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A Report from the 33rd Annual European Academy of Dermatology and Venereology (EADV) Congress

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SUMMARIZING SESSIONS WITH A FOCUS ON PSORIASIS

INTRODUCTION

The 33rd Annual European Academy of Dermatology and Venereology (EADV) Congress was held in Amsterdam, Netherlands, from September 25 to 28, 2024. The annual meeting featured over 650 speakers from more than 50 countries, delivering over 180 presentations to an audience of more than 17,000 delegates worldwide. The following congress report includes a summary of 23 lectures on psoriasis throughout the congress, including a summary of the International Psoriasis Council (IPC) Symposium: Data Driven Care in Psoriasis.

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Big Data: Challenges and Opportunities

Tamar Nijsten, PhD
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Big data refers to five V's: "Volume," meaning the quantity of generated and stored data; "Variety," which refers to how the type and nature of the data varies; "Velocity," referring to the speed at which the data is generated and processed; "Variability," which refers to inconsistency of the data set which can hamper processes to handle and manage it; and "Veracity," referring to the quality of captured data, which can vary greatly affecting accurate analysis.

Data is often unstructured, simple, and rough. It needs transformation before becoming knowledge, metaknowledge, and expertise (structured, sophisticated, and granular). Artificial intelligence (AI) data processing gives more structured outcomes, and machine learning is the future promise for data processing and combining data sets. This can help go from a reactive model to a proactive one in clinics[1].

Current data is much more complicated and complex with multi-level data integration, including phenomics, metabolomics, proteomics, epigenomics, and genomics. Big data with more volume is not always beneficial because adding more data at a certain point means more confusion. At this point, machine learning can be helpful (Figure 1).

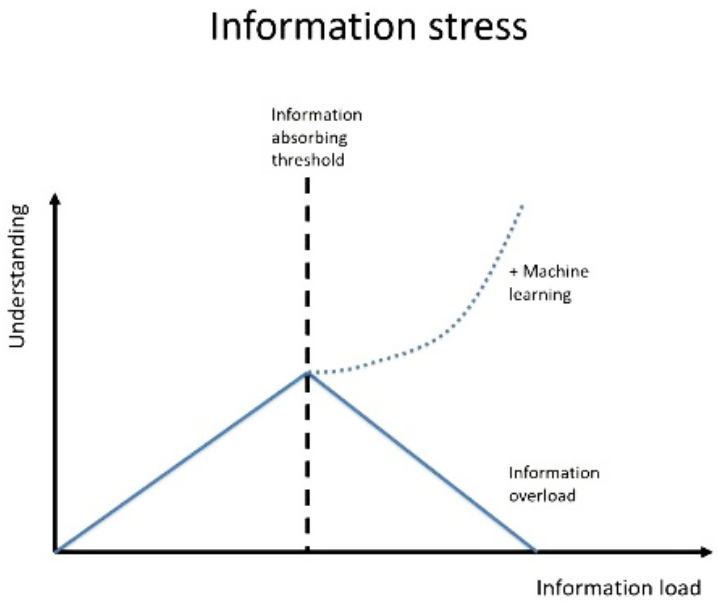

Figure 1: A diagram illustrating that adding more data means more confusion with big data volume at a certain point. At this point, machine learning can be helpful to improve data understanding.

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The Role of AI in Psoriasis Care: A Vision for the Future

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Artificial intelligence (AI) is bringing crucial changes to the field of psoriasis, including 1) psoriasis diagnosis for patients and non-dermatologists; 2) automated psoriasis scoring; 3) omics for personalized treatments and predictive analysis; 4) AI-automated documentation and patient information, telemedicine and remote diagnosis; 5) virtual follow up[1].

Dr. Alexander Navarini illustrated some studies showing how good AI-based diagnosis of psoriasis is. Studies showed that dermoscopy-driven models can distinguish psoriasis from erythrosquamous conditions and scalp psoriasis from seborrheic dermatitis[1].

Another example of AI in psoriasis care is Google Lens. The initial plan was to make a full derm assistant with history taking, including skin type, duration of existence, and other symptoms. However, it was officially abandoned due to insufficient Food and Drug Administration (FDA) approval. In Europe, it is classified as a Class 1 device. ChatGPT4 by Open AI also allows image classification with higher diagnostic accuracy than Google Lens.

AI-based psoriasis diagnosis works very well, at least for plaque-type psoriasis, but prospective studies are pending. Regulations on medical devices are becoming stricter than they should be. Decision support for non-dermatologists is valuable but needs official validation before being rolled out.

AI can also help measure Psoriasis Area and Severity Index (PASI) scores. The United States Food and Drug Administration (FDA) has not reviewed this, but it is helpful as an informal decision-support tool. Smartphone-based PASI is also available.

On the other hand, machine learning (ML) algorithms for distinguishing benign versus malignant lesions performed significantly worse on pigment-rich pictures. They were less accurate for imaging with darker skin tones (Fitzpatrick V-VI) than for images with lighter skin tones. This highlights the problems of bias in AI systems and the need for diversity training data.

Audio AI can also be used in hospitals for administrative tasks like writing referral letters. This impacts physicians' daily lives by saving time and money.

COVID-19 has told us that telemedicine is beneficial for virtual follow-up. Prescriptions, including systemic drugs, can be given online when laboratory checks can be organized. However, in-person visits are preferred for a whole-body skin examination, severe psoriasis, children, patients refusing prescribed medication, and joint affection[2].

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Preventing Psoriatic Arthritis

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Mortality from psoriatic arthritis (PsA) is higher than mortality in psoriasis and the general population. Nail psoriasis is a significant risk factor for psoriatic arthritis development. Other risk factors include obesity, smoking, severity of disease, trauma, etc.

It is known that there is a common shared immune pathway between psoriasis and PsA. Many organizations define different stages between psoriasis and psoriatic arthritis where there is interception (preclinical PsA, subclinical PsA, and prodromal PsA), and the question is when do we need to intervene to prevent PsA? Regarding the transition from psoriasis to PsA, the ideal time to detect preclinical PsA is when the immune system shifts to affect the musculoskeletal system.

Studies show that imaging can detect structure changes in the joints of patients with psoriasis without symptomatic psoriatic arthritis. These patients have a higher risk of developing psoriatic arthritis[1]. Preliminary data from retrospective studies shows that biologics can prevent the development of PsA compared to phototherapy and methotrexate[2]. Still, more evidence is needed to prove this, as the current studies are liable for bias due to the non-randomization of retrospective studies.

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Sustaining Psoriasis Remission

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Different studies have varying definitions of remission in psoriasis. A consensus is needed to define clinical remission, including the appropriate endpoint and whether the patient should be on or off treatment. Many biologics can achieve PASI 90; complete skin clearance is a viable treatment goal.

Studies showed an improved rate of skin clearance via early intervention. Greater odds of being a super responder are achieved if the patient started a biologic within two years of psoriasis onset or if they are biologic naïve.[1] However, access to care is a challenge for early intervention. Barriers to accessing specialized care include that a diagnosis of psoriasis may be missed or delayed in primary care for up to five years, and referral to specialist care may be delayed to up to 15 years after diagnosis. There are a limited number of dermatologist specialists worldwide, and access to biologics is restricted to individuals with moderate to severe psoriasis.

After reaching the target, there is an opportunity for dose reduction once the skin clearance is achieved. This decreases the health burden on patients. Also, for reducing long-term drug burden, there is an opportunity for personalized and precision management. A study showed that, following biologic withdrawal, half of the patients remain clear at six months following biologic withdrawal. An ongoing study in the United Kingdom, patient-led "as needed" treatment, shows that patients receive therapy based on their needs. This aim is to lower the risk of infection and adverse events, lower the cost, and reduce the long-term drug burden.

Interestingly, single-cell sequencing studies could identify a novel type of proinflammatory fibroblasts that may serve as the mechanism of biologic-induced psoriasis resolution. In addition, Inflammatory memory in tissue has a role. It is probably maintained at multiple levels, from DNA, epigenetics, RNA, and proteins to the actual structure of the skin and the resident memory T-cells. The differentiation of the resident memory T cells is affected by IL-23. The hypothesis is that early intervention with anti-IL 23 biologics may lead to the depletion of the resident memory T cells and the induced disease modification.

