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# SAFETY CONCERNS IN PSORIASIS MANAGEMENT: ADVERSE EFFECTS OF SYSTEMIC TREATMENTS

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## ABSTRACT

Psoriasis is a persistent inflammatory skin condition that frequently necessitates systemic therapy in moderate to severe cases. The expanding range of systemic treatments—including conventional drugs like methotrexate and cyclosporine, targeted oral agents such as apremilast, and various biologic therapies—has brought increased attention to their potential adverse effects. This review offers a detailed examination of the major side effects linked to these treatments, covering systemic toxicities, increased susceptibility to infections, risks of malignancy, and immune-mediated complications. It also compares safety profiles across different drug classes and discusses patient-related risk factors and appropriate monitoring strategies. By providing a thorough overview of the adverse effect spectrum, this article aims to guide clinicians in selecting and managing systemic therapies for psoriasis with greater confidence and precision.

**KEYWORDS:** Psoriasis, Systemic therapies, Adverse effects, Biologics, Methotrexate, Apremilast, Ciclosporin.

## INTRODUCTION

Psoriasis is a long-standing, immune-mediated skin condition marked by sharply defined, red plaques covered with thick, silvery-white scales. These lesions typically appear on the elbows, knees, lower back, and scalp, though they can affect any area of the body. The disease has a global presence and affects about 2% of the population. While it can develop at any age, it most commonly begins during two age ranges: between 20–30 years and again between 50–60 years. Psoriasis considerably diminishes a patient's quality of life. Psoriasis is linked to various systemic comorbidities beyond skin symptoms, such as psoriatic arthritis, metabolic syndrome, cardiovascular problems, and mental health conditions like depression and anxiety. A range of treatment options exists, including both topical and systemic therapies. However, topical treatments can be time-consuming and difficult to use, and traditional systemic drugs are

often linked with serious side effects. These challenges frequently lead to poor patient adherence and low treatment compliance.[1,2]

Psoriasis develops due to a combination of genetic vulnerability and exposure to specific environmental factors. Research from genome-wide association studies has pinpointed several genes that may contribute to the disease.[3] External elements like infections, stress, and tobacco use are thought to trigger or exacerbate psoriasis. The condition is driven by an immune-mediated inflammatory process involving cells such as dendritic cells, T lymphocytes, keratinocytes, and neutrophils, along with the cytokines they secrete.[4]

Although there is no permanent cure for psoriasis, various treatments are available to manage its symptoms effectively. Treatment approach typically involves two phases: induction therapy to achieve remission and maintenance therapy to keep the disease under control. Mild cases are usually treated with topical medications as a first-line approach. About 20% to 30% of patients with moderate to severe psoriasis, second-line options like phototherapy or systemic treatments are needed.[5]

**Systemic Therapies in Psoriasis**

The International Psoriasis Council has recently established guidelines for determining eligibility for systemic treatment. Patients are considered candidates if they meet any of the following criteria:[6]

- Psoriasis lesions cover 10% or more of their body surface.
- Lesions are located on sensitive areas such as the hands, feet, face, genitals, or scalp.
- Topical therapies have failed to adequately control symptoms.

The approved systemic treatments for psoriasis are grouped into the following categories:[7]

- Conventional systemic agents: ciclosporin, methotrexate, acitretin, fumaric acid esters
- Small molecules: apremilast, deucravacitinib
- Biologics:
  - Tumour necrosis factor-alpha (TNF-alpha) inhibitors: etanercept, infliximab, adalimumab, certolizumab;
  - Interleukin 12/23 inhibitors (IL 12/23i): ustekinumab;
  - Interleukin 17 inhibitors (IL 17i): secukinumab, ixekizumab, brodalumab, bimekizumab;
  - Interleukin 23 inhibitors (IL 23i): guselkumab, tildrakizumab, risankizumab.

The introduction of biologics and targeted therapies has greatly broadened systemic treatment options in the last 20 years, emphasizing the importance of closely evaluating their safety. While clinical trials are a key source of safety and efficacy data, they frequently exclude patients with multiple health conditions or elevated risk factors. As a result, real-world adverse effects—such as infections, liver and kidney damage, cancer, and heart-related events—may not be fully reflected in trial outcomes.[8]

## TOXICITY PROFILES OF SYSTEMIC AGENTS

### A. TRADITIONAL SYSTEMIC AGENTS

#### 1. Ciclosporin

Ciclosporin is an immunosuppressive agent that works by suppressing the activation and proliferation of lymphocytes. Its immunosuppressive effect is both rapid in onset and reversible. While ciclosporin quickly improves the severity of

psoriatic lesions, prolonged use can be challenging due to time-dependent side effects, notably an increase in serum creatinine levels.[9] Renal toxicity is the most critical side effect associated with ciclosporin. Acute renal impairment, which is usually reversible, may appear within the first month of therapy and is characterized by elevated serum creatinine levels and decreased glomerular filtration rate (GFR). With long-term use extending beyond two to four years, irreversible kidney damage—such as interstitial fibrosis and tubular atrophy can occur.[10]

