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Understanding Psoriasis: Insights from Les Journées Dermatologiques de Paris

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ABSTRACT

Drs. Joël Claveau & Julien Ringuet, two Canadian dermatologists with prominent clinical and research practices, attended the Les Journées Dermatologiques de Paris *conference in Nov-Dec 2022, with a focus on presentations and posters about psoriasis. This article reviews key insights they obtained at the meeting. In brief:*

- *Psoriasis has a profound and multifaceted impact, but remains undertreated*
- *Progression to psoriatic arthritis is common; dermatologists can facilitate earlier detection*
- *The presence of comorbidities may inform the choice of biologic treatment*
- *New topical and systemic options enable treatment optimization for various subgroups*
- *Adverse effects of cancer immunotherapy include psoriasis, which requires treatment*

Psoriasis is a chronic inflammatory skin disease that affects an estimated 2% of people worldwide, with higher rates in Caucasian than Asian populations.[1] Plaque psoriasis is by far the most common form of the disease, accounting for about 90% of cases.[1] A relapsing condition with a wide range of severity, psoriasis often requires long-term therapy.[1]

High Impact & Complex Comorbidities

The impact of psoriasis extends across all dimensions of life. The skin manifestations alone, which typically include thick, scaly and sometimes pruritic plaques, can significantly impact psychosocial well-being. Research has found that about 80% of patients feel embarrassment and shame, while 75% see themselves as unattractive and sexually undesirable.[2] A 2020 French study found that psoriasis also affected the quality of life and sexuality of patients' life partners.[3] In patients who develop psoriatic arthritis, inflamed joints, pain and fatigue can significantly impair mobility and occupational functioning.[2]

Now recognized as an immune-mediated inflammatory disorder, psoriasis extends to several other body systems.[1] Characteristic comorbidities are listed in Table 1.

Psoriatic arthritis, the most prevalent comorbidity of psoriasis, develops in about 30% of patients and appears about 10 years after the onset of psoriasis, on average.[6] A heterogeneous disease, psoriatic arthritis may affect a few or many hand and foot joints (peripheral disease) and/or may involve the spine and sacroiliac joints (axial disease). Depending on how it is defined, axial involvement occurs in 25% to 70% of people with psoriatic arthritis.[7]

Related to systemic inflammation	Related to lifestyle or quality-of-life factors	Genetically related
Psoriatic arthritis Metabolic syndrome/obesity Cardiovascular disease Non-alcoholic fatty liver disease	Anxiety Depression Smoking & alcohol abuse Suicidal ideation	Inflammatory bowel disease (IBD) * risk of IBD 4x greater than in the general population

Table 1: Comorbidities associated with psoriasis[4,5]

Presenters at the meeting emphasized that psoriatic arthritis develops along a "pathological continuum" that is often undetected. Indeed, about 15% of psoriasis patients followed by dermatologists have undiagnosed psoriatic arthritis.[4] Dermatologists are in a unique position to identify early psoriatic arthritis. They should question their psoriasis patients about joint pain, stiffness, and search for signs of dactylitis and enthesitis. They could also consider referring patients for imaging and rheumatologic evaluation when deemed appropriate.[6,8]

Treatment Trends & Unmet Needs

New advances in psoriasis treatment have raised the expectations and goals of treatment. Ninety-percent improvement in the Psoriasis Area Severity Index (PASI 90), or even PASI 100, has become a realistic treatment goal.[9] The focus has also shifted toward absolute outcomes (e.g. PGA clear or almost clear).[9] Efficacious treatments improve not only psoriasis symptoms, but also quality of life.[2] Treatment should be initiated early, especially when psoriatic arthritis is involved, to prevent disabling joint damage.[8]

Current medical treatment classes include topical agents (e.g. corticosteroids, vitamin A and D derivatives), traditional systemic agents (e.g. methotrexate, cyclosporine, acitretin), the oral phosphodiesterase-4 (PDE-4) inhibitor apremilast, and an expanding array of biologic agents (Table 2), sometimes recommended as first-line agents for moderate-to-severe plaque psoriasis.[10] Historically, phototherapy (UVB and PUVA) was widely used to treat moderate to severe psoriasis, and narrow-band UVB phototherapy continues to be a good option for some patients.[10]

