse effects. Risankizumab treatment particularly resulted in short- and long-term skin clearance while having a safe profile, making it a potential candidate for first-line biologic therapy, especially when the more common TNF- α or IL-17 inhibitors are contraindicated.

A reduction in microbial diversity in the skin or gut can worsen psoriatic inflammation and predispose individuals to comorbidities. Treatments that seek to restore the microbiome through FMT, probiotics, and prebiotics have shown conflicting results, with some lowering disease severity, while others remain inconclusive. Standardized protocols and larger clinical trials are warranted to clarify the mechanisms of microbial imbalance in PsO. On the other hand, new drug delivery systems like nanofibers, nanogels, liposomal gels, overall have had positive results and are being explored for their abilities to enhance topical penetration and minimal systemic toxicity. Combination therapies (biologics plus phototherapy or topicals used together) have also shown a synergistic effect that can minimize exposure to toxic agents.

In conclusion, PsO treatment strives to be more targeted and personalized, considering the genetic, immune, and environmental factors inherent to its pathogenesis. Biologics, especially IL-23 and IL-17 inhibitors, have consistently achieved high levels of disease clearance, while TNF- α inhibitors remain valuable, particularly for patients with psoriatic arthritis or certain comorbidities. Topical agents and phototherapy remain the staple for milder or localized disease. Adjunctive therapies such as weight control, anti-inflammatory diets, and microbiome therapy can provide holistic care, although these areas need further research. Future research should mainly prioritize trials of newer biologics and nanotechnology-based formulations, refine dose optimization, especially for patients with obesity, and better integrate genetic and microbiome data to match individuals with the most effective combinations. By merging pharmacologic treatments

with lifestyle and microbiome modulation strategies, PsO treatment can then confidently boast long-lasting remission and improved quality of life.

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