Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies

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Psoriasis is a chronic inflammatory disease involving multiple organ systems and affecting approximately 2% of the world's population. In this guideline, we focus the discussion on systemic, nonbiologic medications for the treatment of this disease. We provide detailed discussion of efficacy and safety for the most commonly used medications, including methotrexate, cyclosporine, and acitretin, and provide recommendations to assist prescribers in initiating and managing patients on these treatments. Additionally, we discuss newer therapies, including tofacitinib and apremilast, and briefly touch on a number of other medications, including fumaric acid esters (used outside the United States) and therapies that are no longer widely used for the treatment of psoriasis (ie, hydroxyurea, leflunomide, mycophenolate mofetil, thioguanine, and tacrolimus). (J Am Acad Dermatol 2020;82:1445-86.)

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DISCLAIMER

Adherence to this guideline will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, nor should they be deemed either inclusive of all proper methods of care, or exclusive of other methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of circumstances presented by the individual patient and the known variability and biologic behavior of the disease. Furthermore, the treatment dosages used in clinical trials may not be effective in certain cases, and some patients may require shorter intervals between doses and/or higher treatment doses of a particular treatment methodology. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

SCOPE

This guideline will cover the use of oral-systemic, nonbiologic medication in the treatment of psoriasis.

METHOD

For a full description of the methodology used herein, please refer to Appendix 1.

DEFINITION OF REVIEW

See section below for full definition statement (Table I).

INTRODUCTION

In the treatment of psoriasis, topical therapies, such as vitamin D analogues and corticosteroids, may be effective and sufficient for managing limited disease and offer the additional benefit of fewer significant adverse effects due to the lack of systemic exposure. Although helpful and important in most psoriasis treatment regimens, topical therapies are frequently inadequate to obtain and maintain skin clearance. Hence, phototherapy or systemic treatments can be pursued. Many oral medications have been used for decades to treat psoriasis, each with its own benefits and risks. Most work by targeting the immune system, whereas others, such as acitretin, work predominantly by decreasing keratinocyte hyperproliferation, thus restoring the normal epidermal differentiation.

The rapidity of onset is an important pharmacologic trait guiding treatment selection in many cases, particularly with inflammatory or erythrodermic psoriasis, while in other cases, individual patient circumstances and comorbidities, including concomitant obesity, psoriatic arthritis, inflammatory

Abbreviations used:

AAD:	American Academy of Dermatology
ACR:	American College of Rheumatology
AE:	adverse event
BB-UVB:	broadband ultraviolet B
BSA:	body surface area
BUN:	blood urea nitrogen
CBC:	complete blood count
CI:	confidence interval
CYP3A4:	cytochrome P450 3A4 subtype
FAE:	fumaric acid ester
FDA:	Food and Drug Administration
GI:	gastrointestinal
IL:	interleukin
NB-UVB:	narrowband ultraviolet B
OPT:	Oral treatment Psoriasis Trial
PASI:	Psoriasis Area and Severity Index
PUVA:	psoralens with ultraviolet A
RR:	relative risk
UV:	ultraviolet
UVA:	ultraviolet A
UVB:	ultraviolet B

bowel disease, and infections, including viral hepatitis, latent tuberculosis, and HIV, may be potent drivers toward or away from a specific medication.[1,2]

Although the advent of biologic therapies has changed the treatment landscape, the medications discussed in this guideline are still widely used, either as monotherapy or in combination with biologic medications. These therapies can benefit widespread psoriasis, have a comparatively low cost (in the case of older medications), have increased availability, and ease of administration.

DEFINITIONS

Psoriasis vulgaris is a chronic inflammatory skin disease that typically presents with well-demarcated pink plaques with silvery scale, commonly involving the scalp, elbows, knees, and presacral region. Any area of skin may be involved, including the palms and soles, as well as the genital regions in up to 60% of patients.[3] The severity of psoriasis is generally defined by the total body surface area (BSA) involved, and BSAs of <3%, 3% to 10%, and >10% are considered as mild, moderate, and severe disease, respectively. The Psoriasis Area and Severity Index (PASI) is a more specific means of quantifying the extent and severity of psoriasis. The PASI takes into account not only the BSA but also intensity of redness, scaling, and plaque thickness, ultimately producing a score from 0 (no disease) to 72 (maximal disease severity).[4] The PASI is an important research tool but is used infrequently in clinical practice. It is time consuming and provides little additional information about the individual patient that is not provided by the physician's global assessment or BSA estimate.

Table I. Clinical questions

What are the efficacy, effectiveness, adverse effects, contraindications, and recommended monitoring for oral systemic therapies used to treat psoriasis in adults?

1. Methotrexate—FDA approval 1972
2. Apremilast—FDA approval 2014
3. Cyclosporine—FDA approval 1997
4. Acitretin—FDA approval 1997
5. Tofacitinib—Not FDA approved for psoriasis
6. Fumaric acid esters—Not FDA approved for psoriasis
7. Hydroxyurea—Not FDA approved for psoriasis
8. Mycophenolate mofetil—Not FDA approved for psoriasis
9. Azathioprine— Not FDA approved for psoriasis
10. Leflunomide—Not FDA approved for psoriasis
11. Tacrolimus—Not FDA approved for psoriasis
12. Thioguanine—Not FDA approved for psoriasis

FDA, Food and Drug Administration.

Psoriasis is an immune-mediated condition caused by inappropriate activation of T cells and dendritic cells with subsequent release of inflammatory cytokines including interleukin (IL) 17, IL-23, and tumor necrosis factor-α.[5] These soluble mediators are responsible for keratinocyte hyperproliferation, increased vascularity, and the inflammatory infiltrate present in psoriatic plaques.[6] These cytokines have also been implicated in a number of psoriasis comorbidities, including metabolic syndrome, heart disease, and arthritis.[7] Because psoriatic plaques have robust infiltration of inflammatory cells, a number of systemic medications that suppress inflammatory responses have been evaluated.

METHOTREXATE

Methotrexate was FDA approved in 1972 and has been used for more than 4 decades in the treatment of psoriasis. It is a competitive inhibitor of dihydrofolate reductase, decreasing folate cofactors required for the synthesis of nucleic acids.[8] In addition, polyglutamate derivatives of methotrexate are potent inhibitors of 5-aminoimidazole-4-carboxamide ribonucleotide transformylase, an effect that results in increased amounts of endogenous adenosine, an anti-inflammatory molecule.[9-12] These inhibitory actions have a large effect on rapidly dividing cells. In psoriasis, a theoretic inhibitory effect on keratinocytes was originally suspected to be responsible for its therapeutic benefit, but studies have since failed to show a significant influence of methotrexate on epidermal

cells.[13] Instead, low-dose methotrexate (<25 mg per week) decreases proliferation of lymphoid cells, and this direct immunosuppressive effect is considered to be the mechanism by which methotrexate improves psoriatic disease.[13,14]

Dosing

For psoriasis, methotrexate is typically administered in doses ranging from 7.5 mg to 25 mg weekly as 1 dose or divided into 3 dosages over 24 hours. In a direct comparison study, 10 mg weekly dosing was slower acting than 25 mg weekly dosing but with fewer severe adverse effects.[15] Daily dosing (2.5 mg daily for 6 days of the week) showed less benefits than weekly dosing (15 mg divided into 3 doses every 8 hours over a 24-hour period) and was also more likely to cause elevation in liver enzymes.[16] In some patients, the gastrointestinal (GI) adverse effects of methotrexate were better tolerated when the dose was divided into 3 doses, given every 12 hours. This split-dosing schedule (3 divided doses given every 12 hours each week) was based on "current knowledge concerning the epidermal cell proliferation kinetics of psoriasis and chemotherapy with cell-cycle specific drugs."[17] Because psoriatic keratinocytes traverse the cell cycle in approximately 7 days, the rationale for the prolonged dosing period was to attempt to interfere with a prolonged S phase of the cell cycle.

Methotrexate is usually given orally, although a parenteral preparation is available for weekly subcutaneous or intramuscular administration. Some physicians prefer to start with a test dose of 2.5 to 5 mg, followed by a complete blood count (CBC) 5 to 7 days after the test dose to gauge individual susceptibility to bone marrow suppression (expert consensus). Alternatively, it is reasonable to begin at a therapeutic dose, such as 15 mg weekly, with subsequent laboratory evaluation, using test doses only for patients with an increased risk of having adverse effects (potential drug interactions, diabetes, decreased kidney function, or other significant comorbidities).[18,19] The methotrexate dose can be adjusted as needed to achieve adequate skin clearance while minimizing adverse effects. Dosage changes frequently take at least a month for a clinical response.

Subcutaneous administrations of methotrexate may be particularly useful for patients receiving higher doses that increase the risk of GI adverse effects when taken orally. In a randomized controlled trial with 120 patients with psoriasis receiving subcutaneous methotrexate weekly (n = 91) or placebo (n = 29), a PASI 75 score was achieved in 41% (n = 37) of the subcutaneous methotrexate group compared with 10% of the placebo group (relative risk, 3.93; 95% confidence interval [CI], 1.31-11.81; $P = .0026$).[20] Subcutaneous methotrexate was well tolerated, with no patient deaths and no reported malignancies, serious infections, or major adverse cardiovascular events.[20]

Parenteral methotrexate solution can be administered orally: 0.6 mL of (25 mg/mL) methotrexate is equal to six 2.5-mg tablets and is less expensive. Although the drug labels for subcutaneous and oral routes of administration report different bioavailabilities,[21] the bioavailability of parenteral solution when taken orally is thought to be similar to that of oral formulations (expert consensus).

Folate supplementation

Concomitant supplementation with folic acid is recommended to decrease the rate of adverse effects associated with methotrexate therapy. Folate is typically given daily, except for the days in which methotrexate is given, to avoid influencing efficacy.[18] Folic acid or folinic acid has been reported to decrease hepatic laboratory abnormalities and GI adverse effects in patients with rheumatoid arthritis.[22] Whether there is a lower incidence of hematologic adverse effects with folic acid supplementation is uncertain (expert consensus). There is no difference in efficacy between folinic acid and folic acid, but folic acid is less expensive.[22] The influence of folate supplementation on the efficacy of methotrexate therapy could not be analyzed due to variations across pooled studies, but folinic acid may slightly decrease methotrexate efficacy in psoriasis.[18,23,24]

Efficacy

Methotrexate was FDA approved in 1972 at a time when randomized clinical trials were not required for regulatory approval. As such, there were few large, high-quality studies analyzing the safety and efficacy of methotrexate. Nonetheless, several studies have demonstrated the benefit of methotrexate in psoriasis.[25,26]

One study randomized 868 methotrexate-naïve patients (3:1) to receive infliximab, 5 mg/kg, at weeks 0, 2, 6, 14, and 22, or methotrexate, 15 mg weekly, with a dose increase to 20 mg weekly at week 6 if the PASI response was <25%.[27] After 16 weeks of treatment with methotrexate, 42% achieved PASI 75, and 38% of patients were clear or almost clear; however, this study did not include a placebo group and thus may overestimate clinical response. The efficacy of methotrexate in this study

was significantly lower compared with biologic therapy.

A large randomized clinical trial compared methotrexate (n = 110) to adalimumab (n = 108) and placebo (n = 53), with PASI 75 serving as the primary end point after 16 weeks of treatment.[28] Methotrexate group performed significantly better than placebo (35.5% of patients achieved PASI 75 compared with 18.9%) but was less effective than adalimumab (79.6% with PASI 75). Of concern in this study is the high PASI 75 rate seen in the placebo group (18.9%). Adalimumab cleared 16.7% of patients compared with 7.3% with methotrexate and 1.9% with placebo. On the basis of direct comparison studies, infliximab, adalimumab, etanercept, ustekinumab, and narrowband ultraviolet B (NB-UVB) are more effective than methotrexate.[26,27,29,30]

Although not FDA approved for this indication, methotrexate is a disease-modifying drug for psoriatic arthritis. Further studies are needed to assess both in terms of efficacy disease activity and prevention of radiographic progression. A recent randomized controlled trial found no evidence that methotrexate improves synovitis in psoriatic arthritis and failed to demonstrate significant treatment effects for a number of end points, including tender and swollen joint counts, Health Assessment Questionnaire scores, pain, erythrocyte sedimentation rate, and C-reactive protein.[31] The study has been criticized because it may not have had adequate statistical power. A more recent study did find statistically significant improvements in the number of patients with dactylitis (62.7% reduction) and enthesitis (25.7% reduction) and American College of Rheumatology (ACR) outcomes, with ACR20 achieved in 40.8%, ACR50 in 18.8%, and ACR70 in 8.6%.[32] Skin disease also improved, with 27.2% attaining PASI 75 after 12 weeks.

Combination therapy with methotrexate and tumor necrosis factor inhibitors results in improved efficacy over methotrexate monotherapy for the treatment of psoriasis.[33,34] A large randomized study of 239 patients demonstrated that the addition of methotrexate to etanercept was associated with a better clinical response than etanercept alone.[35] At 24 weeks, PASI 75 was achieved in 77.3% on the combination therapy compared with 60.3% treated with etanercept monotherapy, and 71.8% of patients were "clear" or "almost clear" with combination therapy compared with 54.3% with etanercept monotherapy. Adverse events were slightly more common in the combination group (74.9% vs 59.8%), but there was no difference in the proportion of patients experiencing serious adverse events between the 2 groups. A systematic review concluded that etanercept plus methotrexate was more beneficial than etanercept monotherapy (PASI 75; relative risk [RR], 1.28; 95% CI, 1.14-1.45).[36] There was an increased rate of adverse effects with combination therapy (RR, 1.25; 95% CI, 1.10-1.42), but its overall safety profile remained acceptable.

Methotrexate has also been used with NB-UVB phototherapy. This combination results in increased efficacy and more rapid skin clearing at lower cumulative doses of methotrexate and UVB compared with monotherapy with either treatment.[37-39] The long-term effects of this combination on photocarcinogenesis remains to be determined.

Toxicity

Common toxicities of methotrexate tend to occur shortly after the medication is initiated and include fatigue, anorexia, nausea, and stomatitis.[40] Alterations in the dose, route, or frequency of administration (eg, oral to subcutaneous or intramuscular routes or from single weekly dose to three divided doses over 24-hour period) can help mitigate these effects. Taking the medication with food can also be helpful.[40] Given the immunosuppressive nature of methotrexate, treatment may increase the risk of infection and reactivation of latent tuberculosis, hepatitis, and lymphoma (especially Epstein-Barr virus–associated B-cell lymphoma). These conditions have been reported in patients with psoriasis treated with methotrexate, supporting the importance of regular laboratory monitoring and the need to maintain a high level of suspicion for these complications.[41-44] Hepatitis B and C screening and baseline tuberculosis testing (purified protein derivative, T-Spot [Oxford Immunotec USA, Inc, Marlborough, MA],[45] or QuantiFERON Gold [Qiagen, Germantown, MD][46]) should be considered, depending on the individual patient's risk factors.

Other methotrexate adverse events include pneumonitis, myelosuppression, epidermal necrolysis, and hepatotoxicity.[47] Although pneumonitis is a potentially devastating consequence, it is more commonly seen in rheumatoid arthritis and rarely occurs in psoriasis.[48] A systematic review and meta-analysis including 7 studies found 504 respiratory events occurred in 1630 participants and concluded that methotrexate was not associated with a significant increase in the risk of respiratory infections, adverse respiratory events, and noninfectious respiratory events (RR 1.03, 95% CI 0.90-1.17). In addition, no pulmonary deaths occurred.[49]

Table II. Methotrexate supporting information*

Supporting statement	References
Absolute contraindications	50
• Pregnancy	
• Nursing	
• Alcoholism	
• Alcoholic liver disease or other chronic liver diseases	
• Immunodeficiency syndromes	
• Bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia	
• Hypersensitivity to methotrexate	
Relative contraindications	
• Abnormalities in renal function	
• Abnormalities in liver function	
• Active infection	
Risk factors for methotrexate-associated hepatotoxicity	51
• History of or current use of greater than moderate alcohol consumption	
• Persistent abnormal liver function test findings	
• History of liver disease including chronic hepatitis B or C	
• Family history of inheritable liver disease	
• Diabetes mellitus	
• Obesity	
• History of exposure to hepatotoxic drugs or chemicals	
• Hyperlipidemia	
Baseline/ongoing monitoring	50
• History and physical examination	
• Hepatitis B and C (baseline monitoring)	
• Pretreatment test for latent TB (PPD, T-Spot [Oxford Immunotec USA, Inc, Marlborough, MA], or QuantiFERON Gold [Qiagen, Germantown, MD])	
• Referral for a chest radiograph for a positive TB test	
• Monitor CBC and LFT every 3-6 months assuming no abnormal laboratory results	
• Additional monitoring recommended for patients with impaired kidney function	
○ Blood urea nitrogen and creatinine levels	
○ Check CBC 5 to 7 days after a test-dose	

Medications that may increase the risk of methotrexate toxicity

Nonsteroidal anti-inflammatory drugs	Antibiotics	Others	
Salicylates	Trimethoprim/sulfamethoxazole†	Barbiturates	50
Naproxen	Sulfonamides	Colchicine	
Ibuprofen	Penicillin	Dipyridamole	
Indomethacin	Minocycline	Ethanol	
Phenylbutazone	Ciprofloxacin	Phenytoin	
		Sulfonylureas	
		Furosemide	
		Thiazide diuretics	

CBC, Complete blood count; *LFT*, liver function test; *PPD*, purified protein derivative; *TB*, tuberculosis.
*Supplemental information is expert consensus and not part of evidence-based recommendations.
†Greater potential for methotrexate toxicity.