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Recent Treatment Advances in Pediatric Psoriasis

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Unfortunately, pediatric plaque psoriasis is frequently misdiagnosed as atopic dermatitis, seborrheic dermatitis, or dermatophyte infection. In children, plaques have thinner scales and are not as well circumscribed. Children have more facial involvement. Scalp involvement is up to 79% more common in girls than boys. Nail changes are in 39% or more in boys. Pediatric psoriasis dramatically impacts the quality of life, especially on scalp itch. Comorbidities in children include juvenile idiopathic arthritis, inflammatory bowel disease, particularly Crohn's disease, and obesity. Obesity precedes psoriasis in over 90% of cases and persists with the disease.

Approved treatments in pediatric psoriasis are an issue. Topicals in pediatric psoriasis largely reflect the use in adults without specific efficacy and safety studies in pediatrics. Mid to potent topical corticosteroids, calcineurin inhibitors (on face and groin), retinoids/tazarotene, topical vitamin D analogs, tar, anthralin: Almost none is approved in pediatric psoriasis. Calcitriol plus betamethasone dipropionate is FDA-approved in various formulations for ≥12 years old.

Emerging topicals include once-daily roflumilast cream 0.3% and foam (phosphodiesterase-4 inhibitor), now approved for children 6 to 17 years old (October 2023). Phase 3 trial extended to children as young as two years old. Tapinarof (aryl hydrocarbon receptor agonist) is expected to be approved for children over six years old soon.

Beyond topical therapy, phototherapy is not always convenient. The requirement for twice or three times treatment per week for months is untenable. Home units are costly and require training. However, the advantage of phototherapy is that there is no systemic immunosuppression.

For other systemic agents, retinoids can be used for hyperkeratotic sites but have less impact on inflammation. It is mainly used in combination, especially for palmoplantar involvement. Cyclosporine is an effective agent, but it has the most significant toxicity. Methotrexate is the most common conventional systemic drug used, with decades of experience in its use in children. It is less costly than biologics but slow and takes months to achieve the best effect.

The FDA-approved biologics for pediatric psoriasis include etanercept, adalimumab, ustekinumab, secukinumab, and ixekizumab. A progressive, better efficacy was observed for psoriasis in children with IL 23/Th17 targeting. Ustekinumab is approved from six years of age. Ustekinumab is most effective for the CARD-14 function variant (consistent with pathogenesis). CARD-14 associated papulosquamous eruption (CAPE) is a monogenic disorder that involves early onset of disease (most in the first year of life), no remission without treatment, and often shows features of psoriasis and Pityriasis Rubra Pilaris, prominent facial involvement in the cheek chin and ears, usually spare periorbital area, usually truncal involvement, sometimes erythroderma, and may be patterned.

Regarding the benefits versus risks of biologics, infrequent dosing with biologics is convenient with fewer lab monitoring. Efficacy keeps improving with newer biologics, best with Th17/IL-3p19 biologics. This is particularly important for impacting quality of life and managing hard-to-treat areas like nails, palms/soles, etc. Significant side effects are unusual with biologics; there is no difference in the risk of serious infection of biologics versus systemic non-biologic therapies.

Regarding TNF inhibitors, etanercept is approved for ≥ 4 years of age, but it is the least effective and needs weekly shots. Adalimumab is given every two weeks. All TNF inhibitors require TB monitoring. Ustekinumab is approved for ≥ 6 years of age. It achieves a higher PASI 75 than TNF inhibitors; the shots are given every three months, and there is less concern for the reactivation of TB infection. Th17 inhibitors have the highest PASI 75 among available agents, injections are

monthly, and there is the potential risk of inflammatory bowel disease and Candidal infections (but phase 3 data are reassuring).

Of note is that the reduction in the quality of life of pediatric psoriasis patients is directly related to disease severity. The greatest improvement in quality of life is associated with PASI 90 or greater, ≥90% decrease in body surface area involvement, and the use of systemic treatment.

Biologics in phase 3 clinical trials in pediatric patients with moderate to severe psoriasis include Guselkumab, Tildrakizumab, Risankizumab, Certolizumab, Bimekizumab, Brodalumab. Some data is available for using apremilast in pediatrics, while deucravacitinib is currently in trial.

Overall, psoriasis in children differs morphologically from that in adults, but the central pathogenesis is similar concerning targets for therapy. More targeted and safer therapy that does not require blood monitoring now lowers the bar for systemic treatments for moderate to severe pediatric psoriasis to treat hard-to-treat nails, scalp, and palmoplantar psoriasis. The question remains: will earlier initiation of treatment in severe disease reduce the risk of developing comorbidities?

Recategorization of Disease Severity in Pediatric Psoriasis

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Dr. Marieke Seyger addressed the questions, "What is the definition of severe psoriasis in pediatrics?" and "When should systemic treatment be initiated?" The proposed Rule of tens for current severe psoriasis from the clinician's point of view defines that severe psoriasis means involvement of body surface area of more than 10%, and/or PASI more than 10, and/or DLQI score more than 10. The IPC consensus statement says psoriasis patients should be classified as topical or systemic therapy candidates. The latter are patients who meet at least one of the criteria: body surface area of more than 10, disease involving special areas (face, palms, soles, genitalia, scalp, or nails), and failure of topical therapy.

The objective of this study was to determine the percentage of pediatric patients with psoriasis fulfilling the Rule of 10 and IPC's definition and based on which criterion and to determine the influence of clinical characteristics (high impact size involvement, age, sex, psoriasis duration, type of therapy, and BSA) on cDLQI. Study data were retrieved from the childCAPTURE registry [Nijmegen, 2008 to present]. This is a prospective longitudinal observational daily practice Pediatrics psoriasis registry with more than 700 children, including referrals from GPs and dermatologists, and includes all treatments. Each visit, the patient is scored for cDLQI, PASI, BSA, and side effects.

According to the Rule of 10, 49% of children in the registry will fulfill the definition of severe psoriasis. Surprisingly, according to the IPC criteria, 90.6% of children have high-impact site involvement, and 92.4% of children would be candidates for systemic treatment, which is not applicable. This is likely explained by the fact that children are highly involved in the scalp, intertriginous areas, and face. Results also showed that age (teenage 13-17), PASI, and high-impact site involvement significantly impact cDLQI.

In conclusion, R10 is stricter than IPC's definition: 49% versus 92% qualify for systemic treatment. Almost all children have high-impact site involvement (90.6%), even if the threshold scalp involvement was identified as more than 50% of the area affected (73.9%). Therefore, the adult definition in current forms does not apply to pediatric patients. Data from this study mandates establishing a new definition for systemic therapy initiation in pediatric psoriasis patients.

Challenging Case with a Focus on Pediatrics

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Dr. Mona El-Kalioby presented a case of a 9-year-old boy who presented with plaque psoriasis. The child was born to consanguineous parents and had no family history of psoriasis. Psoriasis started at the age of 6. The child had a long history of systemic symptoms since infancy, before the onset of psoriasis. During the first year of life, the child had persistent watery diarrhea and hepatomegaly. Gastrointestinal endoscopy showed intraepithelial lymphocyte infiltration in a celiac-like pattern. However, anti-tissue transglutaminases (IgA and IgG) were negative. A liver biopsy showed distorted architecture & portal fibrosis. By the third year of age, the child developed severe autoimmune hemolytic anemia & immune thrombocytopenia (positive direct positive Coombs test and hypercellular bone marrow). Hemoglobin repeatedly fell to 4 g/dl, and the child required frequent blood transfusions (10 times during that year. The child was investigated for immunodeficiency, and the investigation revealed a low level of IgG and IgM, a reduced number and percentage of $CD19^+$ B cells (humoral immune defect), and defects in regulatory T cells (Tregs). In the period between 3-6 years of age, the child develops recurrent attacks of pneumonia. At the age of 6, the child developed plaque psoriasis that appeared on the scalp, arms, and legs, with no arthritis and no nail affection, and it was confirmed by skin biopsy. On reviewing the literature, it was found the child's manifestations can be explained by having LRBA deficiency disorder, for which the child was investigated. Flow cytometry confirmed that the child had a marked deficiency of LRBA protein, and a genetic, molecular diagnosis confirmed a homozygous frameshift deletion affecting the LRBA gene.

