Current and Future Oral Systemic Therapies for Psoriasis

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KEYWORDS

• Psoriasis • Methotrexate • Cyclosporine • Acitretin • Apremilast • Tofacitinib • Mycophenolate mofetil

KEY POINTS

- Methotrexate is a relatively safe, long-term treatment of appropriately screened and monitored patients who can be expected to achieve a 75% reduction in the Psoriasis Area and Severity Index in approximately 40% of cases.
- For patients without any contraindications, cyclosporine in most cases is a rapidly effective, short-term medication frequently used as a bridge to longer term maintenance approaches to the control of psoriasis.
- Carefully selected and monitored patients, especially those with the pustular, palmoplantar or erythrodermic forms of psoriasis, may derive significant benefit from acitretin therapy.
- Apremilast (approved in the US for both psoriasis and psoriatic arthritis) and tofacitinib (approved in the US for rheumatoid arthritis) are novel oral medications that have shown effectiveness in clinical trials; these medications are likely to be approved for use in patients with moderate to severe psoriasis within the near future.
- Mycophenolate mofetil, 6-thioguanine, leflunomide, and other oral agents remain reasonable alternatives, but various aspects of their efficacy, monitoring requirements, and adverse event profiles relegate these drugs to patients who have failed both oral and biologic medications.

Psoriasis is a chronic, immunodysregulatory disease with significant prevalence and a range of severity in its dermatologic and rheumatologic signs and symptoms. Topical agents remain the first-line treatments for mild disease. For patients with greater percent body surface area (BSA) of involvement, or with disease that has significant quality of life impact, systemic therapy or phototherapy is indicated.[1] Strong evidence indicates that psoriasis is an independent risk factor for cardiovascular risk and that the inflammatory comorbidities of psoriasis merit systemic therapy even in the absence of joint disease, though prospective data to assess whether there is a morbidity or mortality benefit to doing so are in their infancy.[2–4]

Systemic medication for psoriasis can be broadly divided into small molecules, which are usually given orally, and biologics, which are large molecules that must be delivered by injection or infusion. Systemic medications are often used as monotherapy but, in many, instances are combined or used with phototherapy to increase or maintain efficacy; decrease undesired effects; or,

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out of necessity, for refractory disease.[5] In some cases oral systemics are given in combination with biologics for synergistic effects or to forestall the development of biologic immunogenicity.

The small molecules used in therapy for psoriasis include mature drugs, such as methotrexate, cyclosporine, and acitretin, as well as newer compounds discovered through targeted development and understanding of molecular pathways, such as tofacitinib and apremilast.[6] This article focuses on the, small molecule systemic therapies with clinical data supporting their efficacy.

PATIENT ASSESSMENT

A thorough medical history, prior treatment history and focused physical examination should be the starting point from which systemic therapy for psoriasis is considered, with a review of systems that covers the cutaneous, immune, hematologic, cardiac, gastrointestinal, musculoskeletal, neurologic, reproductive, and family and social history. Concerns of the patient regarding mode of administration and risk aversion need to be considered (**Table 1**). This evaluation should include laboratory investigations, and it is prudent to include baseline studies necessary for the whole spectrum of possible systemic treatments. A suggested list of these tests is included in **Table 2**. A complete picture of the patient's disease severity, impact on their quality of life, overall health and comorbidities, and their willingness to attempt available treatment should coalesce, and a patient-centered, mutually agreeable therapeutic approach enacted. The nonbiologic, nonphototherapy options for modern systemic treatment of psoriasis are as follows.

METHOTREXATE

Methotrexate is the oldest systemic therapy for moderate to severe psoriasis having been approved over 40 years ago. Its anti-inflammatory effects are primarily mediated through its metabolism to polyglutamate derivatives that are potent inhibitors of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase.[7] In so doing, methotrexate increases the endogenous levels of adenosine, a potent anti-inflammatory compound.[8] Methotrexate also has been shown to decrease primary and secondary antibody responses.[7–10] Generally, it is available in 2.5 mg tablets and is typically prescribed at 7.5 to 25 mg, taken once weekly; higher doses produce better response.[9] Older dosing schemes were split between 3 administrations, every 12 hours, but this is unnecessary from an efficacy or side-effect standpoint. Additionally, subcutaneous methotrexate dosed once weekly has displayed better bioavailability, efficacy, and tolerability relative to the oral formulation in studies of patients with rheumatoid arthritis.[10–18] Daily or weekly folic or folinic acid supplements are recommended to decrease side effects (particularly bone marrow suppression) and improve gastrointestinal tolerability.[19,20]

Because methotrexate use for psoriasis predates the modern drug approval process, there have been, until the last decade, a lack of robust clinical data regarding its efficacy. This, however, is no longer the case. A multicenter, prospective, randomized, double-blind, placebo-controlled study involved 110 subjects receiving methotrexate doses from 7.5 to 25 mg/wk (plus folate 5 mg 2 days after the methotrexate dose). At 16 weeks, using the Psoriasis Area and Severity

Table 1
Selected patient considerations in systemic psoriasis therapy

Parameter	Consideration
Extent or severity of psoriasis	Typically >10% BSA, or involved areas significantly impede quality of life
Presence of psoriatic arthritis	Consider systemic, disease-modifying therapy regardless of level of skin involvement
Woman of childbearing potential	Not a good candidate for most oral psoriasis medications
Man attempting to conceive a child	Not a good candidate for methotrexate
Chronic or binge alcohol user	Avoid concomitant therapies with significant risk of hepatotoxicity
History of hepatitis	Avoid therapies with significant risk of hepatotoxicity
History of hematologic malignancy	Use immunosuppressants with caution
Immunodeficiency	Avoid immunosuppressants
Smoker	Counsel on quitting