However, patients on methotrexate should be still monitored for rare, serious lung reactions.

The risk of hematologic and hepatic adverse effects is determined by patient characteristics and risk factors (Table II[50,51] and Figs 1 and 2). In addition, drug-drug interactions, especially involving sulfonamides, can significantly increase the likelihood of methotrexate toxicity. Thus, an

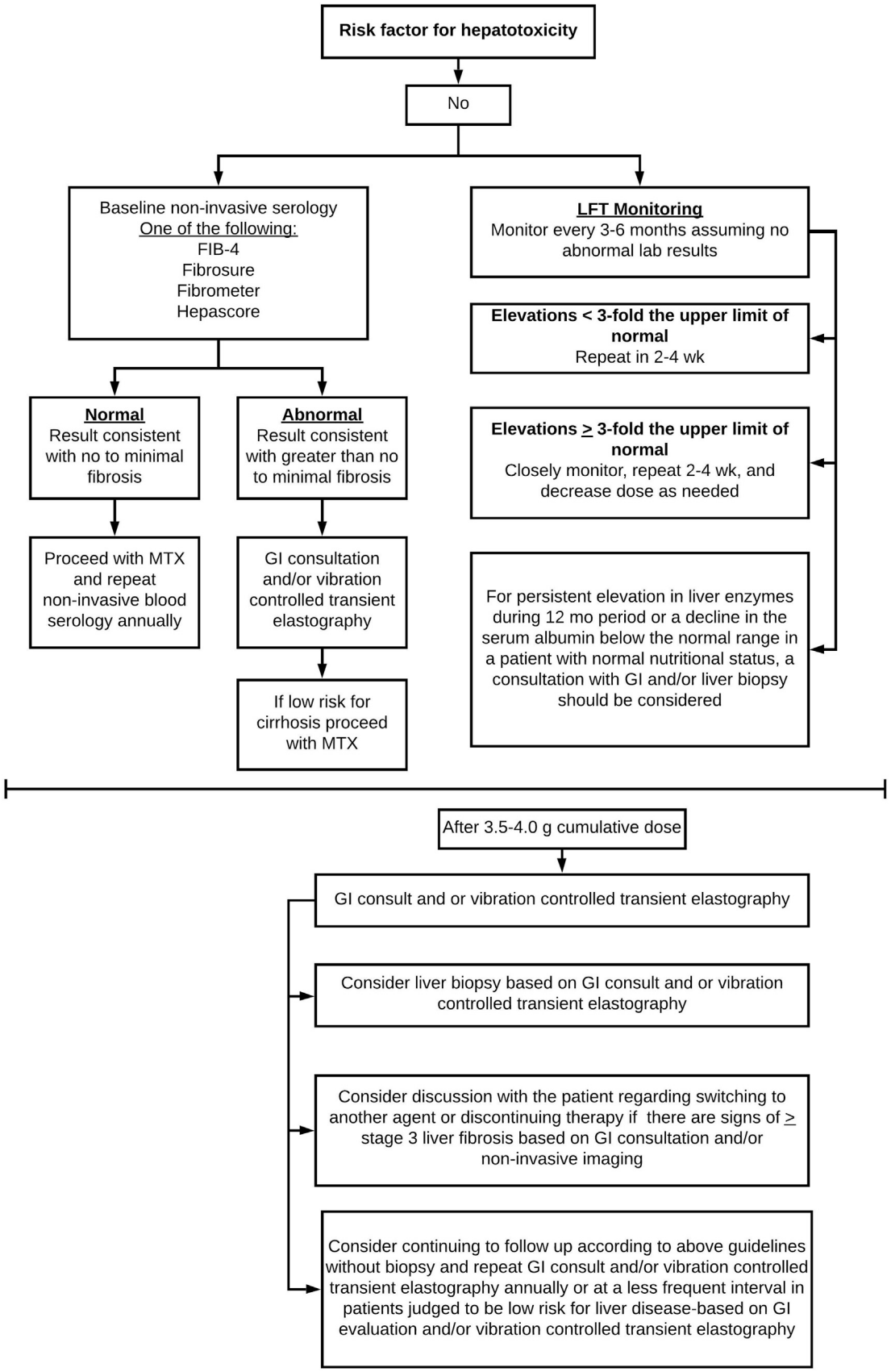

Fig 1. Monitoring for hepatotoxicity in patients on methotrexate without risk factors for hepatotoxicity (baseline liver biopsy not recommended). The following is a link to a Fibrosis-4 (FIB-4) Index for Liver Fibrosis online calculator (https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis). *GI*, Gastrointestinal; *LFT*, liver function test; *MTX*, methotrexate.

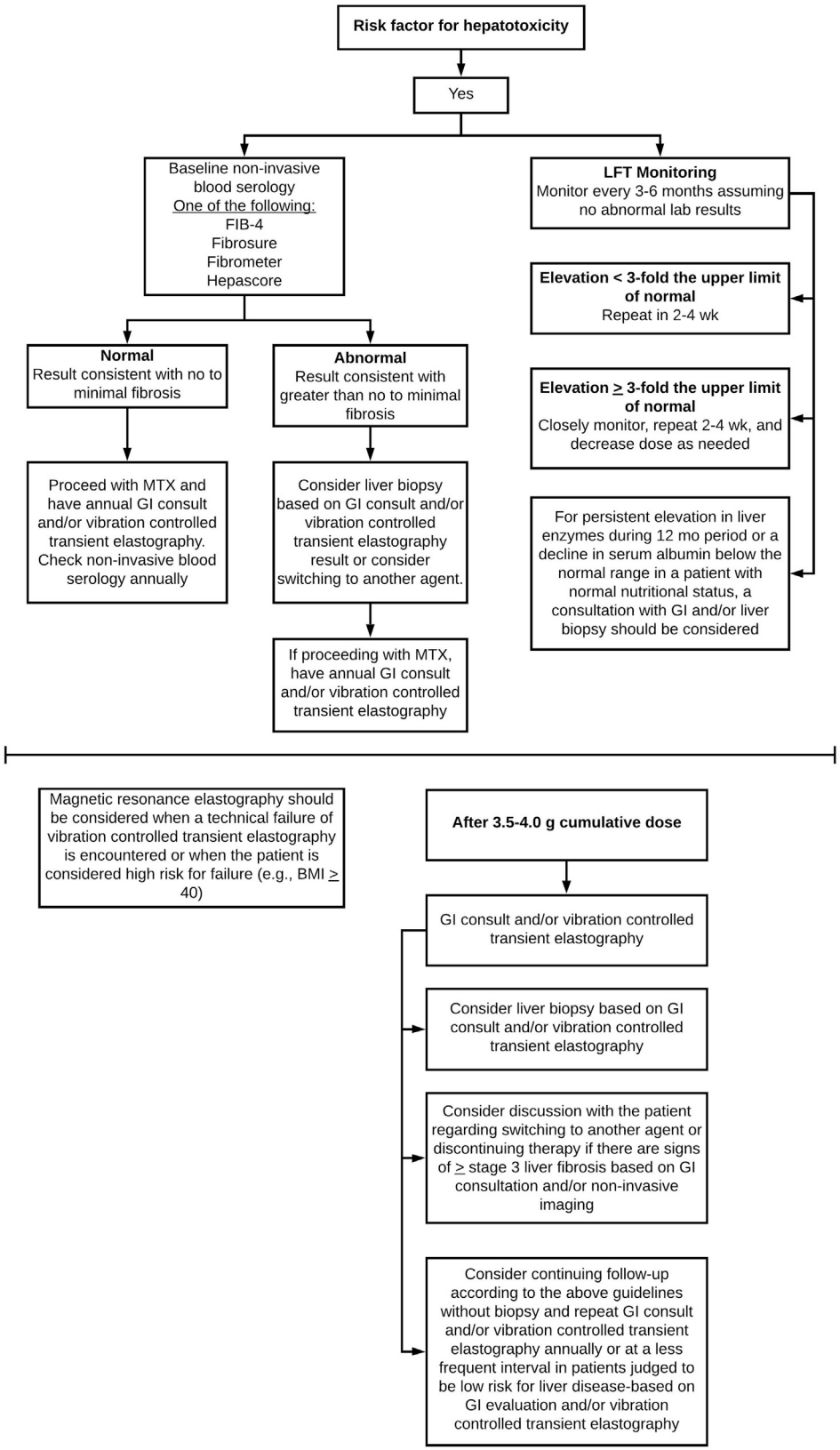

Fig 2. Monitoring for hepatotoxicity in patients on methotrexate with risk factors for hepatotoxicity (baseline liver biopsy not recommended). The following is a link to a Fibrosis-4 (FIB-4) Index for Liver Fibrosis online calculator (https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis). *BMI*, Body mass index; *GI*, gastrointestinal; *LFT*, liver function test; *MTX*, methotrexate.

ongoing review of patient medications is important to identify potential drug interactions that may increase methotrexate toxicity (Table II).

Hematologic toxicity is more likely seen in patients with renal insufficiency, advanced age, methotrexate dosing errors, drug interactions, hypoalbuminemia, and greater than moderate alcohol intake.* Most literature concerning myelosuppression by methotrexate reports studies that were conducted in the rheumatoid arthritis population. Whether this information can be extrapolated to psoriasis is uncertain. Methotrexate-induced myelosuppression is a rare adverse effect in psoriasis as long as there are no other risk factors and there is appropriate monitoring.[40,52,53]

A test dose should be considered in patients with risk factors for developing complications, such as decreased kidney function. If there is no evidence of signs and symptoms of myelosuppression or hepatotoxicity, then the weekly dose can be increased as needed. Pancytopenia can result after even a single dose of methotrexate and can occur at any time during treatment, typically in patients with at least 1 risk factor (see Table II). Close laboratory monitoring is recommended after each methotrexate dose increase, because pancytopenia can occur as late as 6 weeks.[54] Regular laboratory monitoring (CBC and liver function tests) should be performed every 3 to 6 months, assuming no abnormalities in laboratory test results. Periodic renal monitoring should be considered in patients with poor renal function.

Hepatotoxicity is an important adverse event of methotrexate therapy and is more common in psoriasis than in rheumatoid arthritis.[48] Patients with obesity, diabetes, and hyperlipidemia are at increased risk for nonalcoholic fatty liver disease and thus are more likely to experience methotrexate-induced hepatotoxicity. Nonalcoholic steatohepatitis is also a common comorbidity of psoriasis, which can be aggravated by methotrexate treatment.[55,56] Other risk factors for methotrexate-induced hepatotoxicity include greater than moderate alcohol use,* persistent abnormal liver function test results, chronic liver disease, such as hepatitis B and C, prior exposure to other hepatotoxic drugs or chemicals, and family history of inheritable liver disease (eg, Wilson disease, hemochromatosis, and α-1 antitrypsin deficiency).[40]

*Moderate alcohol use: >1 alcoholic drink for women per day (or binge drinking of >7 drink equivalents per week) and >2 alcoholic drinks per day for men (or binge drinking of 14 drink equivalents per week) is considered harmful. Drink equivalent is 1 shot liquor = 12 oz beer = 5 to 6 oz wine.

High cumulative doses of methotrexate may be associated with an increased risk of liver damage. Cumulative methotrexate doses of 1 to 2 grams were less associated with clinically significant hepatotoxicity, but inflammation and fibrosis were seen with cumulative doses of 3 to 4 grams.[57] Although prior AAD guidelines recommended consideration of liver biopsy after 3.5 to 4 cumulative grams of methotrexate, reliable noninvasive options to evaluate the severity of liver disease are now available, including serologic tests and liver stiffness assessment by transient elastography. Serologic tests include the Fibrosis-4 (FIB-4), an algorithm based on liver enzymes, platelet count and age (available online), and other patented tests such as FibroTest/FibroSure (BioPredictive, Paris, France), FibroMeter (Echosens, Waltham, MA), and Hepascore (Quest Diagnostics, Wilmington, DE). FibroScan (Echosens, Waltham, MA) is a vibration-controlled transient elastography and the most used to assess liver stiffness. A combination of FibroTest and FibroScan or other elastography with additional measurement of type III serum procollagen has been proposed as the ideal method for monitoring hepatotoxicity with methotrexate use. However, type III procollagen is not widely available in the United States, and these tests have not been proven to eliminate the risk of serious liver complications due to chronic methotrexate use.[58] Magnetic resonance elastography is a more accurate technique that should be considered if there is a technical failure with vibration-controlled transient elastography or in patients with a particularly high risk of such failure (ie, body mass index $\geq$40 kg/m^2).

The algorithm for methotrexate hepatotoxicity screening differs depending on whether patients do not (Fig 1) or do have risk factors (Fig 2). A noninvasive baseline liver fibrosis assessment is recommended before starting treatment with methotrexate. Baseline liver biopsy is not recommended, regardless of the presence of risk factors. Abnormal laboratory results or risk factors for hepatic fibrosis should prompt consideration of a GI or hepatology specialist referral or imaging with vibration-controlled transient elastography, or both. Methotrexate can be continued only if risk of cirrhosis is low. Annual GI/hepatology referral or vibration-controlled transient elastography, or both, should be performed if methotrexate is continued despite abnormal baseline liver fibrosis laboratory results. Because liver fibrosis is a process that typically takes years to develop, screening more frequently than annually is not generally necessary.

Table III. Strength of recommendation for methotrexate in psoriasis therapy

Recommendation No.	Recommendation	Strength of recommendation
1.1	Methotrexate is recommended for the treatment of moderate to severe psoriasis in adults.	A
1.2	Methotrexate is less effective than adalimumab and infliximab for cutaneous psoriasis.	A
1.3	Methotrexate is efficacious for treatment of psoriatic arthritis (peripheral arthritis, but not for axial involvement); in psoriatic arthritis, the efficacy of methotrexate is lower than TNF-inhibitors.	B
1.4	Recommended methotrexate dosage typically ranges from 7.5 to 25 mg weekly. The dose can be given as a single dose or in 3 doses over 24 hours.	B
1.5	Methotrexate can be administered orally or subcutaneously.	A
1.6	A test dose should be considered, especially in patients with impaired kidney function.	B
1.7	Administration of folic acid or folinic acid is recommended to reduce the incidence of GI and hepatic adverse effects. Large folic acid and folinic acid doses may reduce the efficacy of methotrexate.	A
1.8	Combination therapy with methotrexate and NB-UVB phototherapy can be considered for adult patients with generalized plaque psoriasis to enhance efficacy and lower cumulative doses of both treatments.	B

GI, Gastrointestinal; *TNF*, tumor necrosis factor; *NB-UVB*, narrowband ultraviolet B.

Liver function test monitoring is recommended every 3 to 6 months, assuming there are no laboratory abnormalities in the results. Abnormal elevations should prompt a repeat laboratory check in 2 to 4 weeks. For persistent elevations, a GI referral is recommended. For patients with risk factors for hepatotoxicity, it may be reasonable to consider an alternative therapy to methotrexate. If methotrexate is chosen, recommended hepatotoxicity monitoring is similar to that in low-risk individuals, except noninvasive hepatic specific serology should be performed at baseline and annually thereafter, irrespective of total cumulative dose.