LRBA deficiency is an acronym that stands for Lipopolysaccharide-Responsive and Beige-like Anchor protein. It is a rare, autosomal recessive disorder characterized by autoimmunity, lymphoproliferation, and immune deficiency. It has a broad spectrum (variable presentations), including chronic diarrhea, hypogammaglobulinemia, organomegaly, recurrent infections, lung abnormalities, autoimmune disorders (autoimmune hemolytic anemia, immune thrombocytopenic purpura, inflammatory bowel diseases, and type I diabetes mellitus, autoimmune thyroiditis). LRBA protein functions by preventing the breakdown of Cytotoxic T lymphocyte antigen-4 (CTLA-4), an inhibitory receptor on the surface of Tregs, and therefore it maintains the regulatory functions of the Tregs. With LRBA deficiency, CTLA-4 degradation is uninhibited, and this results in immune dysregulation & autoimmunity.

Relation of LRBA deficiency to psoriasis can be explained by 1) stimulation of T cells, immune dysregulation, and autoimmunity, which is a shared part of the pathogenesis of psoriasis), 2) recurrent infections due to immunodeficiency in LRBA deficiency patients and receiving therapies like systemic corticosteroids, which can trigger the development of associated psoriasis.

For systemic conditions, the patient was treated with systemic corticosteroids (methylprednisolone), immunosuppressives (cyclosporine and azathioprine), and IVIG. For psoriasis, sequential therapies were tried with topical calcipotriol/betamethasone ointment, which showed only a modest response. The psoriasis remained treatment-resistant despite increasing cyclosporine to 75 mg/day and trying acitretin and rapamycin. During this period, the patient experienced another infection, triggering erythrodermic psoriasis, which required hospitalization. Treatment of the general condition and management of infection improved psoriasis, after which the patient was prepared for bone marrow transplantation. In conclusion, thorough history-taking and assessment in pediatric psoriasis are crucial. Systemic disorders are important when systemic symptoms are present.

Challenging Case with a Focus on Data Driven Care

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Dr. Ravi Ramessur presented a case of a 30-year-old woman. She had a nine-year history of psoriasis and had extensive disease with scalp and nail involvement. She is a single mother with three children, one of them has a learning disability. She smokes ten cigarettes per day and drinks 20 units of alcohol per week. She had a family history of psoriasis, diabetes, and heart disease. She was started on UVB phototherapy (30 sessions) and initially had a good response (PASI 20→ 2.3). Later, she relapsed and started methotrexate for recurrent disease. But it has to be stopped after two months due to a deranged liver function test. She started apremilast but had to be stopped due to an episode of depression after five months. At the age of 36, she developed acute ischemic stroke with a left-sided paresis, and she was started on aspirin, clopidogrel, atorvastatin, and bisoprolol.

The patient's quality of life was markedly affected by the stroke event, and she had several questions, including, "Is there a connection between psoriasis and cardiovascular disease?" and "If my cardiovascular disease is well controlled with my stroke medication, will that help my psoriasis?"

Cardiovascular comorbidity is more prevalent in psoriasis, where there is an increased risk (3-4 times) of stroke and increased risk (4-5 times) of myocardial infarction. There is an increased incidence of cardiovascular mortality where there are 3.5 excess deaths from cardiovascular disease in psoriasis per 1000 patients-years. However, the relation between psoriasis and cardiovascular disease is not fully understood. One theory is that cutaneous inflammation propels systemic inflammation, which can lead to cardiovascular disease. There is evidence from clinical trials that plaques of cardiovascular disease improve with biologic treatment of psoriasis. If psoriasis leads to cardiovascular events, this will lower the threshold for systemic treatment as this can potentially decrease the risk of cardiovascular events.

Psoriasis and cardiovascular disease share confounding factors, e.g., metabolic syndrome and smoking. The objective of the current study was to evaluate the bidirectional relationship between psoriasis and cardiovascular disease and to identify the influence of crucial confounding factors. Mendelian Randomization technique was used. Results showed no evidence that genetic predictors of psoriasis are associated with cardiovascular disease; however, results showed that genetic predictors of cardiovascular disease increase psoriasis risk. The association between cardiovascular disease and psoriasis and the association between stroke and psoriasis was no longer significant when adjusted for other factors.

In conclusion, the biology of cardiovascular disease probably influences the biology of psoriasis. The value of this research is reflected in the future by the identification of biomarkers that can help with risk stratification to help identify individuals who are at high risk of developing cardiovascular disease early and, secondly, identifying the molecular that could potentially identify new drug targets for both psoriasis and cardiovascular disease. Genetics can be a powerful computational tool to help understand the relationship between psoriasis and its comorbidities. Awareness of this association is needed at the patient and the health professional level to help screen for risk factors. Dermatologists must consider a more proactive multidisciplinary approach to identifying and treating early atherosclerosis, particularly in high-risk patients with psoriasis.

Inflammatory Memory and Disease Modification

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Theoretically, prerequisites to establish disease modification include: 1) objective measurements of the inflammatory activity exist, 2) knowledge exists of how a disease would evolve without intervention, 3) objective measurements exist that quantify clinically meaningful outcomes, 4) evidence for cutoff values and their effects on the natural clinical course of the disease. Psoriasis is far away from these prerequisites.

Super response in psoriasis is associated with disease duration and independent of other factors. Ultra-short disease duration probably performs even better. Another aspect of disease modification is the prevention of comorbidities. There is evidence that this is possible, as studies show that biologics can decrease coronary artery plaques. Real-world studies show that early treatment of psoriasis may also increase the likelihood of developing psoriatic arthritis. However, putting all patients on biologics early is not possible. Therefore, the challenge in the future is to determine the patients at risk so they can start treatment early. There are two theories for disease modification: modifying resident memory T-cells or modifying epigenetics. Some studies show that Guselkumab can decrease resident memory T-cells, but the question is whether they disappear entirely with treatment. Regarding epigenetics, DNA methylation in lesional skin was normalized only in new-onset psoriasis by week 16 after using Secukinumab but not in the chronic cohort, leading to a residual DNA methylation signature that may represent tissue memory.

The definition of disease modification is still under debate in psoriasis. The maximum definition for disease modification is a cure involving molecular mechanisms that influence disease activity beyond drug withdrawal. Insights from clinical trials and real-world evidence provide that there is probably a window of opportunity for disease modification, especially with short duration, and that the level of response depends on disease duration. Upon withdrawal, several psoriasis patients maintain a lower or no activity for more than a year after effective treatment with biologics (e.g., Anti-IL-23). Early and effective treatment may reduce the development of comorbidities such as psoriatic arthritis. Potential mechanisms of IL-23-mediated disease modifications include epi-genetic resolution and normalization of tissue-resident memory cells.

Population Differences in Psoriasis

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Psoriasis can start at any age but most often develops in adults between 20 and 30 years old and between 50 and 60 years old. It affects men and women equally. Psoriasis occurs more frequently in adults than in children. The lowest prevalence of psoriasis is in East Asia, while the highest is in Australia, New Zealand, Europe, and the United States[1]. In a study in the United States, the highest prevalence of psoriasis was found in white ethnic groups and lower in Asian, Hispanic, and Black individuals[2]. However, more severe psoriasis is recognized in Black and Asian individuals. Psoriasis on darker skin tones looks more violaceous than the usual erythematous scaly plaques seen on lighter skin tones. This may be related to genetic background. In Asians, HLA-CW6 is more prevalent, and HLA-CW6 is probably responsible for more severe psoriasis, erythrodermic psoriasis, and pustular psoriasis. HLA cw12 is more common in the Turkish population. Besides genetic background, the onset of psoriasis is triggered by extrinsic and intrinsic mechanisms, including epigenetics. The gut microbiomes can also be another factor in psoriasis diversity, as different populations eat differently. Metabolism and Mitochondria can also affect psoriasis trigger; this is adjusted by medications, e.g., Metformin and semaglutide. Exposure to air pollution may also trigger psoriasis, probably through mitochondrial mediation.

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Pustular Psoriasis: Is It Really Psoriasis?

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The connection between generalized pustular psoriasis (GPP) and plaque psoriasis is based on epidemiology, where almost half of GPP patients are also affected by psoriasis. Palmoplantar pustulosis is also associated with psoriasis. These associations cannot be random. Conversely, psoriasis is primarily polygenic, whereas pustular psoriasis is probably monogenic. Still, some genetic mutations connect psoriasis with pustular psoriasis. For example, CARD14 Gain-of-Function mutations identify psoriasis vulgaris, pityriasis rubra pilaris, and pustular psoriasis. Animal and human studies support the central pathogenic role of IL-23/IL-17-driven inflammation in CARD-14 mutated genotypes[1]. CARD14 is a gain-of-function (GOF) mutation of the innate immunity gene, resulting in increased NFKB signaling and an IL23/IL17-driven cascade. Mainly in GPP, loss-of-function IL36RN mutations lead to dysregulated IL-36 pathway in a monogenic model. On the other hand, the deficiency of the IL36 receptor antagonist (DITRA) is usually not associated with plaque psoriasis.