Several presentations at the meeting focused on biologics that inhibit the IL-17 and IL-23 cytokine pathways. In patients with moderate-to-severe arthritis, high levels of these cytokines are associated with an increased risk of comorbidities.[13] IL-17 and IL-23 inhibitors, which target psoriasis immunopathology and show an overall superior skin efficacy, have been gradually displacing anti-TNF agents and IL-12/23 inhibitors as first-line biologic options.[9,13] A meta-analysis of 44 studies established the overall safety and tolerability of IL-17 and IL-23 inhibitors.[14] Common adverse events with these classes include infections, nasopharyngitis, and headaches,[14] although the causality of these effects remains uncertain.

Despite the effectiveness of current treatments, psoriasis remains undertreated. In a 2019 online survey conducted in Germany, 59% of patients who received medical care for psoriasis were only moderately or less satisfied with their treatment.[15] In the US, a study of registry patients found that, while most showed an "acceptable" treatment response after 6 and 12 months of systemic therapy, fewer than half reached their treatment targets.[16] Clinicians are advised to optimize treatment in such patients. Effective strategies include increasing the dose, reducing the interval between treatments, or switching to another agent.[9]

Considerations in the Choice of Biologic Treatment

While both IL-17 and IL-23 are involved in the pathogenesis of psoriatic arthritis, IL-17-mediated inflammation may play a greater role in the development of axial disease and cardiometabolic comorbidities, while IL-23 may have greater involvement in the development of IBD.[13] These distinctions can inform the choice between the two classes (Table 3).

Axial psoriatic arthritis: If patients require biologic therapy, anti-TNF agents are often used first-line, but IL-17 inhibitors are preferred if skin involvement is significant.[7] In the MAXIMIZE study, over 60% of patients receiving the IL-17 inhibitor secukinumab showed an ASAS20 response at week 12, compared to 31% in the placebo group, and response was maintained through week 52.[7] Drugs targeting the IL-12/23 pathway are not currently recommended due to a lack of studies showing clear efficacy[7] as well as negative studies for ankylosing spondylitis.

Peripheral psoriatic arthritis: Evidence exists for all classes of biologics used to treat psoriasis, as well as for the PDE-4 inhibitor apremilast.[8] The JAK inhibitors tofacitinib and upadacitinib have also shown efficacy and are approved for this indication.

Inflammatory bowel disease: For psoriasis with comorbid IBD, positive data exist for the use of anti-TNF inhibitors, the IL-12/23 inhibitor ustekinumab, and IL-23 inhibitors.[11] Of note, Health Canada approved the IL-23 inhibitor risankizumab for Crohn's disease in late 2022. On the other hand, the IL-17 inhibitors secukinumab and brodalumab have failed studies in Crohn's disease.[11] Cases of new-onset IBD have been observed in psoriasis patients treated with IL-17 inhibitors, though the signal is low and these cases may arise from the disease process itself, rather than as an outcome of IL-17 inhibition.[11]

Speed of onset of action has become an important differentiator among systemic treatments, as patients place high value on rapid clearance.[9] Dosing regimen also comes into play, with many patients showing a preference for less frequent administration.