Details about less common adverse effects of methotrexate are not well defined.[54] Hair loss has been seen rarely in patients using methotrexate.[59] However, its mechanism of action is unknown. Rare cases of photosensitivity have been reported in patients treated with methotrexate.[60]

Pregnancy and lactation

Methotrexate use is contraindicated during pregnancy. It is essential for women of child-bearing age to be on contraception while taking methotrexate. Fetal abnormalities have been reported after exposure to methotrexate at all gestational ages, but the critical period for its teratogenic effects appears to be within the first 6 to 8 weeks of pregnancy. If a female patient wishes to become pregnant after methotrexate therapy, she should wait at least 3 months after discontinuation to ensure that methotrexate is fully cleared from her liver and other tissues.[54]

Methotrexate has been detected in human milk. There is potential risk for serious adverse reactions in breast-fed infants. Methotrexate is therefore contraindicated in nursing mothers.

Male fertility. Although methotrexate is not mutagenic, findings are conflicting about whether it affects spermatogenesis.[61] Some studies have demonstrated reversible oligospermia in men taking methotrexate, whereas others have found no changes in sperm count.[62-64] Data are lacking regarding the teratogenicity of methotrexate when used by the father. Given the mixed data and level of uncertainty, it is reasonable for men to wait 3 months after discontinuing the medication before attempting to father a child, because the average cycle of spermatogenesis lasts 74 days, and the presumed effects of methotrexate on the sperm should theoretically be cleared by that time.

Contraindications

Given the risk of potential serious hematologic and hepatic adverse effects, methotrexate is contraindicated in patients with cirrhosis, significant thrombocytopenia, leukopenia or anemia, in pregnancy, and while nursing. Relative contraindications (Table II) include concomitant use of sulfa drugs and acitretin, although this combination may be used if necessary, especially in palmar-plantar psoriasis, as long as there is appropriate hepatic monitoring. Recommendations for the use of methotrexate are outlined in Table III. Practitioners should carefully consider who should receive

Table IV. Level of evidence of methotrexate therapy in psoriasis

Recommendation	Recommendation No.	Level of evidence	Studies
• Methotrexate use in psoriasis patients	1.1	I-III	19,27,28,33,35,37-39,65-69
• Methotrexate less effective than ADA or IFX	1.2	I-II	27,28,33,68,69
• Methotrexate treatment for psoriatic arthritis	1.3	I	31,32
• Methotrexate weekly dosage	1.4-1.7	I, III	15,16,18,20,22,23
• Methotrexate taken orally or subcutaneously			and expert
• Methotrexate test dose			consensus (1.7)
• Folic acid and folinic acid use with methotrexate treatment			
Combination therapy	1.8	I	37-39
• Methotrexate and NB-UVB			

ADA, Adalimumab; *IFX,* infliximab; *NB-UVB,* narrowband ultraviolet B.

methotrexate, because it requires regular laboratory monitoring and lifestyle modifications, such as reduction in alcohol consumption and avoidance of pregnancy. Patients must be reliable and willing to adhere to instruction to ensure safety. Levels of evidence of methotrexate therapy in psoriasis are outlined in Table IV,[‡] and supporting statements for methotrexate associated hepatotoxicity are available in Table V.[58,70-85]

APREMILAST

Apremilast was approved by the FDA in 2014 and is the first oral medication for psoriasis in decades. It inhibits phosphodiesterase 4, resulting in an increased level of intracellular cyclic adenosine monophosphate, with subsequent downregulation of inflammatory responses involving T helper 1, T helper 17, and type 1 interferon pathways.[86] The additional ability to modulate the levels of anti-inflammatory cytokines, such as IL-10, further enables apremilast to improve the inflammatory profile underlying psoriasis.

Dosing

The maintenance dosing for apremilast is 30 mg twice daily by mouth, with an initial dose of 10 mg daily that is titrated up by 10 mg per day over the first 5 days to minimize the risk of GI adverse effects. For patients with severe renal impairment (creatinine clearance <30 mL/min), the dose of apremilast should be reduced to 30 mg once daily. (Refer to Table VI[87] for dosing schedule.)

Efficacy

The Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) 1 trial evaluated the efficacy of apremilast in psoriasis. The trial randomized 844 patients to receive apremilast 30 mg twice daily (n = 562) or placebo (n = 282).[86] At week 16, the placebo group was switched to receive apremilast until week 52. At week 32, 154 patients from the apremilast group who achieved PASI 75 were rerandomized to continue apremilast or switch to placebo until week 52. The PASI 75 rate at week 16 was higher in the apremilast group compared with the placebo group (33.1% vs 5.3%, $P < .001$). Of the 77 patients who were rerandomized at 32 weeks to receive apremilast, 61.0% maintained PASI 75 at week 52. Of the 77 patients who were rerandomized to receive placebo at 32 weeks, 83.11% lost PASI 75 response and reinitiated apremilast, and only 11.7% achieved PASI 75 by week 52. Between week 0 and 16, there were reports of 1 or more adverse events in 69.3% of patients treated with apremilast compared with 55.7% of those in the placebo group. Apremilast is effective for psoriasis, especially for scalp and palmar-plantar involvement, with a promising safety profile.

Apremilast is also effective in psoriatic arthritis. A large randomized controlled trial (n = 504) evaluated ACR20 scores and found that dosages of 20 mg twice a day and 30 mg twice a day were significantly more effective than placebo at 16 weeks (30.4% and 38.1% compared with 19.0%, respectively), with even greater proportions of patients with ACR20 response after 52 weeks of continuous therapy (63.0% of 119 patients on 20 mg twice a day and 54.6% of 130 patients on 30 mg twice a day).[8,88] There are no data to date on the impact of apremilast in the prevention of radiologic damage in psoriatic arthritis.

High-quality data supporting the use of apremilast in combination with other systemic or phototherapy treatments are lacking, but multiple case reports and small case series have found benefit of apremilast when used in conjunction with other treatments, including biologic agents such as adalimumab.[89-91]

[‡]References[15,16,18-20,22,23,27,28,31-33,35,37-39,65-69].

Table V. Supporting statements for methotrexate associated hepatotoxicity*

Statement No.	Statement	References
1	Patients with psoriasis are at higher risk of developing fatty liver disease, fibrosis, and cirrhosis from methotrexate than patients with other diseases commonly treated with methotrexate such as rheumatoid arthritis.	70-72
2	The frequency of serious liver complications associated with methotrexate is lower than previously reported. However, the risk of serious liver complications related to methotrexate treatment of psoriasis is difficult to quantify accurately.	56
3	Liver biopsies are expensive, invasive, and associated with risk of serious complications such as internal bleeding. Furthermore, inter-rater reliability is a limitation for liver biopsy.	73-76
4	Noninvasive blood tests have been developed to predict fibrosis in patients with nonalcoholic steatohepatitis and viral hepatitis with a reasonable negative predictive value for cirrhosis (ie, a normal test result accurately predicts low risk of cirrhosis). However, the negative predictive value will depend on the pretest probability of cirrhosis. Testing (such as imaging techniques) for most patients should be considered to lower the probability of fibrosis further. The positive predictive value is less reliable, and thus, a positive test does not preclude use of methotrexate if follow-up testing with imaging (vibration-controlled transient elastography) or liver biopsy are reassuring.	77
5	There are limited data regarding the test characteristics of noninvasive blood tests in patients with psoriasis treated with methotrexate compared with liver biopsy. Patients can be monitored with noninvasive blood tests while minimizing use of liver biopsies.	78-80
6	Imaging with vibration-controlled transient elastography is a direct measure of liver fibrosis. Its use has been validated in nonalcoholic steatohepatitis and viral hepatitis compared with liver biopsy. Its limitations include operator experience, obesity, hepatic inflammation, cholestasis, congestion (right-sided heart failure), and recent food intake (should be done fasting for at least 3 hours). Vibration-controlled transient elastography has been used to monitor fibrosis in psoriasis patients treated with methotrexate and is useful in lowering the need for liver biopsy.	56,81-83
7	Elastography can also be performed using magnetic resonance imaging techniques. Compared with vibration-controlled transient elastography, magnetic resonance elastography (MRE) is less studied, with unclear generalizability between centers/radiologists. Both methods showed equal benefit in excluding advanced fibrosis/cirrhosis; however, MRE appears to be more accurate overall and is technically successful in patients with severe obesity. Given its high cost, it is an option for patients who are not candidates for vibration-controlled transient elastography. MRE has been studied in the evaluation of methotrexate-induced liver disease in a single-center study.	84,85

*Supplemental information is expert consensus and not part of evidence-based recommendations.

Toxicity

In the ESTEEM 1 trial, the most common adverse effects were diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, tension headache, and headache.[86] In those experiencing GI adverse effects, 70% to 80% occurred within the first 2 weeks, 75% to 80% were mild in severity, and 60% to 65% resolved within the first month. Depression was reported in approximately 1% of patients. Appropriate discussion and patient counseling are thus recommended before apremilast therapy initiation to prevent worsening of pre-existing depression or suicidality. Decreases of 5% to 10% in body weight occurred in 12% of patients treated with apremilast compared with 5% treated with placebo.[87,92]

Contraindications

The safety profile of apremilast is a positive feature. It can be used in a wide variety of patients, including those with complex medical issues in which other systemic agents are contraindicated. Although severe renal impairment is not a contraindication, it does warrant a dose decrease to 30 mg daily instead of twice daily. For any individual experiencing weight loss (>5% from baseline) due to apremilast, consideration should be given to its discontinuation. Patients prone to dehydration (eg, the elderly) should be aware that GI adverse effects may be more severe and could result in hospitalization. There have been no significant studies evaluating the effect of apremilast on human pregnancies.[87]

Table VI. Supporting statements for apremilast in psoriasis

Statement No.	Supporting statement	Reference
1	Patients should initially start at a lower dose (10 mg), which is titrated up over 5 days to reduce the risk of gastrointestinal adverse effects. Thereafter, apremilast is dosed 30 mg by mouth twice daily. Dosage titration schedule: Day 1—10 mg (AM) Day 2—10 mg (AM & PM) Day 3—10 mg (AM); 20 mg (PM) Day 4—20 mg (AM & PM) Day 5—20 mg (AM); 30 mg (PM) Day 6—30 mg (AM & PM)	87
2	The most common adverse effects of apremilast are diarrhea, nausea, upper respiratory tract infections, and headache (those 65 and older are prone to experience dehydration and its complications).	87
3	Apremilast may be associated with the emergence or worsening of depression. Discuss the risk of depression with patients in advance of therapy.	87
4	Apremilast is metabolized in the liver by cytochrome P450. Use with strong inducers of cytochrome P450 (eg, rifampin, phenobarbital, carbamazepine, phenytoin) may result in decreased efficacy and is not recommended.	87
5	Apremilast should be reduced to 30 mg once daily in patients with severe renal impairment (creatine clearance <30 mL/min).	87
6	A small percentage of patients may lose weight on apremilast. Weight should be monitored regularly, and if weight loss occurs (>5% from baseline), discontinuation of apremilast should be considered.	87
7	Routine laboratory screening and monitoring can be considered on an individual basis.*	
8	There is currently no strong evidence to support the combined use of apremilast with other systemic or phototherapy treatments for psoriasis.*	
9	Pregnancy Should only be used in pregnancy if benefit justifies potential risk to fetus.	87

*Supplemental information is expert consensus and not part of evidence-based recommendations.

Apremilast is metabolized in the liver by cytochrome P450 and is thus susceptible to the forms of drug interactions that are typical of medications metabolized by this route. Use of apremilast in conjunction with strong inducers of cytochrome P450 (eg, rifampin, phenobarbital, carbamazepine, and phenytoin) is not recommended, because this combination may result in decreased efficacy. Dangerous drug interactions have not yet been reported, but medication lists should be reviewed before initiating therapy and periodically thereafter.

Overall, apremilast as monotherapy is beneficial to treat psoriasis and psoriatic arthritis. These benefits include oral administration and the lack of a requirement for laboratory monitoring. For patients who would prefer to avoid frequent injections as well as laboratory monitoring and are willing to accept a slower onset of skin clearance and lower likelihood of clearing, apremilast is an appropriate choice. Table VII provides the strength of recommendation and Table VIII[86,93-97] provides the level of evidence for apremilast in psoriasis therapy.

CYCLOSPORINE

Cyclosporine received FDA approval for psoriasis in 1997. It is a potent immunosuppressant that functions by binding cyclophilin, which then inhibits calcineurin and blocks proinflammatory signaling.[98-100] Several inflammatory cytokines, including interferon-γ and IL-2, are consequently reduced, leading to decreased activation of T cells.[99,100] Because of the long list of potential serious adverse effects, cyclosporine is not used as a long-term treatment for psoriasis. Nevertheless, it does have an important role as a rapid-acting medication for severe, recalcitrant disease, acute flares, and erythroderma. It can also be used as a bridge therapy in the transition to a safer long-term treatment.

Dosage

There are 2 main approaches in the use of cyclosporine for the treatment of psoriasis. Some clinicians prefer to start at an intermediate dose of 2.5 to 3.0 mg/kg/day given twice daily for approximately 4 weeks before gradually increasing

Table VII. Strength of recommendation for the apremilast in psoriasis therapy

Recommendation No.	Recommendation	Strength of recommendation
2.1	Apremilast is recommended for the treatment of moderate to severe psoriasis in adults.	A

Table VIII. Level of evidence for apremilast in psoriasis therapy

Recommendation	Recommendation No.	Level of evidence	Studies
Apremilast and psoriasis	2.1	I	86,93-97

the dose by 0.5 mg/kg/day until adequate control is obtained. This method may be better for moderate disease and identification of adverse effects as the dose is increased. Alternatively, patients with severe disease who require rapid improvement can be started at a dose of up to 5 mg/kg/day and subsequently tapered once improvement has been achieved.[50,101-104] Another consideration is the type of preparation. In addition to the unmodified form, cyclosporine is available as a modified microemulsion that is more steadily absorbed and is recommended in low (2-3 mg/kg/d) or ultralow (1-2 mg/kg/d) doses.[105]

Obese patients are more effectively treated when dosed according to their actual body weight. In fact, weight loss in obese (body mass index ≥30 kg/m^2) patients with psoriasis treated with cyclosporine can increase treatment efficacy, suggesting a pharmacokinetic benefit of matching dose to actual body weight.[106] A study randomized 61 obese patients to receive treatment with cyclosporine in combination with a low-calorie diet or without dietary intervention.[106] At 24 weeks, the intervention group lost 7.0% ± 3.5% of body weight and two-thirds achieved PASI 75, whereas the control group lost only 0.2% ± 0.9% of body weight and only 29% achieved PASI 75.

Although evidence for dosing by weight is available, one study sought to determine whether a fixed dose of cyclosporine regardless of weight could be used.[105] The study compared 2 different fixed dosing schedules of the cyclosporine microemulsion—100 mg once daily or 50 mg twice daily.[105] There were no statistically significant differences in the percentage of patients achieving PASI 75 and PASI 90 between the 2 groups.[105] Improvement rates were 69.4% ± 4.8% in the once-daily group and 73.4% ± 4.3% in the twice-daily group.[105]

Efficacy

The demonstration that cyclosporine was an effective treatment was instrumental in establishing the role of aberrant T-cell activation in the pathogenesis of psoriasis, rather than a sole consequence of abnormal keratinocyte proliferation. Cyclosporine is dosed at 2.5 to 5 mg/kg/d for 12 to 16 weeks and produces swift and dramatic improvement in up to 80% to 90% of patients with psoriasis.[98,101,107-110] At a dose of 3 mg/kg/d, 50% to 70% of patients with psoriasis achieved PASI 75 and 30% to 50% achieved PASI 90.[111] In a large systematic review that included 10 studies (randomized controlled trials, prospective studies, and case series), a cyclosporine dose of 5 mg/kg/d produced PASI 75 rates between 50% and 97%, while cyclosporine 2.5 mg/kg/d achieved PASI 75 in 28% to 85% of patients.[112]

Cyclosporine-treated patients frequently relapse after discontinuation (ie, ~ 3 months), unless other treatments are substituted. In 365 patients who achieved ≥90% clearance of plaque psoriasis after intermittent short courses of cyclosporine, 2.5 mg/kg microemulsion formulation daily, abrupt cyclosporine termination led to slightly quicker relapse (median time to relapse of 109 days) compared with gradual tapering of 1 mg/kg/d weekly (median time to relapse of 113 days).[109] Short courses of cyclosporine were well tolerated, although 8% discontinued treatment due to adverse effects, primarily elevations in blood pressure and creatinine.