Other genes associated with pustular psoriasis include: 1) AP1S3: involved in innate immunity, keratinocytes autophagy, increased IL36A mRNA; 2) SERPINA3: LOF mutation impairing negative regulator function on Cathepsin G, an activating protease of IL36 agonists; 3) MPO: Myeloperoxidase gene involved in neutrophils homeostasis (and IL36 pathway).

The prevalence of IL36RN mutations in GPP varies across studies (geographic area/ethnicity). IL36RN mutations are usually not associated with plaque psoriasis. This led to the assumption that GPP/DITRA (but not all GPP subtypes) and plaque psoriasis are genetically and functionally distinct, where IL23/IL-17 pathway is responsible for plaque psoriasis, while IL-36 is responsible for GPP. However, both pathways are involved in both diseases, which is probably the difference in what takes the upper hand. For example, transcriptomic studies in lesional skin from plaque psoriasis: A type I interferon signature is observed in a subset of patients with PPP, but also psoriasis vulgaris that is resistant to most of the currently available biologics. Spesolimab (IL-36 receptor antagonist) showed clearance only in around 50% of GPP patients. This supports the idea that GPP pathogenesis does not rely solely on the IL-36 pathway.

In summary, recent epidemiological, population-based studies prove that the association between pustular psoriasis and plaque psoriasis is not random. This association's genetic and mechanistic architectures in a single patient are only known for a small proportion of patients (CARD14) but support the hypothesis that pustular psoriasis and plaque psoriasis belong to the same disease(s) spectrum. Even though targeted therapies have been recently approved in GPP, whatever the genetic background, more and more scientific data suggest that different mechanistic scenarios operate in pustular disease, paving the way for precision medicine approaches.

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Personalized Medicine Approaches for Tailored Treatments

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The opportunity for personalized care is based on data and biomarkers. Tailoring disease prevention and treatment approaches are based on interindividual differences in genetic, molecular, environmental, and lifestyle factors. Personalized medicine can enable prevention of disease onset and progression, early targeted treatment, and improved long-term prognosis.

Analysis of predictive biomarkers can be a prediction tool to assess the risk of severe disease. This helps in the early allocation of ideal treatment, and this can achieve drug-induced remission and, eventually, drug-free remission. Real-world studies show the durability of biologic response.

Mechanistic biomarkers (those involved in disease pathogenesis or drug mechanisms) are more implicated in psoriasis. However, none is validated for clinical use. High-quality biomarkers should be reliable, have clinical validity, be relevant, have positive predicted value, and be cost-effective. A successful example of the biomarkers is drug level measurement; for example, serum adalimumab drug level as early as four weeks into treatment predicts response at six months. Genomic biomarkers of response in psoriasis, e.g., HLA-C*06:02, are of interest. HLA-C*06:02 negative individuals were found to be more likely to achieve treatment success with adalimumab compared to ustekinumab.

A potential role for risk scores [PRS] based on factors like smoking and BMI is used as a stratification tool to identify those at higher risk of severe disease.

Dose reduction is another opportunity for personalized and precision management. Reducing the long-term drug burden can be achieved by reducing the dose of biologics, including patient-led as-needed treatment and therapeutic drug monitoring guided treatment.

New Topicals

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Regarding psoriasis, the recommendations for topicals, ultraviolet therapy, climate, and psychological therapy were not updated, and the 2015 guidelines remain valid.

Appropriate topical treatments for psoriasis vary based on the affected site and the expected timeline for treatment outcomes. Long-term treatment strategies with topicals present a dilemma. Studies indicate that twice-weekly proactive management with topical calcipotriene/betamethasone dipropionate aerosol foam can be effective for maintenance.

The German guidelines recommend combining topical calcipotriene/corticosteroid and anthralin for mild psoriasis. In the US, topical corticosteroids, topical vitamin D analog, topical retinoids, topical tapinarof, and topical Roflumilast are FDA-approved.

Tapinarof is an AhR agonists. It was first isolated from metabolites of Photorhabdus luminescens, a species of obligate symbiotic bioluminescent bacteria that live within the gut of insect-specific pathogenic nematodes. Tapinarof is a small molecule with a low molecular weight (254 g/mol). It affects Th2, Th17, resident memory T cell, epidermal differentiation, and oxidative pathway. All leads to reduced inflammation in psoriasis. Side effects include folliculitis and contact dermatitis. Studies show that Tapinarof cream 1% reduces PASI, BSA, DLQI, and itch scores. A study showed clinical remission after 24 weeks of stopping Tapinarof. Roflumilast also shows good efficacy in psoriasis. It can be used in flexures. Side effect includes diarrhea.

In addition to new molecules, there are recent advancements and trends in topical drug delivery systems in psoriasis, e.g., nanocrystals and polymer-based carriers. Skin penetration pathways of novel drug delivery systems include the transfollicular, transcellular, and intercellular routes. An example is topical tacrolimus microemulsion, which was approved in June 2024 in Germany for scalp psoriasis. Also, topical calcipotriene/betamethasone dipropionate cream based on PAD technology shows a good response in plaque psoriasis. A newer technology is nanodiamond-based berberine aquasomes for enhancing penetration across the epidermis, which will have many implications for the future treatment of psoriasis.

Another example is the topical Delivery of microRNA-125b by Framework Nucleic Acids for Psoriasis Treatment. miR-125b is one of the most downregulated miRNAs in psoriasis skin, and its overexpression in primary human keratinocytes would inhibit cell proliferation and upregulate multiple markers of differentiation.[1]

In summary, most patients have localized disease and have no indication for systemic therapy as a first approach. Topical corticosteroids alone or in association with vitamin D analogs are established in treating mild to moderate psoriasis; they will remain the mainstay therapy. Breakthrough knowledge on psoriasis pathogenesis allows the discovery of new therapeutic targets, and promising topical drugs are emerging, e.g., AhR, JAK-STAT, and PDE-4. Tapinarof, an AhR modulator, and roflumilast, a PDE-4 inhibitor, are the most promising topical molecules already approved by the FDA. Efforts are also ongoing to investigate new therapeutic targets and more effective formulations.

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Do We Need Oral Treatment Options?

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Some patients have a true needle phobia, while others can tolerate injections but strongly prefer oral therapy. Oral treatments are more convenient and easier to prescribe, and, in theory, they can be dispensed on the day of consultation. Immunogenicity is another concern with first-generation biologics.

Deucravacitinib is an oral-specific inhibitor of TYK2. TYk2 pathway is part of the Janus kinase family. In one study, 60% of patients on Deucravacitinib achieved PASI 75 at 16 weeks, which was superior to apremilast [1]. PASI responses were maintained among patients with up to 4 years of Deucravacitinib treatment. Another TYK2 inhibitor that is being studied is the TAK-279.

Apart from apremilast, other PDE-4 inhibitors are studies, e.g., orismilast. It has higher potency against PDE-4 B and D. Phase 2 data for another oral PDE-4 inhibitor, ME3183, were published among patients with moderate to severe psoriasis.

Accordingly, we have novel TYK 2 / PDE 4 agents available or in development. TYK 2 has good but not exceptional efficacy - not equivalent to modern biologics. They maintain response well; arguably, deucravacitinib is the best oral currently available. Ideally, future TYK2s need higher efficacy. Screening and minimal labs mean they struggle to compete completely with PDE-4. PDE-4 offers "safety" in terms of no need for screening/monitoring, and new generation PDE4 may have higher efficacy, but the overall response remains modest.

Cytokines are small proteins secreted by cells of both innate and adaptive immune systems and can regulate diverse functions in the immune response. We are all familiar with regulatory cytokines, e.g., IL-23, and effector cytokines, such as IL17 A/F. Targeting cytokines has only been possible to date by protein-to-protein interactions. That is, forming an antibody (protein) to bind the cytokine or its receptor to prevent its effect. As cytokines are flat and featureless, it is hard to interrogate oral small molecules or peptides. They have struggled to effectively bind and prevent their actions. This is now changing with several examples of oral small molecule or peptide-inhibiting cytokines.
JNJ-77242113, a first-in-class oral IL-23R antagonist peptide, selectively and potently blocks IL-23 signaling and downstream inflammatory cytokine production. Phase 2, a randomized, placebo-controlled, dose-ranging trial of JNJ-77242113, an oral IL-23R antagonist for moderate to severe psoriasis, is published. Due to its GI stability and potency, JNJ-77242113 can block the systemic IL-23 pathway through oral dosing.