Ciclosporin commonly causes hypertension (25–30%) due to renal vasoconstriction and sodium retention. It also increases the risk of infections, particularly upper respiratory tract infections, and raises the likelihood of malignancies such as skin cancer and lymphoma. Metabolic effects like hyperlipidemia and electrolyte disturbances (e.g., hyperkalemia, hypomagnesemia) are dose-dependent and require regular monitoring. Cosmetic side effects, including hypertrichosis and gingival hyperplasia, occur in 5–10% of patients.[11]

Because of the cumulative risk of side effects, the use of ciclosporin should be restricted. Short-term, intermittent therapy lasting 8 to 16 weeks is recommended during flare-ups. When extended treatment is necessary, continuous use should ideally be limited to no more than one year. To ensure safe use, it is essential to routinely monitor kidney function, blood pressure, lipid levels, and liver enzymes.

**2. Methotrexate**

Methotrexate is an antimetabolite that functions by inhibiting folic acid activity. At low doses, it has anti-inflammatory and immunomodulatory effects. The safety and tolerability of methotrexate largely depend on the dosage, with lower doses being generally well-tolerated and considered safe for long-term use.[12]Methotrexate, while effective for treating psoriasis, is associated with several important adverse effects, especially with long-term use. Hepatotoxicity is the most significant concern, with elevated liver enzymes occurring in 23–33% of patients. Severe liver damage is linked to alcohol use, NSAIDs, obesity, diabetes, and high cumulative doses.[13]

Gastrointestinal side effects like nausea, vomiting, and abdominal discomfort are common but can often be managed by reducing the dose or adding folic acid, though excessive folic acid may reduce methotrexate's efficacy. Hematological toxicity, particularly pancytopenia, may also occur but is typically reversible with dose adjustment or temporary withdrawal. Renal impairment has been reported in about 3% of patients on long-term therapy.[14] Methotrexate is teratogenic and therefore contraindicated during pregnancy. Pulmonary toxicity, including pneumonitis and pulmonary fibrosis, is rare but potentially serious. The drug has also been associated with an increased risk of certain malignancies, such as lymphoma and squamous cell carcinoma, particularly in patients with prior PUVA treatment.[15]

Other side effects include fatigue, headache, malaise, alopecia (in about 4% of cases), and rare but severe skin reactions. Certain NSAIDs may increase methotrexate toxicity and should not be administered at the same time. Despite these risks, methotrexate maintains an acceptable risk–benefit profile when prescribed at low doses with careful monitoring. With proper supervision and patient selection, it remains a key option in systemic psoriasis therapy.[16]

**3. Acitretin**

Acitretin, a second-generation retinoid that regulates keratinocyte growth and inflammation, is generally less potent than other conventional systemic agents but has a distinct adverse-effect profile. Its principal cumulative toxicity is

skeletal hyperostosis, whereas common early, dose-related mucocutaneous reactions include xerosis, cheilitis, and alopecia.Hepatotoxicity and abnormal liver-function tests appear uncommon at typical starting doses (25–30 mg/day), yet require periodic monitoring. The drug is highly teratogenic: effective contraception is mandatory during treatment and for at least two years after cessation because of risks of fetal malformation, spontaneous abortion, and stillbirth. Acitretin can cause hyperlipidaemia and occasionally myalgias, arthralgias, or benign intracranial hypertension; psychiatric symptoms are infrequent but patients should be counselled to report mood changes.[17]

Acitretin is unique among systemic therapies for not causing immunosuppression and carries the lowest infection risk among non-biologic treatments. However, adverse effects tend to appear early and are dose-dependent, so dosing is typically guided by patient tolerability rather than maximum effectiveness. Long-term use may be restricted due to risks such as teratogenicity, liver toxicity, and skeletal effects, though evidence for end-organ damage is inconsistent. Therefore, its use requires individualized risk–benefit assessment and careful monitoring for adverse events.[18]

### 4. Fumaric Acid Esters

Fumaric acid esters (FAEs), derived from an unsaturated dicarboxylic acid, are used orally in psoriasis treatment and primarily contain dimethyl fumarate (DMF) and monoethyl fumarate (MEF) salts. They work by suppressing T-cell proliferation, exerting anti-inflammatory effects.[19] The European Medicines Agency (EMA) has identified key adverse events, including reductions in leukocyte and lymphocyte counts, flushing, gastrointestinal issues,serious and opportunistic infections, malignancies, and liver or kidney damage. Rare but serious events like progressive multifocal leukoencephalopathy have also been reported.[20]

Eosinophilia is another potential side effect of FAE therapy, though it is typically temporary. Long-term use may lead to elevated liver enzymes and increased serum creatinine levels. Current clinical guidelines support the use of FAEs both for initiating treatment and for long-term management. Given their generally favorable risk–benefit profile, FAEs are considered a suitable option for treating moderate-to-severe psoriasis, especially in patients who are not candidates for more toxic systemic therapies.[21]