Lower doses of cyclosporine can be beneficial in maintaining skin clearance in patients treated initially with higher-dose cyclosporine induction therapy for psoriasis.[102,113] One trial with 217 patients used cyclosporine doses of 1.25, 2.5, or 5.0 mg/kg/d over an extended course of 6 to 30 months, and 12.5% of patients were successfully maintained at the 1.25 mg/kg/d dose without any apparent worsening of the disease.[114] Adverse effects were less common during the maintenance phase. After eventual discontinuation, 55.5% experienced worsening of their psoriasis, sufficient to require further therapy. In another study, 181 patients who achieved ≥70% BSA improvement after cyclosporine induction therapy at 5 mg/kg/d were

randomized to receive placebo or cyclosporine at 1.5 or 3.0 mg/kg/d.[115] While the placebo and 1.5 mg/kg/day groups showed a median time to relapse of 6 weeks, median relapse time was not observed for the 3.0 mg/kg/d group during the 24-week trial because <50% of patients relapsed. Of those who received the 3.0 mg/kg/d dosage, 58% maintained improvement through the entire 24-week trial. Laboratory abnormalities observed during the induction phase tended to partially or completely normalize throughout the maintenance phase of treatment, demonstrating the increased tolerability at lower doses.

The simultaneous administration of cyclosporine and NB-UVB phototherapy is contraindicated due to the increase risk of photocarcinogenesis,[116-118] but this combination is efficacious when used sequentially.[119] A low dose of cyclosporine at 3 mg/kg/d for 4 weeks, followed by a rapid taper and initiation of NB-UVB phototherapy, showed faster resolution of pruritus, reduced number of NB-UVB treatments, and reduced cumulative amount of UVB needed to obtain equivalent PASI compared with NB-UVB monotherapy.[119]

Toxicity

Nephrotoxicity and hypertension are the most common adverse effects of cyclosporine. Even with close monitoring, patients will often experience adverse effects on renal function, with reversible nephrotoxicity developing in 19% to 24% during short-term treatment.[109,110] If treatment is continued for more than 2 years, the risk of fibrosis and irreversible kidney damage increases substantially. In one study, 71% of patients treated with cyclosporine for an average of 4.5 years were found to have serum creatinine level of >30% above baseline.[120] The serum creatinine levels in most of these patients did not return to normal after the cyclosporine dose was decreased.[120] In a larger systematic review, ≥50% of patients demonstrated an increase in serum creatinine over 30% of baseline when treated with cyclosporine for longer than 2 years.[109,110,112,121] Even though the data suggest that the duration of treatment is the major factor determining renal sequelae, continuous treatment poses a higher risk than does as-needed intermittent treatment with repeated 12-week courses.[122-125]

Hypertension is most likely to develop in elderly patients taking cyclosporine but is typically reversible after the medication is discontinued.[126] Because elevations in blood pressure often precede increases in creatinine, it is important to monitor blood pressure regularly to avoid not only the side effects of chronic hypertension, but also kidney damage.[127] If hypertension is observed on 2 separate occasions, then the dose of cyclosporine should be decreased using the same approach recommended above. If the blood pressure does not normalize (<140/90 mm Hg) after decreasing the dose multiple times, then the medication should be discontinued. Alternatively, cyclosporine can be continued if elevated blood pressure can be adequately treated with antihypertensive medication. Because the hypertensive effects of cyclosporine are thought to result from renal arteriole vasoconstriction, calcium channel blockers are the preferred choice due to their ability to relax vascular smooth muscle.

Some of the more common but less severe adverse effects include headache, paresthesia, and musculoskeletal pain, which occur in approximately 15%, 7%, and 5% of patients, respectively. Approximately 6% of patients experience hypertrichosis, with the most noticeable change typically arising in women with dark hair.[128] Gingival hyperplasia is more commonly seen at higher doses as used for transplant patients but has been reported in patients with psoriasis.[129] Neurologic sequelae include fatigue, tremor, and asthenia. Seizures have also been reported, particularly in patients with a history of seizures.[130] Cyclosporine can lower an individual's seizure threshold.[131] A few cases of pseudotumor cerebri have been reported in young patients receiving cyclosporine; however, these are not psoriasis cases.[132-135] (The risk of pseudotumor cerebri development in patients using cyclosporine is based on extrapolation.) GI adverse effects tend to be mild and short-lived, including abdominal pain, diarrhea, nausea, and vomiting.[128] Approximately 5% of patients will experience respiratory effects such as dyspnea, cough, and rhinitis.[131] Hyperuricemia and hypomagnesemia can also occur.

Pregnancy

The data regarding the use of cyclosporine in pregnancy are derived primarily from studies in organ transplant recipients. In contrast to psoriasis patients, cyclosporine in organ transplant recipients is usually prescribed in conjunction with other medications, such as azathioprine or mycophenolate mofetil, making it difficult to attribute the observed effects specifically to cyclosporine. The complex medical history of these patients, including often numerous comorbidities, further obfuscates the conclusions about pregnancy risk of cyclosporine. On the basis of animal studies, there is no impairment of fertility from cyclosporine. In a study of 67

Table IX. Supporting statements for cyclosporine in psoriasis*

Statement No.	Supporting statement	Studies
1.	Single daily dose of cyclosporine may yield similar treatment response to twice-daily dose when the microemulsion formulation is used.	105
2.	Patients who have achieved a clinical response to cyclosporine may have some benefit by using cyclosporine on 2 consecutive days per week (5 mg/kg/d) compared with placebo over 24 weeks.	149
3.	Weight loss may result in improvement in cyclosporine response in obese patients whose body mass index is $\geq$30 kg/m^2 but $<$45 kg/m^2.	106
4.	Dosage • 2.5-5.0 mg/kg/d in 2 divided doses per day • Dose adjustments downward (by 0.25-1.0 mg/kg) when clearance of psoriasis is achieved or when hypertension or decreased renal function are observed Duration of dosing • Optimally used as interventional therapy; may be repeated at intervals after a rest period	
5.	Contraindications • Prior PUVA treatment (especially $>$200 treatments) or radiation therapy • Abnormal renal function • Uncontrolled hypertension • Malignancy • Hypersensitivity to cyclosporine • Live vaccinations should be avoided • Caution with major infections and poorly controlled diabetes	
6.	Baseline monitoring • History and physical examination • BP $\times$2 • BUN and creatinine • Urinalysis • Consider latent tuberculosis test • LFTs, CBC, lipid profile, magnesium, uric acid, and potassium • Pregnancy test if indicated Ongoing monitoring • Monitor BP (early morning resting BP), BUN, creatinine every other week during first 3 months and then monthly monitoring if no persistent abnormalities are identified • Monthly CBC, LFTs, lipid profile, magnesium, uric acid, and potassium • Pregnancy testing if indicated	
7.	Toxicity • Renal impairment ○ Acute ○ Chronic (increasing glomerular fibrosis with increasing duration of treatment and/or with higher dosages) • Hypertension • Malignancies ○ Cutaneous ○ Lymphoproliferative • Headache, tremor, and paresthesia • Hypertrichosis • Gingival hyperplasia • Worsening acne • Nausea, vomiting, and diarrhea • Myalgias • Flu-like symptoms • Lethargy • Hypertriglyceridemia • Hyperkalemia • Hyperbilirubinemia • Increased risk of infections • May increase risk of cancer	

Continued

Table IX. Cont'd

Statement No.	Supporting statement	Studies
8.	Drug interactions • Inducer/inhibitors of cytochrome P450 3A4 • St John's Wort (decreases cyclosporine concentration) • Cyclosporine may reduce clearance of digoxin, colchicine, prednisolone, and statins • Potassium-sparing diuretics (may cause hyperkalemia) • Thiazide diuretics (increased nephrotoxicity) • Killed and/or recombinant vaccines • Grapefruit juice • Nonsteroidal anti-inflammatory drugs	
9.	Pregnancy • Lower birth weight and shorter duration of pregnancy reported in patients with transplantation; appears not to be teratogenic in patients with transplantation. Nursing • Cyclosporine contains ethanol and has been found in human breast milk; therefore, ethanol will be orally absorbed by the nursing infant • A decision should be made whether to discontinue nursing or cyclosporine based on benefit of therapy to the patient. Fertility • On the basis of animal studies, there is no effect on fertility.	

BP, Blood pressure; *BUN*, blood urea nitrogen; *CBC*, complete blood count; *LFTs*, liver function tests; *PUVA*, psoralen plus ultraviolet A.
*Supplemental information is expert consensus and not part of evidence-based recommendations.

pregnancies after renal transplantation and cyclosporine-containing regimens, the preterm labor rate was >40%, with the most frequent complications in the mother being hypertension, anemia, urinary tract infections, and preeclampsia.[136]

In rabbits, in utero exposure to cyclosporine 10 mg/kg/d between days 14 and 18 of gestation produced offspring with reduced nephron counts and associated renal dysfunction at birth, progressive hypertension, and worsening renal insufficiency with age. There is no evidence that maternal cyclosporine use during pregnancy can have any renal sequelae on children.[137] On the basis of the available evidence, treatment with cyclosporine has yielded increased rates of prematurity in human studies. Additionally, animal studies have shown decreased fetal weight and increased prenatal and postnatal mortality.

Cyclosporine contains ethanol and has been found in human breast milk; therefore, ethanol will be orally absorbed by the nursing infant. A decision should be made whether to discontinue nursing or cyclosporine based on the benefit of therapy to the patient.

Drug interactions

Cyclosporine is metabolized primarily by the cytochrome P450 3A4 subtype (CYP3A4). Therefore, cyclosporine use can increase or decrease the levels of other medications that are metabolized by CYP3A4, such as statins, calcium channel blockers, and warfarin. In a case of concomitant cyclosporine and statin therapy, severe rhabdomyolysis was reported.[138] Increased nephrotoxicity can be seen when other nephrotoxic medications, such as aminoglycosides and nonsteroidal anti-inflammatory medications, are used in conjunction with cyclosporine. Potassium-sparing diuretics can potentiate potassium elevation with concomitant cyclosporine treatment, possibly leading to hyperkalemia.

Although cyclosporine can affect the levels of numerous other medications, other drugs can interfere with cyclosporine levels. Excessive alcohol consumption can increase levels of cyclosporine, whereas mild-to-moderate intake* does not appear to have a major effect.[139] Table IX[105,106,140] highlights a number of clinically relevant drug interactions between cyclosporine and other medications.

Owing to the degree of immunosuppression associated with cyclosporine therapy, vaccinations may be less beneficial, as has been seen in transplant patients on cyclosporine who experienced variable efficacy with the influenza vaccine.[141-143] Even so, vaccinations are highly recommended in these patients, because their immunosuppression places

*Moderate alcohol use: >1 alcoholic drink for women per day (or binge drinking of >7 drink equivalents per week) and >2 alcoholic drinks per day for men (or binge drinking of 14 drink equivalents per week) is considered harmful. Drink equivalent is 1 shot liquor = 12 oz beer = 5 to 6 oz wine.

Table X. Strength of recommendation for cyclosporine therapy in psoriasis

Recommendation No.	Recommendation	Strength of recommendation
3.1	Cyclosporine is recommended for patients with severe, recalcitrant psoriasis.	A
3.2	Cyclosporine can be recommended for the treatment of erythrodermic, generalized pustular, and/or palmoplantar psoriasis.	B
3.3	Cyclosporine can be recommended as short-term interventional therapy in patients who flare up while on a pre-existing systemic therapy.	C

them at risk for severe infections. Live attenuated vaccinations, however, should not be administered to these patients.

Baseline and ongoing monitoring

Patients should be screened with a thorough history and physical examination, including establishment of baseline blood pressure, hepatitis, and tuberculosis status, and family history of renal disease. Because of its potential interactions with prescription and nonprescription medications as well as supplements, it is important to take a thorough medication history. Factors that increase the risk of nephrotoxicity, such as obesity, advanced age, diabetes, and use of other nephrotoxic drugs, should be considered.[126,144] Laboratory monitoring at baseline should include urinalysis, serum creatinine, blood urea nitrogen, CBC, potassium, magnesium, uric acid, lipids, bilirubin, and liver enzymes.

Renal function should be monitored regularly to avoid potential permanent kidney damage. Baseline and biweekly blood urea nitrogen and creatinine monitoring are recommended during the first 3 months of treatment and then monthly thereafter.[130] There should be an annual estimation of the glomerular filtration rate for patients who have been treated with cyclosporine for more than 1 year. According to the package insert, a 25% increase in creatinine over baseline, as measured on 2 separate occasions at least 2 weeks apart, should prompt a 25% to 50% reduction in dose, with monitoring of creatinine every other week for 1 month thereafter.[130] If creatinine does not decrease to within 25% of baseline, another dose reduction of 25% to 50% should be performed with biweekly laboratory monitoring for another month. If the creatinine is not within 25% of baseline after this, cyclosporine should be discontinued. An alternative approach is with a 30% increase in creatinine over baseline, a gradual, stepwise decrease in the cyclosporine dose by 1 mg/kg/d until creatinine falls closer to baseline or, if unobtainable, to discontinue it.

The package insert also recommends monthly CBC, potassium, uric acid, lipids, magnesium, serum bilirubin, and liver enzymes checks.[130] Despite these official recommendations, many physicians gauge their patients' response with biweekly early morning blood pressure, creatinine, and blood urea nitrogen checks over the first 6 to 8 weeks and then monthly monitoring if no persistent abnormalities are identified.[104,128,131] Before starting therapy, women should be informed of the risks associated with cyclosporine during pregnancy.

Patients should regularly monitor their blood pressure to avoid chronic hypertension as well as kidney damage.[127] Early morning resting blood pressure is a more sensitive indicator of early nephrotoxicity than elevated creatinine.[145] If hypertension is observed on 2 separate occasions, the dose of cyclosporine should be decreased using the approach recommended for elevated creatinine levels. If blood pressure does not normalize (<140/90 mm Hg) after multiple dose reductions, then the cyclosporine should be discontinued. Alternatively, elevated blood pressure can be adequately treated with antihypertensive medications. Because the hypertensive effects of cyclosporine results from renal arteriole vasoconstriction, calcium channel blockers are the antihypertensive of choice due to their ability to relax vascular smooth muscles. Isradipine does not interact with cyclosporine metabolism. β-Blockers can also be used for blood pressure control. It is best to avoid thiazide diuretics, because they enhance nephrotoxicity. Potassium-sparing diuretics should also not be used, because cyclosporine can induce hyperkalemia.

Regular monitoring of cyclosporine blood levels is not necessary at the doses used for the treatment of psoriasis, but certain conditions may warrant closer attention. For instance, patients taking medications that might interfere with cyclosporine metabolism or those with liver disease may require closer monitoring. Those on doses greater than 3 mg/kg/day for an extended period of time may also require blood levels or consultation with a nephrologist, or both.

Table XI. Level of evidence for cyclosporine in psoriasis therapy

Recommendation	Recommendation No.	Level of evidence	Studies
Cyclosporine for psoriasis treatment	3.1	I-III	33,105,112,146-149
Cyclosporine treatment in different types of psoriasis • Erythrodermic • General pustular • Palmoplantar	3.2	I	112
Cyclosporine for psoriasis flare	3.3	III	Expert consensus

Contraindications

Caution should be taken when considering the use of cyclosporine in elderly or pregnant patients or those with immunodeficiency disorders. Contraindications to cyclosporine therapy include a history of systemic malignancy (excluding nonmelanoma skin cancer), renal insufficiency, hypertension, prior psoralen plus ultraviolet A (PUVA) treatment, uncontrolled infections, and hypersensitivity to cyclosporine. Caution should be taken when prescribing cyclosporine in patients taking other medications that can interact with CYP3A4. Live vaccinations are contraindicated in patients using cyclosporine.