This may be the start of a new psoriasis treatment paradigm. If this phase 2 data replicates/improves in phase 3, it will set a new standard for oral therapies. Once-daily dosing will be crucial. Other oral small molecules or peptides that inhibit cytokines (e.g., IL17 A and TNF) exist.
Regarding psoriatic arthritis, good efficacy was demonstrated by upadacitinib (JAK inhibitor) versus placebo.

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Therapeutic Drug Monitoring in Your Practice?

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Therapeutic drug monitoring (TDM) is a multidisciplinary clinical specialty focused on improving patient care by individually adjusting drug doses based on clinical experience or trial data demonstrating improved outcomes in general or specific populations. This adjustment can be informed by prior pharmacogenetic, demographic, and clinical information and/or by measuring drug concentrations in the blood through pharmacokinetic monitoring or biomarkers (pharmacodynamic monitoring), supporting either proactive or reactive TDM approaches.

Therapeutic drug monitoring can be helpful in 1) clinical cases having side effects from the biologic as they may overdose and possibly need to decrease the dose, 2) insufficient response in some patients (efficacy), who are possibly underdosed and need to increase the dose, 3) with costly medications to lower the burden on healthcare expenditure, 4) for personalized dosing and evolution through personalized medicine.

Therapeutic drug monitoring requires collecting blood samples and detecting serum drug levels (need to be consistent, sensitive, and specific tests). This is followed by the interpretation of drug level concerning target concentration.

There is evidence for therapeutic drug monitoring of infliximab in inflammatory bowel disease and for adalimumab in Hidradenitis suppurativa. Adalimumab dosing according to TDM is used in psoriasis (Figure 2).[1]

If a patient experiences side effects on a biologic, shifting to another biologic is unnecessary. Instead, according to the BeNeBio study, dose adjustment guided by the blood drug level is possible. Results will be available in 2025, but the hypothesis is that biologic dose reduction may lead to more efficient and rational use of biologics in clinically stable patients.

HELIOS TRIAL is the first RCT comparing proactive TDM versus standard of care for newer biologicals in psoriasis. The challenge is determining target concentrations for psoriasis per biological. The rationale for the HELIOS trial is that the "one dose fits all" principle leads to overdosing and underdosing. The trial includes psoriasis patients on secukinumab, ixekizumab, and guselkumab. The drug concentration is measured in the blood. Accordingly, a decision is made on whether to reduce, maintain, or increase the dose according to the therapeutic drug level. This is expected to decrease the cost of the Belgian healthcare system.

However, TDM has some practical limitations: 1) blood collection has to happen at trough levels, and this is a five-day window before the next injection; 2) The specificity of the tests is relatively low; 3) the cost of the test TDM.

Future perspectives include rapid tests like lateral flow assays. Artificial intelligence could predict dosing more accurately but needs large databases to be trained, potential incorporation of inherent biases in their prediction, and machine learning cannot perform simulations.

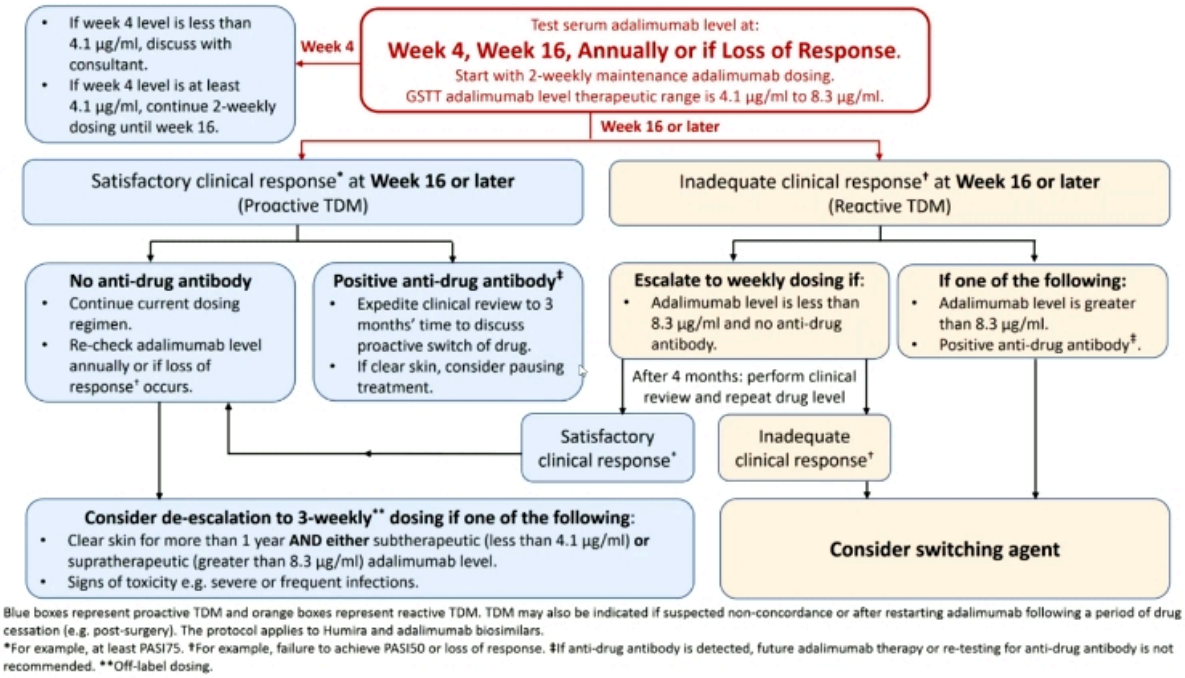

Figure 2: Adalimumab dosing in psoriasis according to therapeutic drug monitoring (Raharja et al., 2023)

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Does Psoriasis Treatment Prevent the Development of Psoriatic Arthritis?

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As patients progress from psoriasis to psoriatic arthritis (PsA), they pass through stages, including preclinical PsA, subclinical PsA, and prodromal PsA. Subclinical inflammation occurs in the synovium during these stages, even though the patient may not exhibit symptoms. Therefore, it is recommended that patients with psoriasis be screened for PsA at every visit. Genetically predisposed patients are likely exposed to a second hit, such as trauma, comorbidities, biomechanical stress, or microbiome-related events, which can trigger PsA. Shared therapies between psoriasis and PsA are illustrated in Figure 3.

There is a mix in literature where some studies show that biologics and systemic DMARDs reduce the risk of psoriatic arthritis, while other studies show that they may increase the risk. The question is, why would biologics and systemic DMARDS increase the risk of psoriatic arthritis? This may be due to Protopathic bias (a form of confounding by indication), which occurs when a medication is initiated for early symptoms of a disease that has not yet been diagnosed, leading to the misclassification of the medication as a cause of the disease when, in fact, it was prescribed in response to early manifestations of the disease. This creates a misleading association between the treatment and the outcome. Also, Survival Bias: A patient must 'survive' longer without PSA to receive a biologic therapy, and they are, thus, had a longer duration of psoriasis and are closer to the development of PSA if they are going to develop it, enhancing the observed risk of PSA in the biologic group.