Oral candidiasis, a rare side effect related to the mechanism of action of IL-17 inhibition, generally responds to treatment and is not a reason for discontinuing the biologic.[11] Reported cases of suicidality with brodalumab have led to further investigations; to date, a causal relationship has not been established.[11]

New Molecules

Several new practice-changing molecules were introduced at the meeting. Topical **tapinarof**, a hydrocarbon receptor-modulating agent, has been investigated for both psoriasis and atopic dermatitis and is expected to enter the Canadian market soon. In two Phase 3 PSOARING trials, a *Physician Global Assessment* (PGA) response occurred at week 12 in 35.4% and 40.2% of patients treated with tapinarof, respectively, compared to 6.0% and 6.3% in the vehicle groups.[17] Of note, 58% of the patients who did not achieve PGA-0 or PGA-1 at week 12 reached this outcome at week 52 in the open-label extension study.[18] In patients who reached PGA-0, the median duration of remission after discontinuation of treatment was 130 days.[18] A second new topical agent, a potent PDE-4 inhibitor called **roflumilast**, showed similar results in the DERMIS 1 and 2 trials: at week 8, 42.4% and 37.5% reached the *Investigator Global Assessment* (IGA) endpoint in the active treatment groups, respectively, versus 6.1% and 6.9% in the control arms.[19] A distinctive feature of this agent is its efficacy and tolerability in special sites such as facial, genital and intertriginous areas.

TNF inhibitors	IL-12/23 inhibitors	IL-17 inhibitors	IL-23 inhibitors
Etanercept Infliximab Adalimumab Certolizumab	Ustekinumab	Secukinumab Ixekizumab Brodalumab Bimekizumab	Guselkumab Tildrakizumab Risankizumab

Table 2: Biologic agents used to treat psoriasis[11,12]

	Anti-TNF	IL17	IL12/23	IL23
Axial PsA				*
Peripheral PsA				
IBD				

Table 3: Choosing a biologic class based on comorbid PsA or IBD[8,11]

PsA = psoriatic arthritis = *effective* = *not effective*

** Negative studies for ankylosing spondylitis suggest that IL-23 inhibition is also ineffective for axial PSA; ongoing studies will answer the question more definitively.*

Deucravacitinib is a new oral JAK inhibitor that specifically targets the TYK2 receptor, which differentiates it from less targeted JAK inhibitors. As shown in the Phase 3 POETYK-1 and -2 trials, the molecule is potent enough to treat moderate-to-severe psoriasis. In the trials, 53-58% of patients in the treatment arms reached the co-primary endpoint of PASI 75, compared to 35-40% in comparator apremalist arms and 9-12% in the control arms.[20] Corresponding results for the other co-primary endpoint (IGA 0-1) were 50-53% for deucravacitinib, 32-34% for apremilast, and 7-8% for placebo.[20] Longer-term data showed that efficacy was maintained for up to 52 weeks. These results led Health Canada to approve this agent in late 2022.

Deucravacitinib has also been investigated for psoriatic arthritis in a recently published Phase 2 study.[21] Patients were randomized to receive placebo or one of two doses (6 mg and 12 mg daily) of deucravacitinib, with ACR-20 response at week 16 as the primary endpoint. Response was significantly higher with deucravacitinib 6 mg (52.9%) and 12 mg (62.7%) than with placebo (31.8%),[21] suggesting this oral agent may play a role in the treatment of psoriatic arthritis. Phase 3 studies are ongoing.

A first-in-class biologic called **spesolimab**, which targets the IL-36 receptor, has recently been approved by the FDA for the treatment of generalized pustular psoriasis (GPP), a severe form of psoriasis that causes pustules on an erythematous base often associated with systemic symptoms. In the Phase 2 trial of patients with severe GPP, spesolimab 900mg IV demonstrated clear superiority over placebo (54% vs. 6%) for the main outcome measure of GPPGA-0.[22] [GPPGA = Generalized Pustular Psoriasis Physician Global Assessment.] Serious adverse events were reported in 6% of patients on spesolimab versus 0% on placebo, and a signal of infectious risk also emerged in the spesolimab group. The ongoing Effisayil 2 trial is evaluating spesolimab as maintenance treatment for GPP.[23]

Cancer Immunotherapy and Psoriasis

The meeting helped raise awareness of an increasing challenge in dermatology: the management of adverse events induced by cancer immunotherapy. Immune checkpoint inhibitors (ICIs) represent a significant leap in cancer treatment, but they come at the cost of various immune-related adverse events, including dermatologic adverse events in about 40% of cases.[24] In a multi-centre study of patients on ICI therapy, psoriasis accounted for 23% of skin-related side effects.[25] While most ICI-induced psoriasis is the plaque subtype, all other subtypes have been reported.[24] Other common dermatologic sequelae of ICI treatment include lichenoid and eczematous eruptions, pruritus, and vitiligo.