Cyclosporine should be avoided in patients with poor health and in those with risk factors for developing severe adverse effects.[112]

Recommendations for the use of cyclosporine are outlined in Table X, and the level of evidence of these recommendations is reported in Table XI.[33,50,105,112,146-149]

ACITRETIN

The oral retinoid, acitretin, is a vitamin A derivative, and the active metabolite, etretinate, is an oral retinoid that was initially used for psoriasis in the early 1980s. Acitretin was approved for treatment of psoriasis by the FDA in 1997. The mechanism of action of retinoids, such as acitretin, is not entirely understood. It does modulate epidermal differentiation and proliferation and also has anti-inflammatory and immunomodulatory effects. Unlike most systemic psoriasis treatments, acitretin is not immunosuppressive.

Dosage

Acitretin is administered for psoriasis in doses ranging from 10 to 50 mg daily. One study set a maximum dose of 70 mg daily, which was reached after gradual upward titration toward the desired clinical effect.[150] The major element in dosing acitretin is balancing efficacy with the individual patient's tolerability. Acitretin is a relatively slow-acting medication that can take 3 to 6 months for full treatment response.

Efficacy

Acitretin is less beneficial than other common systemic psoriasis medications, although head-to-head comparison studies are lacking. The effects of acitretin are dose-dependent, and a number of different dosing schedules have been used.[151-158] In one study, 23% of patients treated with acitretin 50 mg/d achieved PASI 75 after 8 weeks of therapy, with some patients experiencing complete clearance of skin disease.[159] In another trial, patients treated with acitretin 40 mg daily for 4 weeks and then continued on with an individually adjusted dose for the next 8 weeks, had a mean PASI improvement of 75.8%.[160] A different study started patients on 20 mg daily, followed by 10 mg dose increases every 2 weeks, with a maximum dose of 70 mg. Maintenance therapy with acitretin was beneficial, with 75% of patients achieving PASI 50 after 6 months of treatment and 88% achieving PASI 50 after 12 months.[161]

Because acitretin is not immunosuppressive, it is often used in patients with psoriasis on highly active antiretroviral therapy treatment of HIV.[162] Severe psoriasis variants, such as erythrodermic psoriasis, generalized pustular psoriasis, and palmoplantar psoriasis, have been successfully treated with acitretin or in the past with etretinate. One study reported improvement in 84% of patients with pustular psoriasis after treatment with acitretin.[163] Another study of etretinate found it to be effective in both erythrodermic and pustular psoriasis.[164] The response of pustular psoriasis, both generalized and palmoplantar, to systemic retinoids can be quite rapid and remarkable.[165]

Acitretin is of value in hyperkeratotic (plaque-type) palmoplantar psoriasis, as monotherapy or in combination with other treatment modalities, such as NB-UVB, PUVA, or other systemic/biologic agents.[166,167]

Combination treatment

Combined therapy with acitretin and phototherapy is more efficacious than monotherapy alone. The combination helps to limit long-term adverse effects and decreases the cumulative doses of phototherapy, frequency, and duration of phototherapy.[168] Combination therapy is more convenient and more cost-effective for patients. Broadband UVB (BB-UVB) plus acitretin has been compared with acitretin monotherapy[169-172] and was found to improve treatment safety, because lower doses of acitretin and lower cumulative amounts UVB could be used. In another study, treatment with acitretin 25 mg daily plus phototherapy was as effective as acitretin 35 mg daily monotherapy.[171] The median cumulative BB-UVB dose necessary for 75% improvement was 41% lower in the combination group than with BB-UVB monotherapy.[171] In a study in which combination therapy with acitretin 50 mg daily and BB-UVB was compared with either agent alone, there was a 74% improvement in psoriasis severity score in the combination group compared with 42% with acitretin alone and 35% with BB-UVB alone.[170]

The recommended schedule is to begin with 2 weeks of acitretin monotherapy, followed by UVB phototherapy. Acitretin 25 mg/d can also be added to a failing UVB regimen to augment treatment response. Because oral retinoids can increase susceptibility to UVB-induced erythema, an initial UVB dose decrease of 30% to 50% is recommended for the first week, followed by a gradual increase, as tolerated.

While fewer data exist, NB-UVB has also been used with great efficacy in combination with acitretin in the treatment of psoriasis. In 40 patients who were refractory to monotherapy, when treated with combination therapy, 72.5% experienced more than 75% improvement in psoriasis severity.[173]

As with UVB, the addition of acitretin to PUVA is more effective than either treatment alone.[174-176] Patients experiencing inadequate benefit from PUVA monotherapy may have acitretin added to their regimen while simultaneously reducing the UVA dose. When acitretin is combined with PUVA, fewer photochemotherapy sessions are necessary, and the cumulative UVA dosage required to achieve clinical success is reduced. In addition, acitretin, when combined with PUVA, decreases the incidence of cutaneous squamous cell carcinoma compared with PUVA alone.[177] In contrast, treatment with cyclosporine increases squamous cell carcinoma incidence in patients who have been treated with PUVA. A 2-week period of acitretin therapy is recommended before initiating PUVA.

Safety

The most important safety concern with acitretin therapy is teratogenicity when used in women of childbearing potential. This medication is contraindicated in pregnancy. Multiple malformations are associated with the use of acitretin during pregnancy, particularly if used between weeks 3 and 6 of gestation. These include abnormalities on skeletal and craniofacial bones, the central nervous system, and auditory, ocular, and cardiovascular systems.[178] Patients should also not use acitretin before or during nursing. Although the half-life of acitretin is 49 hours, it may undergo spontaneous transformation into etretinate, which has a half-life of 168 days. Alcohol ingestion promotes conversion of acitretin to etretinate, but the actual amount of alcohol necessary to do so is unknown. Given this uncertainty, unintentional exposure to alcohol-containing items may pose a risk. As such, use of acitretin should be avoided in women of childbearing potential and is absolutely contraindicated in women who plan to become pregnant or who do not use sufficient contraception. Women who wish to become pregnant after discontinuing acitretin should wait at least 3 years after completion of treatment. Acitretin apparently does not have an effect on fertility or teratogenicity when men are taking the drug. This is based on limited data.[179]

The other adverse effects of acitretin are minimized by appropriate dosing, monitoring, and patient selection.[179] Nearly all patients experience mucocutaneous adverse effects, including xerosis, dryness of the eye, nasal/oral mucosa, epistaxis, cheilitis, itching or burning skin, and brittle nails, all of which may range from mild to severe, depending on individual patient characteristics and the dose of acitretin. Hair loss is more common in women, especially in doses that exceed 17.5 mg per day. "Retinoid dermatitis" is a less common adverse effect, which manifests as scaly, erythematous plaques with superficial fissuring. Pyogenic granulomas, particularly in periungual locations, have also been associated with long-term acitretin therapy.[156,180]

Hyperlipidemia is present in 25% to 50% of patients and is the most common laboratory abnormality associated with acitretin use.[181] The risk of acitretin-induced hypertriglyceridemia is higher in patients with obesity, diabetes mellitus, or excessive alcohol intake, conditions that are also commonly seen in the psoriatic population.[182]

Rarely, hypertriglyceridemia can reach levels that will cause pancreatitis, which has been fatal in some patients.[183] For those experiencing sustained

Table XII. Strength of recommendations for acitretin in psoriasis therapy

Recommendation No.	Recommendation	Strength of recommendation
4.1	Acitretin can be recommended as monotherapy for plaque psoriasis.	B
4.2	Acitretin can be recommended for treatment of erythrodermic, pustular, and palmar-plantar psoriasis.	B
4.3	Acitretin can be recommended as combination therapy with PUVA for psoriasis.	B
4.4	Acitretin can be combined with BB-UVB for plaque psoriasis.*	B

BB-UVB, Broadband ultraviolet B; *PUVA*, psoralen plus ultraviolet A.
*From the 2019 American Academy of Dermatology/National Psoriasis Foundation phototherapy psoriasis guideline.[192]

Table XIII. Level of evidence for acitretin therapy in psoriasis

Recommendation	Recommendation No.	Level of evidence	Studies
Acitretin monotherapy for psoriasis	4.1	II	33,150,152,154-157,159,161,162,193
Acitretin in other psoriasis types	4.2	II	154-157,159,161,162
• Erythrodermic			
• Pustular			
Combination therapy			
• Acitretin + PUVA	4.3	I-II	154,155,174-177
• Acitretin + BB-UVB	4.4	I-II	170,171

BB-UVB, Broadband ultraviolet B; *PUVA*, psoralen plus ultraviolet A.

elevated triglycerides, there may also be an increased risk of atherosclerosis.

Elevation in transaminases is another laboratory abnormality and is seen in 13% to 16% of patients.[180] While major increases in liver function test results are uncommon, when they do occur, it could suggest the onset of acitretin-induced toxic hepatitis.[184] This requires prompt discontinuation of the medication.[185]

Other less common adverse effects of acitretin therapy include pseudotumor cerebri-like symptoms, mood changes, decreased night and color vision, and minor myalgia/arthralgia. Diffuse idiopathic hyperostosis is a rarely reported adverse effect of systemic retinoids. It presents with skeletal changes of the spine, including vertebral syndesmophytes, extraspinal bones with bone spurs, arthritis of the vertebral articulations, and degenerative spondylosis.[186] In some cases, hyperostosis may be severe and debilitating.[187] Whether acitretin causes osteoporosis is controversial. The risk appears to be highest in patients receiving long-term, high-dose retinoids.[188,189] Although rare, systematic retinoids may cause premature epiphyseal growth plate closure in young patients.[190]

Drug interactions

Drugs that interfere with the cytochrome P450 pathway, such as cyclosporine, may affect the metabolism of acitretin. Drugs that compete for plasma-binding proteins, such as phenytoin, may also affect plasma concentrations. Simultaneous use of oral retinoids and vitamin A supplementation can increase the risk of hypervitaminosis A and should be avoided. Acitretin might interact with the glucose-lowering effect of glyburide (aka glibenclamide) and should be used with caution or avoided in patients taking this drug.

Initiation and monitoring

Patients should have a full history and physical examination before beginning acitretin. Baseline laboratory studies should include fasting cholesterol and triglycerides, renal and liver function tests, and pregnancy tests in women. If acitretin is used in women of child-bearing potential, baseline and monthly pregnancy testing is essential.

After initiation of treatment, patients should be closely monitored to avoid serious adverse effects. Fasting lipid profile and liver enzyme testing should be performed monthly for the first 3 months and then every 3 months.

Triglyceride-lowering medications, such as a fibrate, may be necessary for elevated lipid levels.[191] Because patients with psoriasis have an increased risk of cardiovascular disease, physicians should recommend lifestyle changes that reduce hyperlipidemia in patients taking acitretin.

Table XIV. Acitretin supplementary table*

Statement No.	Supporting statement
1.	Dosing • 10-50 mg/d given as a single dose • Lower doses (≤25 mg/d) are often used to minimize adverse effects, especially in combination regimens. • When acitretin is added to phototherapy, the light dose should be reduced by 30%-50%.
2.	Contraindications • Women of childbearing potential cannot consider pregnancy up to 3 years after completion of treatment. • Severely impaired liver or kidney function • Chronic abnormally elevated blood lipid values
3.	Baseline monitoring • History and physical examination • Lipid profile, CBC, LFTs, renal function tests • Pregnancy test if indicated Ongoing monitoring • LFTs, lipid profile monthly for the first 3 months, then every 3 months • CBC, renal function tests every 3 months • Pregnancy test if indicated
4.	Toxicity • Cheilitis • Alopecia • Xerosis • Pruritus • Xerophthalmia • Night blindness • Dry mouth • Paronychia • Paresthesia • Headache • Pseudotumor cerebri • Nausea • Abdominal pain • Joint pain • Myalgia • Hypertriglyceridemia • Abnormal LFTs
5.	Drug interactions • Etretinate can be formed with concurrent ingestion of acitretin and ethanol. • Acitretin might interact with glucose-lowering effect of glibenclamide. • May interfere with the contraceptive effect of microdosed progestin preparation. • Acitretin and methotrexate can both cause hepatotoxicity; therefore, they should be combined with caution. • Acitretin may reduce the protein binding of phenytoin. • Acitretin and tetracyclines can both increase intracranial pressure; their combined use should be avoided. • Concomitant administration of vitamin A and other oral retinoids with acitretin should be avoided.
6.	Pregnancy • Should not be used by patients who are pregnant or intend to become pregnant for at least 3 years after discontinuation of therapy Nursing • Mothers receiving acitretin should not breast-feed. Fertility • Not a teratogen when used by male patients who are potentially fathering an infant

CBC, Complete blood count; *LFTs*, liver function tests.
*Supplemental information is expert consensus and not part of evidence-based recommendations.

Table XV. Tofacitinib supplementary table*

Statement No.	Supporting statement
1.	Tofacitinib can be considered for treatment of moderate to severe psoriasis but is not currently FDA approved for that indication.
2.	The recommended dose of tofacitinib for psoriasis is 5 mg by mouth 2 times a day or 10 mg by mouth 2 times a day, which is more beneficial in efficacy but with a higher risk of adverse effects (off-label dosing).
3.	Tofacitinib 10 mg twice a day is associated with a higher risk of adverse effects, such as infection and cytopenia, compared with tofacitinib 5 mg twice a day.
4.	Before initiation of tofacitinib, vaccination with zoster vaccine (Shingrix)† should be considered to reduce the risk of herpes zoster.
5.	Tofacitinib should not be initiated, if the a. Lymphocyte count is <500 cells/mm^3 b. Absolute neutrophil count (ANC) is <1000 cells/mm^3 c. Hemoglobin is <9 g/dL
6.	Tofacitinib should be discontinued, at least temporarily, if the a. Lymphocyte count is <500 cells/mm^3 (confirmed by repeat testing) b. ANC is <500 cells/mm^3 (confirmed by repeat testing) For persistent decreases in ANC <1000 cells/mm^3, tofacitinib should be held until ANC is >1000 cells/mm^3. c. Hemoglobin decreases by >2 g/dL or is <8.0 g/dL (confirmed by repeat testing). Tofacitinib should be held until hemoglobin values have normalized.
7.	The recommended tofacitinib dose in patients with moderate and severe renal or hepatic impairment is 5 mg once daily.
8.	Tofacitinib is not recommended in patients with severe hepatic impairment.
9.	The recommended dose of tofacitinib for patients taking potent inhibitors of cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole) or one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (eg, fluconazole) is 5 mg once daily.
10.	Tofacitinib can be used with methotrexate. It should not be combined with potent immunosuppressants, such as azathioprine and cyclosporine, or with biologics used for psoriasis.
11.	Tofacitinib should be avoided during an active serious infection.
12.	Live vaccines should be avoided in patients on tofacitinib.
13.	There is currently not enough evidence to support the combined use of tofacitinib with other systemic agents or phototherapy.
14.	Pregnancy Tofacitinib can be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

FDA, Food and Drug Administration.
*Supplemental information is expert consensus and not part of evidence-based recommendations.
†Shingrix is the brand name for the zoster vaccine manufactured by GlaxoSmithKline, Research Triangle Park, North Carolina.

The strength of recommendations for the use of acitretin in the treatment of psoriasis is provided in Table XII,[192] the level of evidence for acitretin therapy in psoriasis is outlined in Table XIII,[§] and Table XIV is the supplementary table for acitretin therapy.

TOFACITINIB

Tofacitinib is an oral Janus kinase inhibitor approved by the FDA for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis.[194,195] It has shown beneficial effects in psoriasis but is not currently approved for that indication. Tofacitinib interrupts the Janus kinase/signal transducers and activators of transcription signaling pathway necessary for activity of several inflammatory cytokines involved in psoriasis, including interferon-α/-β, interferon-γ, IL-2, IL-12, IL-20, IL-22, and IL-23.[196] It is prescribed at doses of 5 or 10 mg twice daily (expert consensus).

Efficacy

Multiple large phase III clinical trials were completed investigating the use of tofacitinib in psoriasis, including Oral treatment Psoriasis Trial (OPT) Pivotal 1 (n = 901) and OPT Pivotal 2 (n = 960).[197] Across these 2 studies, 745 patients received tofacitinib (5 mg), 741 received tofacitinib (10 mg), and 373 received placebo. At week 16, a

§References[33,150,152,154-157,159,161,162,170,171,193].