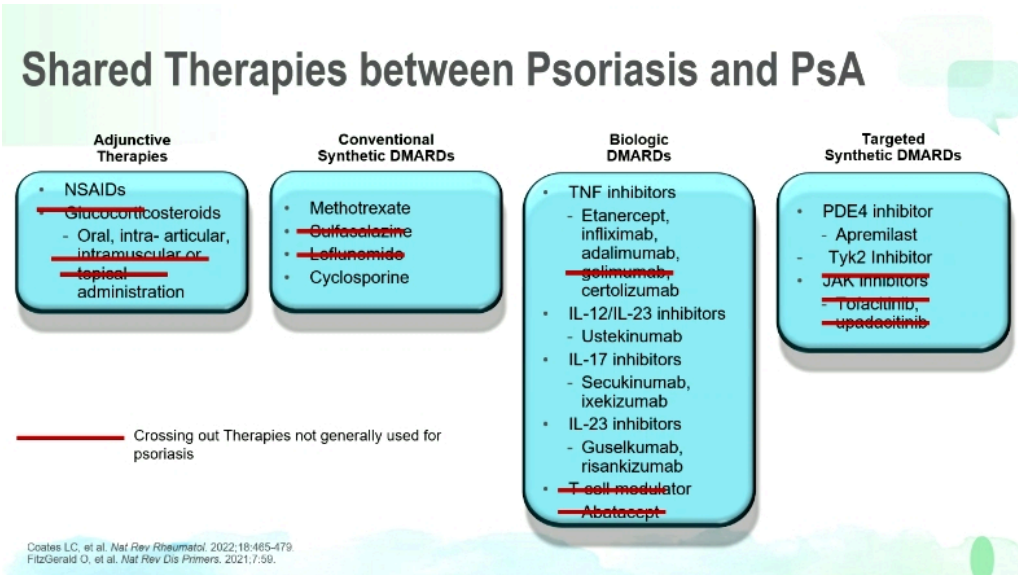

Figure 3: Shared therapies between psoriasis and psoriatic arthritis.

Pathogenesis and the Therapeutic Landscape

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Over the past few years, advances in understanding the pathogenesis of psoriasis and the development of targeted therapy have helped patients to have clear/almost clear skin.

By the beginning of the century, psoriasis was thought to be an infectious disease. By the 1950s, psoriasis was thought to be an epidermal disease with a problem in the keratinocytes. It wasn't until the 1980s and 1990s that psoriasis began to be recognized as an autoimmune disease. Two important turning points were the identification of IL-23 and IL-17 as the main pathogenic pathway in psoriasis.

IL-23 is composed of 2 protein subunits: p19 and p40. MDCs secrete it, and excess levels are found in psoriatic skin. It signals through the JAK-STAT pathway (TYK2/JAK2 signaling). IL-23 pathway promotes "upstream" differentiation, activation, proliferation, and survival of Th17 cells, promoting the production of proinflammatory cytokines, such as IL-17.

IL-17F has 40-55% homology with IL-17A. It signals via a receptor composed of IL-17RA and IL-17RC. Compared to non-lesional tissue, IL-17F levels are elevated in sera and lesional psoriatic skin. It acts similarly to IL-17A. The same immune cell types express it. IL-23 participates in IL-17A and IL-17F co-production. It has a similar gene expression of IL-17A and acts synergically with IL-17A.
IL-17C signals via a receptor composed of IL-17RA and IL-17RE. It has 23% homology with IL-17A. IL-17C is abundantly expressed at the protein level in lesional psoriasis skin. It is produced by keratinocytes and acts in an autocrine manner (with TNF) to induce a pattern of genes like those induced by IL-17A, including proinflammatory cytokines, chemokines, and antimicrobial peptides. IL-17C synergizes with TNF and IL-17A to initiate and sustain KC activation and promote epidermal hyperplasia.

TNF promotes adaptive immune effects of the IL-23/IL-17 axis. It indirectly affects disease pathogenesis and has many effects, as TNF receptors are expressed on multiple cells. It is secreted by mDCs, Th17 cells, keratinocytes, and other cells. It signals through the NF-kB and MAP kinase pathway TNF has a dual effect on psoriasis pathogenesis. It regulates the upstream induction of IL-23, inducing the production of IL-23 by myeloid DCs driving the activation of T17 cells. It also acts downstream, synergistically, with IL-17 to modulate keratinocyte gene responses in psoriatic lesions[1].

TNF inhibitors were the first biologic agents approved for psoriasis, revolutionizing its management. Later, head-to-head studies against IL-17 and IL-23 inhibitors have shown lower efficacy. Real-world evidence demonstrated lower effectiveness and persistence compared to other biologic agents. TNF inhibitors are generally safe and well tolerated. However, their safety profile is less favorable compared to other classes due to the higher risk of opportunistic infections, latent tuberculosis reactivation, severe infections, onset or exacerbation of demyelinating disorders, drug-induced lupus, and worsening of congestive heart failure. Biosimilars are currently available, significantly reducing costs, allowing for earlier treatment with biologics, and providing greater access to these therapies.

The first IL-23 inhibitor (Ustekinumab) was non-selective. Then, selective IL-23 inhibitors (Guselkumab, Tildrakizumab, and Risankizumab) were developed to target the p90 subunit of IL-23 that showed high efficacy. Studies showed increased levels of IL-23 (p19 and p40) but not IL-12 (P-35) in psoriasis vulgaris[2].
JNJ-2113 is the first and only oral IL-23R antagonist peptide. It selectively targets IL-23 receptors and blocks IL-23 From Binding to its Receptor. JNJ-2113 demonstrates exquisite potency and selectivity in reducing IL-23-mediated proximal signaling and downstream proinflammatory effector cytokine production.

Type I Interferon and IL-23 signal through the TYK2 pathway. Deucravacitinib is an oral small molecule that selectively inhibits TYK2.

In conclusion, IL-23/IL-17 axis is the main pathogenic pathway in psoriasis. Drugs targeting the IL-23/IL-17 axis show the most effective clinical response to date. IL-17 inhibition may be performed through several therapeutic strategies (IL-17A, IL-17RA, IL-17A/F), all showing a very high and rapid clinical response with a consistently favorable safety profile. Selective IL-23 inhibitors are highly effective and safe, have a convenient dose regimen, and may allow longer injection intervals in some patients. Small-molecule drugs, also targeting the IL-23 pathway (TYK2 and IL23R), offer an alternative to biologic use. Currently, clearance or almost clearance of the skin should be our goal in managing psoriasis.

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Comorbidities and Their Management

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Comorbidity is defined as any distinct additional clinical condition that exists or may develop during the course of a patient's primary disease. Multi-morbidity refers to the coexistence of two or more chronic conditions.

Comorbidities include joint affection (peripheral arthritis, axial disease, dactylitis, enthesitis), eye affection (iritis/uveitis/episcleritis), gastrointestinal affection (Crohn's disease, ulcerative colitis, gastroesophageal reflux, steatotic liver disease) and cardiometabolic disease (obesity, insulin resistance, dyslipidemia, hypertension, cardiovascular disease, metabolic steatotic liver disease), and quality of life affection (distress, depression, suicidality, substance abuse, stigma, and social avoidance unemployment). Comorbidities are more prevalent in patients having severe psoriasis disease. This comorbidity burden contributes to the cumulative life force impairment in people with psoriasis.
It's important to ask about mental health in psoriasis patients and to use a validated psychological well-being assessment, for example, GAD7 or PHQ 9. Dermatology life quality index (DLQI) will not pick up depression, suicidality, or anxiety. Anxiety/depression influences patient perception of disease and adherence.

Risk factors for psoriatic arthritis include psoriasis phenotypes (nail psoriasis, flexural psoriasis, scalp psoriasis) and clinical factors (1st degree relative with psoriatic arthritis, severe psoriasis, obesity, and subclinical musculoskeletal inflammation). Inquiries of PsA, at least annually, are essential using a screening tool, e.g., PEST score. However, the PEST score for axial arthropathy will be missing. Of note, not all joint pains are psoriatic arthritis, as this population has prevalent fibromyalgia, osteoarthritis, and Gout.

As we look forward, ongoing studies tackle the question, "Would early intervention for psoriasis prevent the comorbid burden?" In conclusion, the comorbid burden is greatest in those with more severe skin disease. Identification of comorbidities will help patients and optimize psoriasis management. Who manages what will depend on your expertise, healthcare system, and setup. Establishing pathways of care for the most common comorbidities with relevant colleagues is important.