## B. SMALL MOLECULES

### 1. Apremilast

Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor that increases anti-inflammatory and reduces pro-inflammatory cytokine production. It is prescribed for moderate-to-severe chronic plaque psoriasis in patients who have not responded to or cannot tolerate other systemic treatments. Common adverse effects include gastrointestinal symptoms (such as nausea and diarrhoea), upper respiratory infections, nasopharyngitis, and headaches, though these typically do not increase with prolonged use. Lab abnormalities are rare and usually temporary.[22]

Apremilast has been linked to weight loss and an increased risk of depression and suicidal thoughts. Although routine blood monitoring isn't required, ongoing clinical vigilance—particularly for psychiatric symptomsis essential.[23] The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have highlighted several significant potential risks linked to apremilast. These include severe hypersensitivity reactions, depression, suicidal thoughts or behavior, vasculitis, increased risk of certain cancers, serious infections, major adverse cardiovascular events (MACEs), and delayed fetal development.

## C. BIOLOGICS

Biologic treatments for psoriasis target specific cytokines to inhibit T cell activity but can disrupt immune function, leading to risks such as infections, inflammatory bowel disease flare-ups, cardiovascular events, and cancer.[24] The FDA also highlights common biologic-related risks such as hypersensitivity and cancer.

### 1. TNF –Alpha Inhibitors

TNF-alpha inhibitors are effective anti-inflammatory treatments but can increase the risk of serious infections, particularly tuberculosis, due to TNF-alpha's role in immune defense. Infliximab and adalimumab are notably linked to higher infection risks, with adalimumab carrying a TB warning. Etanercept shows mixed evidence regarding infection risk.[25] A systematic review by Dommasch et al. found that short-term use of TNF antagonists in adults with psoriatic disease slightly increases the risk of overall infections, but not serious infections. Commonly reported infections included upper respiratory tract infections, flu-like symptoms, and sinusitis.[26] Patients on TNF-alpha blockers require close monitoring due to their heightened susceptibility to infection.

The most frequent side effect of these medications is a reaction at the injection site. Infliximab can cause infusion site reactions in 3–22% of psoriasis patients. Similarly, adalimumab and etanercept administered subcutaneously can lead to local reactions like redness, itching, tenderness, or swelling at the injection site.[27] The association between TNF-alpha inhibitors and cancer risk is still unclear, though some studies suggest a slight increase, especially for non-melanoma skin cancers. These drugs have also been linked to rare blood disorders, including low blood cell counts and clotting abnormalities. Furthermore, they may elevate the risk of neurological complications, such as demyelinating diseases like multiple sclerosis, as well as other CNS conditions like meningitis and encephalitis.[28]

### 2. Interleukin 12/23 Inhibitors

Ustekinumab targets the shared p40 subunit of IL-12 and IL-23, while guselkumab, tildrakizumab, and risankizumab target the p19 subunit of IL-23. The EMA has identified potential adverse effects of ustekinumab, including serious infections, major cardiovascular events (MACEs), depression and suicidal thoughts, as well as reversible posterior leukoencephalopathy syndrome.[29] Ustekinumab has been linked to various skin reactions, such as pustular outbreaks, eczema-like rashes, lymphomatoid drug eruptions, and a few reported cases of eruptive squamous cell carcinoma. Guselkumab carries warnings for hypersensitivity, infections, and the risk of TB reactivation, with the EMA also monitoring for suicide risk, serious infections, cancer, and cardiovascular events. The FDA advises monitoring tildrakizumab for potential neurological issues, suicidal thoughts, and IBD. Risankizumab has a similar safety profile, with infections being the main concern. The FDA also recommends ongoing surveillance for possible biologic-related risks, including cancer, heart events, and allergic reactions.

### 3. Interleukin-17 Inhibitors

IL-17 inhibitors have been linked to various safety issues, including a higher incidence of mucocutaneous candidiasis and rare, usually mild, cases of neutropenia that require periodic monitoring.[30] Brodalumab has been associated with concerns about depression and potential suicidal risk.[31] Both the FDA and EMA recommend ongoing assessment of serious infections, major cardiovascular events, malignancies, and the risk of IBD, especially for ixekizumab, brodalumab, and bimekizumab.

## CONCLUSION

The management of moderate-to-severe psoriasis has significantly advanced with the introduction of various systemic therapies, including traditional agents, small molecules, and biologics. While these treatments effectively control symptoms and enhance quality of life, they also introduce notable safety concerns**.** Each therapy class carries a distinct risk profile, encompassing potential organ toxicity, teratogenicity, and increased risks of infection, malignancy, and psychiatric issues.

Psoriasis requires long-term treatment due to its chronic nature. Understanding the safety and tolerability of therapies is crucial for developing treatment guidelines, advising patients, and ensuring proper ongoing care. Clinicians must carefully balance efficacy with safety, particularly in patients with comorbidities or long-term treatment needs. Continuous monitoring, patient education, and a personalized approach are critical for minimizing adverse effects and optimizing outcomes. This review highlights the critical role of safety awareness in managing psoriasis and offers valuable guidance to help clinicians make more informed and confident treatment decisions.

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