Table XVI. Fumaric acid ester supplementary table[*,‡,†]

Statement No.	Supporting statement
1.	Dimethyl fumarate is approved in the United States for treatment of relapsing forms of multiple sclerosis. It can be recommended for psoriasis.
2.	Dosing • Starting daily dose of 1 pill of lower strength (105 mg of fumaric acid ester mixtures) and then escalate over 8 weeks to 6 pills of regular strength (215 mg of fumaric acid ester mixtures)
3.	Contraindications • Severe liver disease • Severe or chronic GI disease • Severe or chronic kidney disease • Malignancy or a history of malignancy • Leukopenia and other hematologic abnormalities • Pregnancy • Breast-feeding
4.	Baseline monitoring • History and physical examination • CBC and platelet counts • Chemistry screen • Urinalysis Ongoing monitoring • CBC and platelet count every other week for the first 2 months; monthly until 6 months; and bimonthly thereafter
5.	Toxicity • Anaphylaxis/angioedema • GI (abdominal cramps, nausea, diarrhea, fullness, and flatulence) • Flushing • Malaise • Fatigue • Lymphopenia, leukopenia, eosinophilia • Hepatotoxicity and elevated LFT results • Increased cholesterol, triglycerides • Increased serum creatinine, potassium, and proteinuria • Possible renal disease
6.	Drug interactions • Other fumaric acid derivatives, methotrexate, cyclosporine, immunosuppressive, and cytostatic drugs may potentiate toxicity • Drugs that cause renal dysfunction

CBC, Complete blood count; *GI*, gastrointestinal; *LFT*, liver function test.

*Supplemental information is expert consensus and not part of evidence-based recommendations.

†The information presented in the supplementary table is obtained from the previous 2009 American Academy of Dermatology Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis.

‡Reprinted from *Journal of the American Academy of Dermatology*, 61(3), Menter A, Korman NJ, Elmets CA, et al., Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis: Section 4. Guidelines of Care for the Management and Treatment of Psoriasis with Traditional Systemic Agents, 451-485, Copyright (2009), with permission from Elsevier.

larger percentage of patients achieved Physician's Global Assessment responses of "clear" or "almost clear" with tofacitinib 5 and 10 mg twice daily vs placebo (OPT Pivotal 1, 41.9% and 59.2% vs 9.0%; OPT Pivotal 2, 46.0% and 59.1% vs 10.9%; all $P < .001$). Rates of PASI 75 were also higher among patients receiving tofacitinib (OPT Pivotal 1, 39.9% and 59.2%, respectively, for tofacitinib 5 and 10 mg twice daily; OPT Pivotal 2, 46.0% and 59.6%, respectively; all $P < .001$) compared with placebo (OPT Pivotal 1, 6.2%; OPT Pivotal 2, 11.4%). Efficacy persisted through week 28, with PASI 75 rates of 55.6% and 68.8% in patients receiving tofacitinib 5 mg and 10 mg twice daily, respectively, and the proportion of patients with goal Physician's Global Assessment scores measuring 54.7% and 65.9%, respectively. Most patients continued to experience benefit through 2 years of treatment, with serious adverse events and discontinuations occurring in less than 11% of patients over 33 months. In a phase

Table XVII. Hydroxyurea supplementary table[*,†,‡]

Statement No.	Supporting statement
1.	Indication • Not an FDA-approved use for psoriasis
2.	Dosing • Initial dose of 500 mg orally twice daily, increasing to 1.5 g/d as tolerated.
3.	Contraindications • Marked bone marrow suppression, including leukopenia, thrombocytopenia, or anemia
4.	Baseline monitoring • History and physical examination • CBC • Pregnancy test if indicated Ongoing monitoring • Weekly CBC until a stable dose is achieved, then monthly • Semiannual physical examination focusing on evidence of lymphadenopathy and NMSCs • Pregnancy testing if indicated
5.	Toxicity • Bone marrow suppression • GI symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation) • Dermatologic reactions (rash, ulceration, dermatomyositis-like skin changes, alopecia) • Dysuria (rare) • Neurologic disturbances rarely (headache, dizziness, disorientation, hallucinations, and convulsions) • Temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine • Fever, chills, malaise, edema, asthenia • Elevation in hepatic enzymes • Pulmonary fibrosis • Fatal and nonfatal pancreatitis and hepatoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents.
6.	Drug interactions • Concurrent use of hydroxyurea and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow suppression. • May raise the serum uric acid level; therefore, dose adjustment of uricosuric medication may be necessary.
7.	Pregnancy/nursing • Pregnancy and breast-feeding should be avoided during treatment and patients (including men) must use adequate contraception. • Fertility may be compromised in male patients.

BUN, Blood urea nitrogen; *CBC*, complete blood count; *FDA*, Food and Drug Administration; *GI*, gastrointestinal; *NMSCs*, nonmelanoma skin cancers.

*Supplemental information is expert consensus and not part of evidence-based recommendations.

†The information presented in the supplementary table is obtained from the previous 2009 American Academy of Dermatology Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis.

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II study using a higher dosage of 15 mg tofacitinib twice daily, the PASI 75 score at week 12 was 66.7%.[198]

Tofacitinib was also compared with etanercept in a noninferiority trial with 1101 patients with psoriasis.[199] It showed that tofacitinib 10 mg twice daily was noninferior to etanercept 50 mg twice weekly.

Toxicity

In the OPT Pivotal 1 and 2 studies, adverse event rates, including those that led to discontinuation of the medication, were largely comparable across all groups, and rates of serious adverse events, such as malignancy or infection, were low.[197,200] However, the incidence of herpes zoster was greater in those receiving tofacitinib compared with the placebo

Table XVIII. Mycophenolate mofetil supplementary table[*,†,‡]

Statement No.	Supporting statement
1.	Indication
	• Not FDA approved for psoriasis
2.	Dosing
	• 1.0-1.5 g orally 2 times/d
3.	Contraindication
	• Hypersensitivity to mycophenolate mofetil (MMF) and mycophenolic acid
4.	Baseline monitoring
	• History and physical examination
	• CBC and platelet counts
	• TB screen, LFTs
	• Pregnancy test if indicated
	Ongoing monitoring
	• CBC and platelet count weekly for 1 month; every 2 weeks thereafter for 2 months; then monthly thereafter
	• Monthly CMP and LFTs
	• Semiannual physical examination focusing on evidence of lymphadenopathy and NMSCs
	• Pregnancy testing if indicated
5.	Toxicity
	• GI adverse effects (diarrhea, nausea/vomiting, abdominal cramps); occur early and decrease with continued use
	• Hematologic (leukopenia is most common; anemia, thrombocytopenia)
	• Genitourinary (urgency, frequency, dysuria, sterile pyuria)
	• Susceptibility to viral, bacterial and mycobacterial infections
	• Progressive multifocal leukoencephalopathy
	• Hypercholesterolemia, hypophosphatemia, hyperkalemia, hypokalemia
	• Fever and myalgias
	• Headache, insomnia
	• Peripheral edema
	• Hypertension
	• Patients taking MMF should not be given live attenuated virus vaccines
6.	Drug interactions
	• Antacids containing aluminum and magnesium
	• Calcium and iron
	• Cholestyramine
	• Antibiotics, including cephalosporins, fluoroquinolones, macrolides, penems, penicillins, sulfonamides, inhibit enterohepatic recirculation and decrease MMF levels.
	• High-dose salicylates
	• Phenytoin
	• Xanthine bronchodilators
	• Probenecid
	• Acyclovir, ganciclovir, valganciclovir, and valacyclovir
7.	Pregnancy/nursing
	• Pregnancy and breast-feeding should be avoided during treatment, and patients (including men) must use adequate contraceptive precautions.

CBC, Complete blood count; *CMP*, comprehensive metabolic panel; *FDA*, Food and Drug Administration; *LFTs*, liver function tests; *NMSCs*, nonmelanoma skin cancer.

*Supplemental information is expert consensus and not part of evidence-based recommendations.

†The information presented in the supplementary table is obtained from the previous 2009 American Academy of Dermatology Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis.

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groups (n = 5 vs 0). Overall, nasopharyngitis was the most common AE. In the etanercept comparison study, rates of adverse events were similar (~2%) in each of the 4 groups (tofacitinib 5 mg twice daily; tofacitinib 10 mg twice daily; etanercept 50 mg twice weekly, and placebo).[199] Patients taking

Table XIX. Azathioprine supplementary table[*,†,‡]

Statement No.	Supporting statement
1.	Indication • Not FDA-approved for psoriasis
2.	Dosing When thiopurine S-methyltransferase (TPMT) levels are used to guide dosing Suggested daily schedule • TPMT <5.0 U, do not use azathioprine • TPMT 5-13.7 U, 0.5 mg/kg • TPMT 13.7-19.0 U, 1.5 mg/kg • TPMT > 19.0 U, 2.5 mg/kg Without TPMT levels • Begin at 0.5 mg/kg, and monitor for cytopenia • If no cytopenia, increase dose by 0.5 mg/kg/d • After 6-8 weeks, increase by 0.5 mg/kg/d every 4 weeks if necessary • Usual dose for psoriasis is 75-150 mg/d
3.	Contraindications • Absolute ○ Allergy to azathioprine ○ Pregnancy or attempting pregnancy ○ Clinically significant active infection • Relative ○ Concurrent use of allopurinol ○ Prior treatment with cyclophosphamide or chlorambucil
4.	Baseline monitoring • History and physical examination • LFTs, CBC and differential CMP, urinalysis, TB screen, hepatitis B and C screen • Pregnancy test if indicated Ongoing monitoring • CBC and differential every 2 weeks for the first 2 months, monthly for the next 2 months, every 2 months thereafter • LFTs monthly for the first 3 months then every 2 months thereafter • Semiannual physical examination focusing on evidence of lymphadenopathy and NMSCs • Pregnancy testing if indicated
5.	Toxicity • Bone marrow suppression • Malignancies • Cutaneous SCCs • Lymphoproliferative disorders • Increased risk of infections • GI effects (nausea, vomiting, diarrhea) • Hypersensitivity syndrome • Pancreatitis • Hepatitis
6.	Drug interactions • Allopurinol—increases risks of pancytopenia (if used concurrently, lower the azathioprine dose by 75%) • Captopril—may increase risk of anemia and leukopenia • Warfarin—may need an increased dose of warfarin • Pancuronium—may need an increased dose for adequate paralysis • Cotrimoxazole—increased risk of hematologic toxicity • Rifampicin—decreases azathioprine efficacy; also hepatotoxic • Clozapine—increases risk of agranulocytosis

Continued

Table XIX. Cont'd

Statement No.	Supporting statement
7.	Pregnancy/nursing • Pregnancy and breast-feeding should be avoided during treatment with azathioprine, and patients (including men) must use adequate contraception.

CBC, Complete blood count; *CMP*, comprehensive metabolic panel; *FDA*, Food and Drug Administration; *GI*, gastrointestinal; *LFTs*, liver function tests; *NMSCs*, nonmelanoma skin cancers; *SCCs*, squamous cell carcinomas; *TB*, tuberculosis.

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tofacitinib have experienced rare episodes of serious infections, such as tuberculosis (including disseminated disease), opportunistic infections, and bacterial, fungal, and viral infections. The most common serious infections include cellulitis, urinary tract infection, pneumonia, and herpes zoster. Malignancies, including lymphoma, have been reported; with the use of tofacitinib, Epstein Barr virus-associated post-transplant lymphoproliferative disorder was seen in renal transplant patients receiving simultaneous treatment with other immunosuppressive medications.[201,202] Lung and breast cancer were the most common nonhematologic malignancies.[195] Rates of drug discontinuation due to adverse events were highest in the placebo group. Tofacitinib has a box warning for increased risk of blood clots with higher doses that are sometimes used in the treatment of psoriasis.[195] 10 mg twice-daily dosing of tofacitinib has been associated with a higher risk of thromboembolic disease.[195]

Tofacitinib may affect blood counts, liver enzymes, lipid, and creatinine levels. After 3 months of exposure, 0.04% of patients experienced a decrease in absolute lymphocyte count to less than 500 cells/mm^3, and this was correlated with an increased incidence of treated and serious infections. Increases in liver enzymes to more than 3 times the upper limit of normal were also recorded in patients treated with tofacitinib, as were dose-related elevations of serum creatinine and lipid parameters (triglycerides and total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol). The increase in cholesterol occurred after 1 month of therapy and subsequently remained stable.[195]

Monitoring

Given the risk of infection, patients should be screened for tuberculosis, hepatitis, and HIV before starting tofacitinib. Vaccination with recombinant zoster vaccine (Shingrix, GlaxoSmithKline, Research Triangle Park, NC) before initiation of therapy should be considered. Baseline laboratory studies, including CBC with differential, comprehensive metabolic profile, and lipid panel, should be performed at the initiation of treatment and repeated 4 to 8 weeks later. There should be regular monitoring every 12 weeks after that. Because of the small risk of bone marrow suppression with tofacitinib, patients who have low counts at baseline (absolute lymphocyte count <500 cells/mm^3, absolute neutrophil count <1000 cells/mm^3, or hemoglobin <9 g/dL) should not be treated with tofacitinib. Dose interruption is recommended for patients with normal hematologic parameters at baseline who develop lymphopenia, neutropenia, or anemia while on therapy (Table XV).

Tofacitinib is metabolized in the liver and is excreted by the kidney; therefore, the dose should be decreased to 5 mg once daily in patients with renal or hepatic impairment. Tofacitinib is not recommended in patients with severe hepatic impairment. Drug interactions can occur because tofacitinib is metabolized by the CYP3A4 enzyme, with a minor contribution from CYP2C19. Patients taking other medications that act as inhibitors of these enzymes may need to be placed on the lower dose (5 mg daily) to avoid adverse effects from tofacitinib.

Tofacitinib is not recommended in patients with active infections, and the risks and benefits of treatment should be thoroughly considered and discussed with the patient before beginning treatment. The medication should not be combined with other potent immunosuppressive drugs such as azathioprine, cyclosporine, or biologic agents, although it may be used with methotrexate if

Table XX. Leflunomide supplementary table[*,†,‡]

Statement No.	Supporting statement
1.	Indication • Not FDA approved for psoriasis
2.	Dosing • Loading dose of 100 mg/d for 3 days, followed by 20 mg/d thereafter
3.	Contraindications • Patients with hypersensitivity to leflunomide or its metabolites
4.	Baseline monitoring • History and physical examination • CBC and differential • LFTs • Pregnancy test if indicated Ongoing monitoring • Monthly CBC with differential and LFTs for the first 6 months and every 6-8 weeks thereafter • Pregnancy testing if indicated
5.	Toxicity • Most common adverse effects include nausea, diarrhea, loss of appetite, weight loss, headache, dizziness • Severe liver injury ○ May be fatal ○ Most cases occur within 6 months of therapy and in patients with multiple risk factors for hepatotoxicity • Rare reports of pancytopenia, agranulocytosis, and thrombocytopenia in patients treated with or who had recently discontinued methotrexate or other immunosuppressive agents
6.	Drug interactions • No pharmacokinetic interaction between leflunomide and methotrexate, but coadministration of the 2 drugs can lead to increased risk of hepatotoxicity. • Rifampin increases leflunomide levels.
7.	Pregnancy • Should be avoided in pregnant patients Nursing • Leflunomide should not be used by nursing mothers. Patients of reproductive potential • Advise patients to use appropriate contraception during treatment administration and discontinuation.

CBC, Complete blood count; *LFTs*, liver function tests; *FDA*, Food and Drug Administration.
*Supplemental information is expert consensus and not part of evidence-based recommendations.
†The information presented in the supplementary table is obtained from the previous 2009 American Academy of Dermatology Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis.
‡Reprinted from *Journal of the American Academy of Dermatology*, 61(3), Menter A, Korman NJ, Elmets CA, et al., Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis: Section 4. Guidelines of Care for the Management and Treatment of Psoriasis with Traditional Systemic Agents, 451-485, Copyright (2009), with permission from Elsevier.

indicated. For further recommendations about the use of tofacitinib in psoriasis see Table XV.