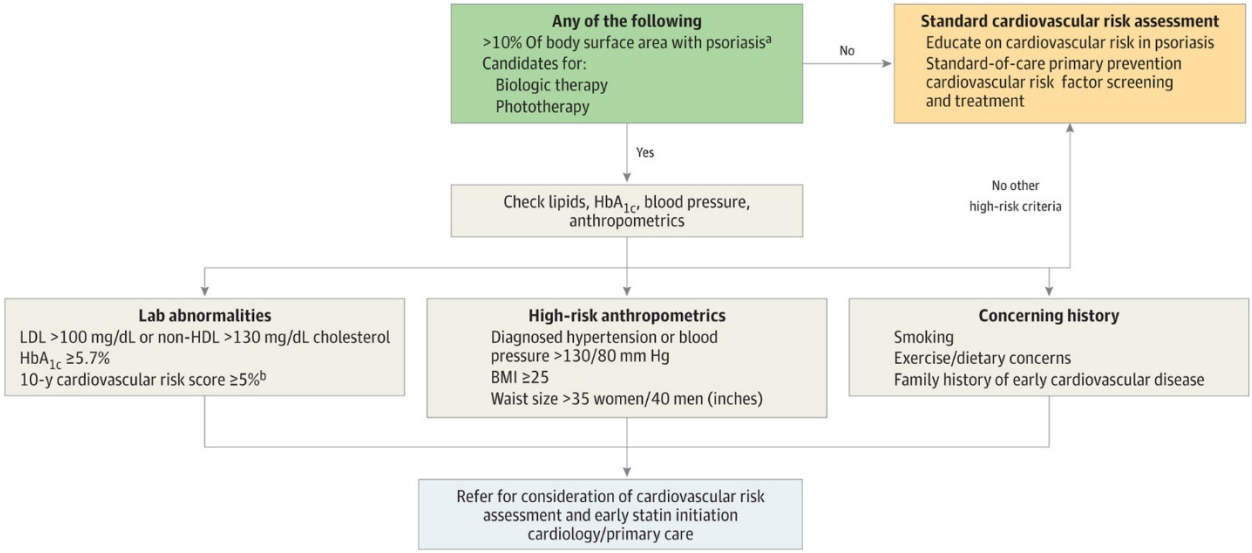

Figure 4: Algorithm for dermatologists and rheumatologists to screen cardiovascular disease in psoriasis (Garshick and Berger, 2022).

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Which Drug for Which Patient?

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To have a targeted treatment for psoriasis, we need to address the immune pathogenesis of the disease. In psoriasis, innate immunity includes upregulated neutrophils and LL37, which is targeted by many psoriasis treatments, including steroids, cyclosporine, methotrexate, phosphodiesterase inhibition, TYK2 inhibitors, and more specifically, dapsone, hydroxychloroquine, anti-TNF, Anti-IL23, and Anti-IL17.

The bowels and joints guide the choice between IL-17 versus IL-23 inhibitors. Gamma delta T cells produce interleukin 17A independent of interleukin 23 and are present in the intestine and synovia. IL-17 protects from candida infection and maintains the integrity of bowel mucosa. Therefore, IL-17 inhibitors can induce inflammatory bowel disease. IL-17 inhibitors help in spondyloarthritis and may work better in axial arthritis, while IL-23 does not.

The choice of the right drug for the right patient depends on the age, severity, comorbidities, patient history, earlier treatments, and other autoimmune disorders. With inflammatory bowel disease, IL-17 inhibitors are avoided. With active HIV, immunosuppressive is better avoided, and acitretin can be used. TNF inhibitors should be avoided with latent TB and demyelinating diseases (Figure 5). The choice of biologics according to comorbidities is shown in Figure 6.

Regarding conventional therapies, for psoriatic arthritis, methotrexate is the best. For inflammatory bowel disease, acitretin will be the preferred conventional drug. For heart failure, avoid cyclosporin. For latent TB, avoid immunosuppression, while acitretin and fumaric acid esters are better choices. In pregnancy, cyclosporin is preferred, while methotrexate and acitretin are contraindicated[1,2]. The future focus on targeted treatment will be on the tissue memory T cells and more targeted treatment.

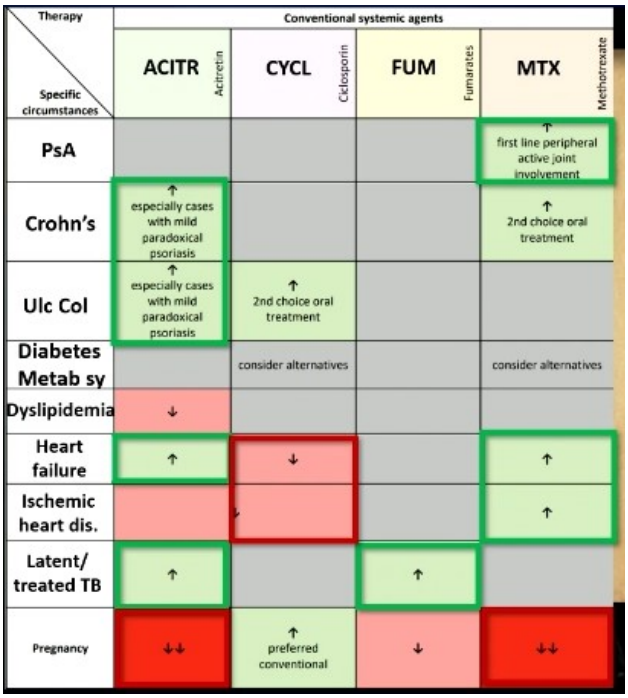

Figure 5: Choice of conventional therapy for psoriasis according to comorbidities (adapted from Nast et al., 2020)

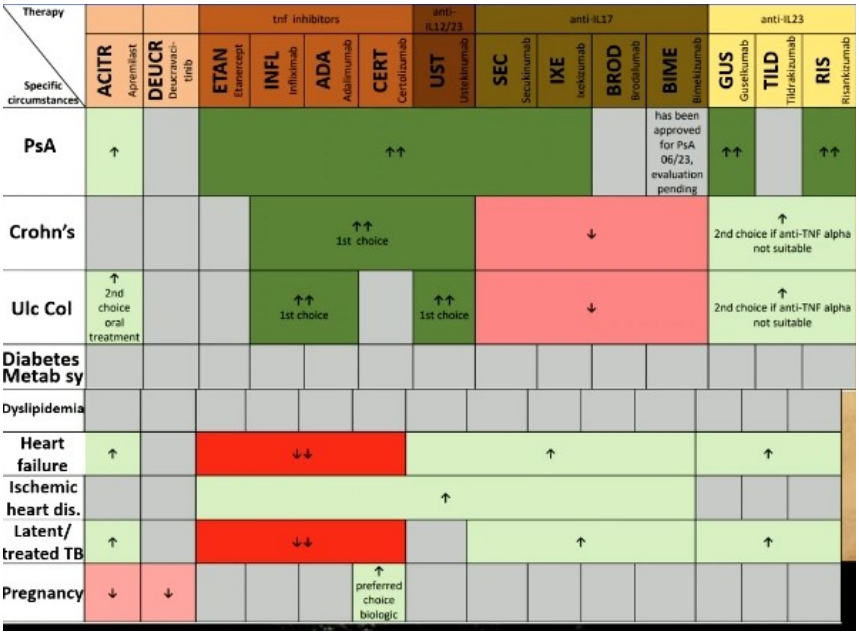

Figure 6: Choice of psoriasis therapy according to comorbidities (adapted from Nast et al., 2021)

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Subtypes and Their Management

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Variants of psoriasis can be classified according to topography (location): scalp, flexural, sebopsoriasis, palmoplantar, and nail psoriasis; morphology: circinate/gyrate, follicular, linear (Blashko lines), and small-plaque (common in Asian populations); stability: acute/unstable forms such as guttate, erythrodermic, and paradoxical psoriasis; and autoinflammatory types, including pustular psoriasis (generalized, AGEP, or localized) and pityriasis rubra pilaris.

For special areas, adding topicals is not always enough. Topicals may not work in some areas, and patients may develop side effects of prolonged corticosteroid use. Regarding biologics, for scalp psoriasis, Guselkumab shows the highest efficacy, followed by Bimakizumab and Secukinumab. Guselkumab also shows the highest efficacy in palmoplantar psoriasis. For nail psoriasis, Ixekizumab showed the highest efficacy, followed by brodalimumab. For genital/intertriginous psoriasis, Il-17 seems to be superior.

Small plaque (SP) psoriasis is the standard or typical form of psoriasis in adults in Korea and other Asian countries. Although SP psoriasis resembles guttate psoriasis clinically, it is distinguished from guttate psoriasis by its onset in adult patients, chronicity, and somewhat larger lesions (1-2 cm lesions are typical), which are thicker. The development of the large plaque psoriasis subtype is probably due to the dysregulation of T cell expansion, which is enabled by the downregulation of immune negative regulators. Probably the opposite occurs with small plaque psoriasis.

There is another type of small plaque psoriasis, which is unstable. It is observed in patients treated with TNFα inhibitors, patients on immune checkpoint inhibitors, and with concurrent systemic lupus erythematosus (SLE) or positive antinuclear antibody (ANA). In the clinical scenarios investigated, small plaque psoriasis demonstrated significantly higher IFNα, LL-37, and IL-36γ expressions than chronic plaque psoriasis. The type-I interferon pathway probably mediates this.