ICI treatment can induce psoriasis *de novo* or cause preexisting psoriasis to flare up.[24] This can complicate treatment decisions and underscores the need for oncologists to consult dermatologists when treating patients with a history of psoriasis or psoriatic arthritis, including during flareups.

On a positive note, the presence of skin toxicities may signal that ICI treatment is working. In a population-level cohort study that reviewed a database of over 200 European and US patients treated with ICI, the development of cutaneous adverse events was strongly associated with therapeutic response and patient survival.[26] If more severe ICI-induced skin toxicities are not managed, however, they may compromise the therapeutic outcome of cancer treatment.[25]

For moderate cases of CI-induced psoriasis, acitretin, methotrexate, and/or apremilast are deemed suitable options.[24] For more severe presentations, the EADV task force "*Dermatology for Cancer Patients*" recommends reinforcing therapy for moderate disease (including dose optimization) and consideration of anti-TNF and IL-23-targeting biologics in non-responders.[24] The paper also advises avoiding IL-17-targeting agents due to their gastrointestinal effects,[24] though this is still a subject of debate.

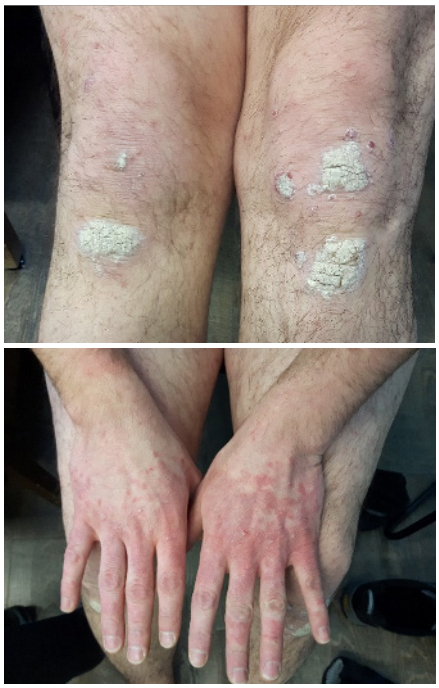

Figure 1: Checkpoint inhibitor-induced psoriasis
From Dr. Joël Claveau's files

Ideally, ICI treatment should be discontinued until the psoriasis improves to grade 0 or 1.[24]

Overall, the management of ICI-induced dermatologic adverse events requires a balance between reducing troubling skin toxicities that compromise patients' quality of life and preserving the benefits of cancer treatment.

Conclusions

The global medical community has come to understand psoriasis as a systemic disease with a profound impact. The optimal treatment choice depends not only on the disease subtype and severity, but on a patient's comorbidity profile. While both systemic and topical treatments continue to improve, many patients remain undertreated. Dermatologists can play a significant role in detecting emergent psoriatic arthritis and in managing psoriasis induced by cancer treatment.

Test Your Knowledge

Q1: Which class of biologic is not suitable for psoriasis patients with comorbid inflammatory bowel disease, and why?

Q2: If patients on cancer immunotherapy develop psoriasis, should they be switched to a different cancer treatment?

Q1 Answer: IL-17 inhibitors are currently not recommended for this group of patients. The IL17 inhibitors secukinumab and brodalumab have failed studies in Crohn's disease, and new-onset IBD has been observed in psoriasis patients treated with IL17 inhibitors (though a causal relationship has not been established).

Q2 Answer: Development of cutaneous side effects, including psoriasis, signals that the immunotherapy is likely working. The psoriasis should be treated with either local or systemic treatments, but the immunotherapy doesn't need to be permanently discontinued or replaced with another therapy.

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