FUMARIC ACID ESTERS

Fumaric acid esters (FAEs), also known as fumarates, are compounds of dimethyl fumarate along with monoethyl fumarate salts. While frequently used in Europe for treatment of moderate to severe psoriasis, fumarates are not currently approved by the FDA for psoriasis, although they are approved in the United States for other indications, including psoriatic arthritis. Their mechanism of action was originally thought to be due strictly to their immunomodulatory actions.[203] However, more recent studies have identified anti-angiogenesis and antioxidant effects as well.[203-205]

In 2015, a Cochrane review investigated the use of FAEs for psoriasis.[206] The review included 6 studies (2 full reports, 2 abstracts, 1 brief communication, and 1 letter) with a total of 544 participants. All studies reported a significant reduction in PASI scores with FAEs. A meta-analysis of 2 additional studies with 247 participants showed superiority of FAEs in achieving PASI 50 over placebo (64% vs 14%; RR, 4.55; 95% CI, 2.80-7.40). Treatment with FAEs resulted in a statistically significant improvement in

Table XXI. Tacrolimus supplementary table[*,†,‡]

Statement No.	Supporting statement
1.	Indication
	• Not FDA approved for psoriasis
2.	Dosage
	• 0.05-0.15 mg/kg
3.	Contraindications
	• Patients with hypersensitivity to tacrolimus or its metabolites
	Adverse effect profile similar to cyclosporine
	• Most common adverse effects include tremor, headache, nausea, diarrhea, hypertension, and abnormal renal function test.
	• Less common adverse effects include hyperglycemia, hyperkalemia, elevated liver function test, anemia, leukocytosis, dyspnea, fever, arthralgias, edema, diabetes, insomnia, and paresthesias.
4.	Baseline monitoring
	• History and physical examination
	• Complete blood count with differential
	• Pregnancy test if indicated
	• BP
	• Renal function test
	• LFTs
	• TB
	Ongoing monitoring—proper frequency is not established
	• Blood pressure
	• Serum chemistry
	• Renal function test
	• Liver function test
	• Pregnancy test if indicated
5.	Drug interactions
	• Numerous drug interactions due to its metabolization by the cytochrome P450 system
	• Tacrolimus and cyclosporine should not be administered together.
6.	Pregnancy
	• Can be used during pregnancy only if the potential benefit to mother justifies the potential risk to fetus.
	Nursing
	• Tacrolimus should not be used by nursing mothers.
	Fertility
	• Advise patients to use appropriate contraception before initiating therapy.
	• On the basis of animal studies, female and male fertility may be compromised by treatment.

BP, Blood pressure; *FDA*, Food and Drug Administration; *LFTs*, liver function tests; *TB*, tuberculosis.

*Supplemental information is expert consensus and not part of evidence-based recommendations.

†The information presented in the supplementary table is obtained from the previous 2009 American Academy of Dermatology Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis.

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participants' quality of life.[203] The same studies also reported that more participants achieved PASI 75 with FAEs. When a combination of methotrexate and FAEs was compared with methotrexate alone, the difference was not statistically significant after adjustment for baseline disease severity.[19]

Adverse effects, mainly GI disturbance and flushing, were more prevalent in patients taking FAEs compared with placebo (76% vs 16%; RR, 4.72; 95% CI, 2.45-9.0).[207] Similar findings have been reported in other studies. GI complaints, including nausea, vomiting, esophageal, and stomach pain, can occur in up to two-thirds of patients.[208] A modest lymphopenia is invariably present but does not appear to be of significant clinical concern.[209] Increases in liver function test results, triglycerides, cholesterol, and creatinine are possible, necessitating regular laboratory monitoring. There are rare cases of renal disease that have been reported with FAEs, although this was not experienced in any randomized controlled trials and FAEs may not be the cause.[210] There have also been rare cases

Table XXII. Thioguanine supplementary table[*,†,‡]

Statement No.	Supporting statement
1.	Indication • Not FDA approved for psoriasis
2.	Dosing • Start at 80 mg 2 times/wk; increase by 20 mg every 2-4 weeks • Maximum dose is 160 mg 3 times/wk
3.	Contraindications • Pre-existing liver disease • Immunosuppression • Anemia, leukopenia, and/or thrombocytopenia
4.	Baseline monitoring • History and physical examination • CBC and platelet counts, CMP, LFTs, hepatitis B and C, TB screen • Pregnancy test if indicated Ongoing monitoring • CBC and platelet count every 2-4 weeks; CMP every 3 months • Semiannual physical examination focusing on evidence of lymphadenopathy and NMSCs • Pregnancy test if indicated
5.	Toxicity • Myelosuppression • Liver toxicity from hepatic veno-occlusive disease • Increased ALT and AST • Hyperuricemia • Photodermatitis • Taste changes • Gastroesophageal reflux, gastric ulcers • Headache • Nausea/vomiting • Aphthous ulcers • Fatigue • Nonmelanoma skin cancer • Verrucae vulgaris, herpes zoster
6.	Drug interactions • Aminosalicylate derivatives (olsalazine, mesalazine, or sulfasalazine) may inhibit thiopurine methyltransferase.
7.	Pregnancy • Pregnancy and breast-feeding should be avoided during treatment, and patients (including men) must use adequate contraception.

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *CBC*, complete blood count; *CMP*, complete metabolic profile; *FDA*, Food and Drug Administration; *LFTs*, liver function tests; *NMSCs*, nonmelanoma skin cancers; *TB*, tuberculosis.

*Supplemental information is expert consensus and not part of evidence-based recommendations.

†The information presented in the supplementary table is obtained from the previous 2009 American Academy of Dermatology Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis.

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of progressive multifocal leukoencephalopathy occurring in patients with psoriasis treated with FAEs.[211] Affected individuals experienced severe antecedent lymphopenia before onset of progressive multifocal leukoencephalopathy.

Starting at low doses and gradually increasing them can help minimize GI adverse effects. A conservative approach is to start with 1 pill of lower strength (105 mg of FAE mixtures) daily and then escalate over 8 weeks to 6 pills of regular strength (215 mg of FAE mixtures), as tolerated (expect consensus).[207,212-214] Dimethyl fumarate has been approved by the FDA for treatment of multiple sclerosis, with a common dosing regimen of 240 mg twice daily.[211] Table XVI describes adverse effects, contraindications, and recommendations regarding the use of FAEs in psoriasis.

OTHER TREATMENTS

Although rarely necessary for psoriasis, systemic immunosuppressants and antimetabolites, including hydroxyurea (Table XVII), mycophenolate mofetil (Table XVIII), azathioprine (Table XIX), leflunomide (Table XX), tacrolimus (Table XXI), and thioguanine (Table XXII), may have value for this disease in certain instances. These medications still have a place in the management of various other autoimmune conditions.

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REFERENCES

1. Kaushik SB, Lebwohl MG. Psoriasis: which therapy for which patient: psoriasis comorbidities and preferred systemic agents. *J Am Acad Dermatol*. 2019;80(1):27-40.
2. Kaushik SB, Lebwohl MG. Psoriasis: which therapy for which patient: focus on special populations and chronic infections. *J Am Acad Dermatol*. 2019;80(1):43-53.
3. Menter A. Psoriasis and psoriatic arthritis overview. *Am J Manag Care*. 2016;22(8 Suppl):s216-s224.
4. Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238-244.
5. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. *J Allergy Clin Immunol*. 2017;140(3):645-653.
6. Heidenreich R, Rocken M, Ghoreschi K. Angiogenesis drives psoriasis pathogenesis. *Int J Exp Pathol*. 2009;90(3):232-248.
7. Lowes MA, Suarez-Farinas M, Krueger JG. Immunology of psoriasis. *Annu Rev Immunol*. 2014;32:227-255.
8. Matthews DA, Alden RA, Bolin JT, et al. Dihydrofolate reductase: x-ray structure of the binary complex with methotrexate. *Science*. 1977;197(4302):452-455.
9. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology (Oxford)*. 2004;43(3):267-271.
10. Chan ES, Cronstein BN. Molecular action of methotrexate in inflammatory diseases. *Arthritis Res*. 2002;4(4):266-273.
11. Montesinos MC, Desai A, Delano D, et al. Adenosine A2A or A3 receptors are required for inhibition of inflammation by methotrexate and its analog MX-68. *Arthritis Rheum*. 2003;48(1):240-247.
12. Morgan SL, Oster RA, Lee JY, Alarcon GS, Baggott JE. The effect of folic acid and folinic acid supplements on purine metabolism in methotrexate-treated rheumatoid arthritis. *Arthritis Rheum*. 2004;50(10):3104-3111.
13. Jeffes EW 3rd, McCullough JL, Pittelkow MR, et al. Methotrexate therapy of psoriasis: differential sensitivity of proliferating lymphoid and epithelial cells to the cytotoxic and growth-inhibitory effects of methotrexate. *J Invest Dermatol*. 1995;104(2):183-188.
14. Saporito FC, Menter MA. Methotrexate and psoriasis in the era of new biologic agents. *J Am Acad Dermatol*. 2004;50(2):301-309.
15. Dogra S, Krishna V, Kanwar AJ. Efficacy and safety of systemic methotrexate in two fixed doses of 10 mg or 25 mg orally once weekly in adult patients with severe plaque-type psoriasis: a prospective, randomized, double-blind, dose-ranging study. *Clin Exp Dermatol*. 2012;37(7):729-734.
16. Radmanesh M, Rafiei B, Moosavi ZB, Sina N. Weekly vs. daily administration of oral methotrexate (MTX) for generalized plaque psoriasis: a randomized controlled clinical trial. *Int J Dermatol*. 2011;50(10):1291-1293.
17. Weinstein GD, Frost P. Methotrexate for psoriasis. A new therapeutic schedule. *Arch Dermatol*. 1971;103(1):33-38.
18. Menting SP, Dekker PM, Limpens J, Hooft L, Spuls PI. Methotrexate dosing regimen for plaque-type psoriasis: a systematic review of the use of test-dose, start-dose, dosing scheme, dose adjustments, maximum dose and folic acid supplementation. *Acta Derm Venereol*. 2016;96(1):23-28.
19. Fallah Arani S, Neumann H, Hop W, Thio H. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. *Br J Dermatol*. 2011;164(4):855-861.
20. Warren RB, Mrowietz U, von Kiedrowski R, et al. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10068):528-537.
21. US Food and Drug Administration. REDITREX (methotrexate) injection [package insert]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210737s000lbl.pdf; 2019. Accessed February 12, 2020.
22. Prey S, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. *Br J Dermatol*. 2009;160(3):622-628.
23. Chladek J, Simkova M, Vaneckova J, et al. The effect of folic acid supplementation on the pharmacokinetics and pharmacodynamics of oral methotrexate during the remission-induction period of treatment for moderate-to-severe plaque psoriasis. *Eur J Clin Pharmacol*. 2008;64(4):347-355.
24. Cline A, Jorizzo JL. Does daily folic acid supplementation reduce methotrexate efficacy? *Dermatol Online J*. 2017;23(11).
25. West J, Ogston S, Foerster J. Safety and efficacy of methotrexate in psoriasis: a meta-analysis of published trials. *PLoS One*. 2016;11(5):e0153740.
26. Sbidian E, Chaimani A, Garcia-Doval I, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Revs*. 2017;12:CD011535.
27. Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol*. 2011;165(5):1109-1117.
28. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol*. 2008;158(3):558-566.
29. Gelfand JM, Wan J, Callis Duffin K, et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. *Arch Dermatol*. 2012;148(4):487-494.
30. Jabbar-Lopez ZK, Yiu ZZN, Ward V, et al. Quantitative evaluation of biologic therapy options for psoriasis: a

systematic review and network meta-analysis. *J Invest Dermatol*. 2017;137(8):1646-1654.
31. Kingsley GH, Kowalczyk A, Taylor H, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology (Oxford)*. 2012;51(8):1368-1377.
32. Coates LC, Helliwell PS. Methotrexate efficacy in the tight control in psoriatic arthritis study. *J Rheumatol*. 2016;43(2):356-361.
33. Takeshita J, Wang S, Shin DB, et al. Comparative effectiveness of less commonly used systemic monotherapies and common combination therapies for moderate to severe psoriasis in the clinical setting. *J Am Acad Dermatol*. 2014;71(6):1167-1175.
34. Zachariae C, Mork NJ, Reunala T, et al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. *Acta Derm Venereol*. 2008;88(5):495-501.
35. Gottlieb AB, Langley RG, Strober BE, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. *Br J Dermatol*. 2012;167(3):649-657.
36. Busard C, Zweegers J, Limpens J, Langendam M, Spuls PI. Combined use of systemic agents for psoriasis: a systematic review. *JAMA Dermatol*. 2014;150(11):1213-1220.
37. Al-Hamamy HR, Al-Mashhadani SA, Mustafa IN. Comparative study of the effect of narrowband ultraviolet B phototherapy plus methotrexate vs. narrowband ultraviolet B alone and methotrexate alone in the treatment of plaque-type psoriasis. *Int J Dermatol*. 2014;53(12):1531-1535.
38. Mahajan R, Kaur I, Kanwar AJ. Methotrexate/narrowband UVB phototherapy combination vs. narrowband UVB phototherapy in the treatment of chronic plaque-type psoriasis—a randomized single-blinded placebo-controlled study. *J Eur Acad Dermatol Venereol*. 2010;24(5):595-600.
39. Soliman A, Nofal E, Nofal A, El Desouky F, Asal M. Combination therapy of methotrexate plus NBUVB phototherapy is more effective than methotrexate monotherapy in the treatment of chronic plaque psoriasis. *J Dermatolog Treat*. 2015;26(6):528-534.
40. Ford AR, Siegel M, Bagel J, et al. Dietary recommendations for adults with psoriasis or psoriatic arthritis from the medical board of the National Psoriasis Foundation: a systematic review. *JAMA Dermatol*. 2018;154(8):934-950.
41. Belzunegui J, Intxausti JJ, De Dios JR, et al. Absence of pulmonary fibrosis in patients with psoriatic arthritis treated with weekly low-dose methotrexate. *Clin Exp Rheumatol*. 2001;19(6):727-730.
42. Brownell I, Strober BE. Folate with methotrexate: big benefit, questionable cost. *Br J Dermatol*. 2007;157(1):213.
43. Kremer JM. Toward a better understanding of methotrexate. *Arthritis Rheum*. 2004;50(5):1370-1382.
44. MacDonald A, Burden AD. Noninvasive monitoring for methotrexate hepatotoxicity. *Br J Dermatol*. 2005;152(3):405-408.
45. Haberman R, Perez-Chada LM, Merola JF, Scher J, Ogdie A, Reddy SM. Bridging the gaps in the care of psoriasis and psoriatic arthritis: the role of combined clinics. *Curr Rheumatol Rep*. 2018;20(12):76.
46. Perez-Chada LM, Cohen JM, Gottlieb AB, et al. Achieving international consensus on the assessment of psoriatic arthritis in psoriasis clinical trials: an International Dermatology Outcome Measures (IDEOM) initiative. *Arch Dermatol Res*. 2018;310(9):701-710.
47. Chen TJ, Chung WH, Chen CB, et al. Methotrexate-induced epidermal necrosis: a case series of 24 patients. *J Am Acad Dermatol*. 2017;77(2):247-255.e242.
48. Helliwell PS, Taylor WJ, Group CS. Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs—comparison of drugs and adverse reactions. *J Rheumatol*. 2008;35(3):472-476.
49. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. *BMJ*. 2015;350:h1269.
50. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol*. 2009;61(3):451-485.
51. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol*. 2009;60(5):824-837.
52. Kivity S, Zafrir Y, Loebstein R, Pauzner R, Mouallem M, Mayan H. Clinical characteristics and risk factors for low dose methotrexate toxicity: a cohort of 28 patients. *Autoimmun Rev*. 2014;13(11):1109-1113.
53. Boffa MJ, Chalmers RJ. Methotrexate for psoriasis. *Clin Exp Dermatol*. 1996;21(6):399-408.
54. US Food and Drug Administration. Methotrexate (Otrexup) [package insert]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204824s009lbl.pdf; 2019. Accessed August 26, 2019.
55. Langman G, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. *J Gastroenterol Hepatol*. 2001;16(12):1395-1401.
56. Rosenberg P, Urwitz H, Johannesson A, et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. *J Hepatol*. 2007;46(6):1111-1118.
57. Carneiro SC, Cassia FF, Lamy F, Chagas VL, Ramos-e-Silva M. Methotrexate and liver function: a study of 13 psoriasis cases treated with different cumulative dosages. *J Eur Acad Dermatol Venereol*. 2008;22(1):25-29.
58. Montaudie H, Sbidian E, Paul C, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. *J Eur Acad Dermatol Venereol*. 2011;25 Suppl 2:12-18.
59. Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *J Am Acad Dermatol*. 2020;82(1):161-201.
60. Hoffmann K, Casetti F, Schempp C. Methotrexate-associated photosensitization [in German]. *Hautarzt*. 2015;66(6):459-461.
61. Morris LF, Harrod MJ, Menter MA, Silverman AK. Methotrexate and reproduction in men: case report and recommendations. *J Am Acad Dermatol*. 1993;29(5 Pt 2):913-916.
62. El-Beheiry A, El-Mansy E, Kamel N, Salama N. Methotrexate and fertility in men. *Arch Androl*. 1979;3(2):177-179.
63. Estop AM, Cieply K, Van Kirk V, Levison F, Buckingham R. Sperm chromosome studies in patients taking low dose methotrexate. *Am J Hum Genet*. 1992;51:A314.
64. Sussman A, Leonard JM. Psoriasis, methotrexate, and oligospermia. *Arch Dermatol*. 1980;116(2):215-217.
65. Akhyani M, Chams-Davatchi C, Hemami MR, Fateh S. Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. *J Eur Acad Dermatol Venereol*. 2010;24(12):1447-1451.