The most common forms of paradoxical psoriasis are plaque and pustular psoriasis with palmoplantar involvement. Forms of special location or special forms are also possible (inverted, guttate, or erythrodermic). It has female predominance (70%) and time of latency (1-3 months). Photosensitive psoriasis is a subtype that may worsen with phototherapy. This subtype overlaps with subacute lupus erythematosus.

Eczema as an adverse effect of anti-TNF-α therapy may occur in approximately 5-20% of patients with various Th1-mediated inflammatory diseases such as psoriasis, inflammatory arthritis, and inflammatory bowel disease. Personal history of atopy appears to increase this risk. Of the anti-TNFα agents indicated for treating moderate to severe psoriasis, infliximab may be more strongly associated with developing or exacerbating preexisting eczema. IL-17 inhibitors are also associated with eczema triggering/worsening, perhaps favoring S. aureus superinfection.

Pustular Psoriasis: Clinical Continuum or Separate Entity?

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There is increased attention on generalized pustular psoriasis (GPP) due to the substantial unmet medical need in treating the disease, the dramatic progress in the science and treatment of psoriasis vulgaris (PSV), where highly effective therapies benefit the majority of patients, the expansion of clinical trials (including biologics and small molecules) investigating subtypes of psoriasis, including pustular forms, and significant scientific and therapeutic advances in distinguishing GPP from PSV.

Many differences exist between psoriasis vulgaris (PSV) and pustular forms: demographics and clinical patterns, inverse prevalence between PSV and PP, genetic backgrounds, immunological mechanisms, responses to targeted therapies, and development of new therapies. However, they share that they frequently co-exist and that all forms are associated with psoriatic arthritis.

A few years ago, ERASPEN classified pustular psoriasis into two forms: generalized (generalized pustular psoriasis) and localized, which includes palmoplantar pustulosis and acrodermatitis continua of Hallopeau. All can occur with or without psoriasis vulgaris. Other forms of psoriasis to consider include 'plaque psoriasis with pustulation (psoriasis cum pustulation)," which is an undifferentiated psoriasis seen in stable disease, and "paradoxical psoriasis" seen in many conditions treated with TNF inhibitors, including rheumatoid arthritis and Crohn's disease probably due to dysregulated type 1 Interferon. Even pustular subforms of psoriasis vary in demographics, clinical patterns, disease biology, and clinical consequences (treatment selection and response to intervention).

Characteristic features of generalized pustular psoriasis (GPP) include primary, sterile, macroscopically visible pustules on a red base at non-acral sites. It occurs with or without systemic inflammations, which can be severe. Mortality rate is 30%. The disease is rare but more common (4 times) in East and Southeast Asia.[1]

Treatment of GPP is difficult and mostly borrowed from psoriasis vulgaris. Evidence for the use of psoriasis biologics in GPP is limited. Low patient numbers and open-label trials for Anti-TNF (adalimumab), Anti-IL17 (secukinumab, ixekizumab, brodalumab), and p19 (guselkumab). Generally speaking, psoriasis biologics do not work well in pustular forms.

Mutations in IL-36RN are associated with GPP (different methodologies and populations). Mutations lead to unopposed IL-36 signaling, resulting in neutrophilic inflammation. 25% of cases of GPP are due to IL-36RN mutations. Other genes are associated with AP1S3, CARD14, and MPO, but interestingly, all impact the IL-36 pathway. Indeed, IL-36 upregulated in lesional skin in all patients with GPP (including those without identified mutations). Of note is that IL-36RN mutations are uncommon in PPP, and IL-36RN mutations are not reported in psoriasis vulgaris. This is particularly important because it is proof of the concept that IL-36 receptor inhibition is possible for the treatment of GPP.

IL-36 receptor inhibition includes Spesolimab FDA (2022) and EMA (2022), approved as an intravenous treatment of acute flares in adults. Imsidolimab is another drug in development. Developmental approaches will probably be intravenous for acute flares and subcutaneous for long-term remission. The question is whether mutation analysis can be a useful biomarker.

Localized pustular psoriasis includes Acrodermatitis continua of Hallopeau (ACH), a chronic, symmetrical, sterile pustular eruption affecting tips of digits extending locally, which can lead to the destruction of nail apparatus. It is rare but severely affects life quality and may evolve into GPP. Several reports of ACH preceding the development of GPP. IL36RN

and AP1S3 mutations were reported in patients. ACH and GPP were reported in families with the same IL36RN mutation. There is a case report on a 9-year-old girl with Acrodermatitis continua of Hallopeau with IL-36RN missense mutation dramatically responding to 2 IV infusions of Spesolimab at weeks 0 and 4[2].

Localized pustular psoriasis also includes palmoplantar pustulosis (PPP), presented by acral, sterile pustules associated with thickened, red, scaly skin. It often has a very significant functional burden and pain. It is the most common form of pustular psoriasis (1-10 per 100,000 general population) and is x10 more common in Japan than in the United States. Female: Male ratio = 5:1. It is strongly associated with smoking, and 90% are present or past smokers. Regarding genetics, it has no association with HLA-C*06:02 (HLA-Cw6), but it has a weak association with IL-36RN (<5% cases). Its immunology is complicated, and autoinflammation is more prominent than in psoriasis vulgaris.

Efficacy studies of psoriasis biologic and oral agents for PPP have few subjects. No studies have an active comparator. The hierarchy and magnitude of response of systemic treatments are attenuated in PPP compared to psoriasis vulgaris, even with Secukinumab and Guselkumab. Further, treatment targeted at neutrophilic inflammation is ineffective in PPP as there is no benefit with anti-IL-1 Rx (Anakinra), and spesolimab (anti-IL-36) failed to achieve the primary endpoint in PPP. This likely indicates there is more to biology than pustule formation. PPP has complex immune and adaptive immune mechanisms, including Th17 and Th2-mediated pathways (adaptive immune plasticity). This may open the door for the possible role of small molecules, e.g., JAK inhibitors or apremilast, in treating PPP.

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Psoriasis and Ethical Aspects

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Ethical considerations in psoriasis involve various issues, including stigmatization, access to treatment, and research. Stigmatization occurs when someone or something is unfairly labeled or treated as inferior or undeserving of respect. Psoriasis is often wrongly perceived as a contagious disease associated with poor hygiene.

Psoriasis can affect relationships at home, school, or work, as well as sexual relationships, and thus reduce the quality of life and cause psychological strain. Patients are frequently stigmatized and excluded from normal social environments, including schools, workplaces, and swimming pools. As a result, they often avoid social activities and commonly reported experiencing loneliness, isolation, feelings of being unattractive, and frustration. Shame has been the most often reported emotion, especially by women, patients in the countryside, and patients with long disease duration. This impacts social life and leads to avoidance of public places, reducing social opportunities, employment, and relationships.

Protecting patients from discrimination in the workplace is a critical ethical issue. Employers should be educated about psoriasis to prevent bias.

Patients should be fully informed about treatment options, including the potential benefits, risks, and side effects. Ideally, a shared decision should be advocated between the doctor and the patient.
Ensuring all patients have access to effective treatments for psoriasis, regardless of socioeconomic status, is a major ethical concern. The high cost and limited accessibility of newer treatments pose a significant barrier that needs to be addressed.

In conclusion, the ethical aspects of managing psoriasis are various, involving access, stigmatization, resource allocation, and the integration of new medical advancements. Addressing these issues requires healthcare providers, policymakers, researchers, and society to ensure that patients with psoriasis receive comprehensive, respectful, and equitable care.

Erasing Inequities: Strategies for Addressing Bias in Dermatology

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Inequity can lead to inequality, resulting in differences in healthcare outcomes. Equality means giving everyone the same resources, while equity means providing each person with what they need to achieve equal outcomes.

Under stress, individuals may rely on implicit bias, which operates unconsciously. Bias can arise from both exposure and non-exposure to diverse experiences. Education is vital to reducing bias; for example, dermatologists should be trained to recognize skin diseases in various skin tones, and medical images should represent all ethnicities. Bias also exists in dermatology research, where white patients are more often included than patients with darker skin. To reduce bias in clinical settings, we can follow the CARE acronym: Communication, Assess for bias, Reassess diagnosis, and Enact a plan (tailoring care to the patient's culture).