66. Barker J, Horn EJ, Lebwohl M, et al. Assessment and management of methotrexate hepatotoxicity in psoriasis patients: report from a consensus conference to evaluate current practice and identify key questions toward optimizing methotrexate use in the clinic. *J Eur Acad Dermatol Venereol*. 2011;25(7):758-764.
67. Ho SG, Yeung CK, Chan HH. Methotrexate versus traditional Chinese medicine in psoriasis: a randomized, placebo-controlled trial to determine efficacy, safety and quality of life. *Clin Exp Dermatol*. 2010;35(7):717-722.
68. Reich K, Signorovitch J, Ramakrishnan K, et al. Benefit-risk analysis of adalimumab versus methotrexate and placebo in the treatment of moderate to severe psoriasis: comparison of adverse event-free response days in the CHAMPION trial. *J Am Acad Dermatol*. 2010;63(6):1011-1018.
69. Revicki D, Willian MK, Saurat JH, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *Br J Dermatol*. 2008;158(3):549-557.
70. Ogdie A, Grewal SK, Noe MH, et al. Risk of incident liver disease in patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis: a population-based study. *J Invest Dermatol*. 2018;138(4):760-767.
71. van der Voort EA, Koehler EM, Nijsten T, et al. Increased prevalence of advanced liver fibrosis in patients with psoriasis: a cross-sectional analysis from the Rotterdam Study. *Acta Derm Venereol*. 2016;96(2):213-217.
72. van der Voort EA, Koehler EM, Dowlatshahi EA, et al. Psoriasis is independently associated with nonalcoholic fatty liver disease in patients 55 years old or older: results from a population-based study. *J Am Acad Dermatol*. 2014;70(3):517-524.
73. Robert M, Sofair AN, Thomas A, et al. A comparison of hepatopathologists' and community pathologists' review of liver biopsy specimens from patients with hepatitis C. *Clin Gastroenterol Hepatol*. 2009;7(3):335-338.
74. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology*. 1994;20(1 Pt 1):15-20.
75. Ratziu V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology*. 2005;128(7):1898-1906.
76. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol*. 2002;97(10):2614-2618.
77. Tapper EB, Lok AS. Use of liver imaging and biopsy in clinical practice. *N Engl J Med*. 2017;377(8):756-768.
78. Laharie D, Seneschal J, Schaeverbeke T, et al. Assessment of liver fibrosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: a case-control study. *J Hepatol*. 2010;53(6):1035-1040.
79. Bauer B, Chyou PH, Stratman EJ, Green C. Noninvasive testing for nonalcoholic steatohepatitis and hepatic fibrosis in patients with psoriasis receiving long-term methotrexate sodium therapy. *JAMA Dermatol*. 2017;153(10):977-982.
80. Maybury CM, Samarasekera E, Douiri A, Barker JN, Smith CH. Diagnostic accuracy of noninvasive markers of liver fibrosis in patients with psoriasis taking methotrexate: a systematic review and meta-analysis. *Br J Dermatol*. 2014;170(6):1237-1247.
81. Rongngern P, Chularojanamontri L, Wongpraparut C, et al. Diagnostic performance of transient elastography for detection of methotrexate-induced liver injury using Roenigk classification in Asian patients with psoriasis: a retrospective study. *Arch Dermatol Res*. 2017;309(5):403-408.
82. Bray AP, Barnova I, Przemioslo R, Kennedy CT. Liver fibrosis screening for patients with psoriasis taking methotrexate: a cross-sectional study comparing transient elastography and liver biopsy. *Br J Dermatol*. 2012;166(5):1125-1127.
83. Tapper EB, Castera L, Afdhal NH. FibroScan (vibration-controlled transient elastography): where does it stand in the United States practice. *Clin Gastroenterol Hepatol*. 2015;13(1):27-36.
84. Park CC, Nguyen P, Hernandez C, et al. Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. *Gastroenterology*. 2017;152(3):598-607. e592.
85. Hoganson DD, Chen J, Ehman RL, et al. Magnetic resonance elastography for liver fibrosis in methotrexate treatment. *Open J Rheumatol Autoimmune Dis*. 2012;2(2):6-13.
86. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol*. 2015;73(1):37-49.
87. US Food and Drug Administration. Apremilast (Otezla) [package insert]. Celgene Corporation. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205437s006lbl.pdf; 2017. Accessed May 2, 2019.
88. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. *J Rheumatol*. 2015;42(3):479-488.
89. Danesh MJ, Beroukhim K, Nguyen C, Levin E, Koo J. Apremilast and adalimumab: a novel combination therapy for recalcitrant psoriasis. *Dermatol Online J*. 2015;21(6).
90. AbuHilal M, Walsh S, Shear N. Use of apremilast in combination with other therapies for treatment of chronic plaque psoriasis: a retrospective study. *J Cutan Med Surg*. 2016;20(4):313-316.
91. Rothstein BE, McQuade B, Greb JE, Goldminz AM, Gottlieb AB. Apremilast and secukinumab combined therapy in a patient with recalcitrant plaque psoriasis. *J Drugs Dermatol*. 2016;15(5):648-649.
92. Zerilli T, Ocheretyaner E. Apremilast (Otezla): a new oral treatment for adults with psoriasis and psoriatic arthritis. *P T*. 2015;40(8):495-500.
93. Gottlieb AB, Matheson RT, Menter A, et al. Efficacy, tolerability, and pharmacodynamics of apremilast in recalcitrant plaque psoriasis: a phase II open-label study. *J Drugs Dermatol*. 2013;12(8):888-897.
94. Nast A, Jacobs A, Rosumeck S, Werner RN. Efficacy and safety of systemic long-term treatments for moderate-to-severe psoriasis: a systematic review and meta-analysis. *J Invest Dermatol*. 2015;135(11):2641-2648.
95. Papp K, Cather JC, Rosoph L, et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial. *Lancet*. 2012;380(9843):738-746.
96. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br J Dermatol*. 2015;173(6):1387-1399.
97. Strand V, Fiorentino D, Hu C, Day RM, Stevens RM, Papp KA. Improvements in patient-reported outcomes with apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of

moderate to severe psoriasis: results from a phase IIb randomized, controlled study. *Health Qual Life Outcomes*. 2013;11:82.
98. Mueller W, Herrmann B. Cyclosporin A for psoriasis. *N Engl J Med*. 1979;301(10):555.
99. Gottlieb AB, Grossman RM, Khandke L, et al. Studies of the effect of cyclosporine in psoriasis in vivo: combined effects on activated T lymphocytes and epidermal regenerative maturation. *J Invest Dermatol*. 1992;98(3):302-309.
100. Prens EP, van Joost T, Hegmans JP, t Hooft-Benne K, Ysselmuiden OE, Benner R. Effects of cyclosporine on cytokines and cytokine receptors in psoriasis. *J Am Acad Dermatol*. 1995;33(6):947-953.
101. Faerber L, Braeutigam M, Weidinger G, et al. Cyclosporine in severe psoriasis. Results of a meta-analysis in 579 patients. *Am J Clin Dermatol*. 2001;2(1):41-47.
102. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol*. 2010;63(6):925-946; quiz 947-928.
103. Christophers E, Mrowietz U, Henneicke HH, Farber L, Welzel D. Cyclosporine in psoriasis: a multicenter dose-finding study in severe plaque psoriasis. The German Multicenter Study. *J Am Acad Dermatol*. 1992;26(1):86-90.
104. Griffiths CE, Dubertret L, Ellis CN, et al. Ciclosporin in psoriasis clinical practice: an international consensus statement. *Br J Dermatol*. 2004;150(Suppl 67):11-23.
105. Shintani Y, Kaneko N, Furuhashi T, Saito C, Morita A. Safety and efficacy of a fixed-dose cyclosporin microemulsion (100 mg) for the treatment of psoriasis. *J Dermatol*. 2011;38(10):966-972.
106. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. *Am J Clin Nutr*. 2008;88(5):1242-1247.
107. Berth-Jones J, Henderson CA, Munro CS, et al. Treatment of psoriasis with intermittent short course cyclosporin (Neoral). A multicentre study. *Br J Dermatol*. 1997;136(4):527-530.
108. Ellis CN, Fradin MS, Messana JM, et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med*. 1991;324(5):277-284.
109. Ho VC, Griffiths CE, Albrecht G, et al. Intermittent short courses of cyclosporin (Neoral(R)) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomized study. The PISCES Study Group. *Br J Dermatol*. 1999;141(2):283-291.
110. Ho VC, Griffiths CE, Berth-Jones J, et al. Intermittent short courses of cyclosporine microemulsion for the long-term management of psoriasis: a 2-year cohort study. *J Am Acad Dermatol*. 2001;44(4):643-651.
111. Nast A, Kopp I, Augustin M, et al. German evidence-based guidelines for the treatment of psoriasis vulgaris (short version). *Arch Dermatol Res*. 2007;299(3):111-138.
112. Maza A, Montaudie H, Sbidian E, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. *J Eur Acad Dermatol Venerol*. 2011;25 Suppl 2:19-27.
113. Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: part II. *J Am Acad Dermatol*. 2010;63(6):949-972. quiz 973-944.
114. Mrowietz U, Farber L, Henneicke-von Zepelin HH, Bachmann H, Welzel D, Christophers E. Long-term maintenance therapy with cyclosporine and posttreatment survey in severe psoriasis: results of a multicenter study. German Multicenter Study. *J Am Acad Dermatol*. 1995;33(3):470-475.
115. Shupack J, Abel E, Bauer E, et al. Cyclosporine as maintenance therapy in patients with severe psoriasis. *J Am Acad Dermatol*. 1997;36(3 Pt 1):423-432.
116. Lebwohl M, Ali S. Treatment of psoriasis. Part 2. Systemic therapies. *J Am Acad Dermatol*. 2001;45(5):649-661;quiz 662-644.
117. Naldi L. Malignancy concerns with psoriasis treatments using phototherapy, methotrexate, cyclosporin, and biologics: facts and controversies. *Clin Dermatol*. 2010;28(1):88-92.
118. van de Kerkhof PC. Therapeutic strategies: rotational therapy and combinations. *Clin Exp Dermatol*. 2001;26(4):356-361.
119. Calzavara-Pinton P, Leone G, Venturini M, et al. A comparative non randomized study of narrow-band (NB) (312 +/-2 nm) UVB phototherapy versus sequential therapy with oral administration of low-dose Cyclosporin A and NB-UVB phototherapy in patients with severe psoriasis vulgaris. *Eur J Dermatol*. 2005;15(6):470-473.
120. Markham T, Watson A, Rogers S. Adverse effects with long-term cyclosporin for severe psoriasis. *Clin Exp Dermatol*. 2002;27(2):111-114.
121. Laburte C, Grossman R, Abi-Rached J, Abeywickrama KH, Dubertret L. Efficacy and safety of oral cyclosporin A (CyA; Sandimmun) for long-term treatment of chronic severe plaque psoriasis. *Br J Dermatol*. 1994;130(3):366-375.
122. Soleymani T, Vassantachart JM, Wu JJ. Comparison of guidelines for the use of cyclosporine for psoriasis: a critical appraisal and comprehensive review. *J Drugs Dermatol*. 2016;15(3):293-301.
123. Ramirez-Fort MK, Levin AA, Au SC, Gottlieb AB. Continuous versus intermittent therapy for moderate-to-severe psoriasis. *Clin Exp Rheumatol*. 2013;31(4 Suppl 78):S63-S70.
124. Chaidemenos GC, Mourellou O, Avgoustinaki N, Papakonstantinou M, Karakatsanis G, Katsambas A. Intermittent vs. continuous 1-year cyclosporin use in chronic plaque psoriasis. *J Eur Acad Dermatol Venerol*. 2007;21(9):1203-1208.
125. Ohtsuki M, Nakagawa H, Sugai J, et al. Long-term continuous versus intermittent cyclosporin: therapy for psoriasis. *J Dermatol*. 2003;30(4):290-298.
126. Lowe NJ, Wieder JM, Rosenbach A, et al. Long-term low-dose cyclosporine therapy for severe psoriasis: effects on renal function and structure. *J Am Acad Dermatol*. 1996;35(5 Pt 1):710-719.
127. Silverman AK, Emmett M, Menter A. Can maintenance cyclosporine be used in psoriasis without decreasing renal function? *Semin Dermatol*. 1992;11(4):302-312.
128. Berth-Jones J. The use of ciclosporin in psoriasis. *J Dermatolog Treat*. 2005;16(5-6):258-277.
129. Salman BN, Vahabi S, Movaghar SE, Mahjour F. Proliferative and inductive effects of Cyclosporine a on gingival fibroblast of child and adult. *Dent Res J (Isfahan)*. 2013;10(1):52-58.
130. US Food and Drug Administration. Sandimmune® Oral Solution (cyclosporine oral solution, USP) [package insert]. Novartis. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050573s041,050574s051,050625s055lbl.pdf; 2015. Accessed January 7, 2020.
131. Lebwohl M, Ellis C, Gottlieb A, et al. Cyclosporine consensus conference: with emphasis on the treatment of psoriasis. *J Am Acad Dermatol*. 1998;39(3):464-475.
132. Blasco Morente G, Tercedor Sanchez J, Garrido Colmenero C, Martinez Garcia E, Molina-Carballo A. Pseudotumor cerebri associated with cyclosporine use in severe atopic dermatitis. *Pediatr Dermatol*. 2015;32(2):237-239.

133. Costa KM, Almeida JB, Felix RH, Silva Junior MF. [Pseudotumor cerebri associated with cyclosporin use following renal transplantation]. *J Bras Nefrol*. 2010;32(1):136-139.
134. Somech R, Doyle J. Pseudotumor cerebri after allogeneic bone marrow transplant associated with cyclosporine a use for graft-versus-host disease prophylaxis. *J Pediatr Hematol Oncol*. 2007;29(1):66-68.
135. Gonzalez Vicent M, Diaz MA, Madero L. "Pseudotumor cerebri" following allogeneic bone marrow transplantation (BMT). *Ann Hematol*. 2001;80(4):236-237.
136. Ghanem ME, El-Baghdadi LA, Badawy AM, Bakr MA, Sobhe MA, Ghoneim MA. Pregnancy outcome after renal allograft transplantation: 15 years experience. *Eur J Obstet Gynecol Reprod Biol*. 2005;121(2):178-181.
137. Cochat P, Decramer S, Robert-Gnansia E, Dubourg L, Audra P. Renal outcome of children exposed to cyclosporine in utero. *Transpl Proc*. 2004;36(2 Suppl):208S-210S.
138. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother*. 2001;35(9):1096-1107.
139. Paul MD, Parfrey PS, Smart M, Gault H. The effect of ethanol on serum cyclosporine A levels in renal transplant recipients. *Am J Kidney Dis*. 1987;10(2):133-135.
140. Colombo D, Cassano N, Altomare G, Giannetti A, Vena GA. Psoriasis relapse evaluation with week-end cyclosporine A treatment: results of a randomized, double-blind, multicenter study. *Ing J Immunopathol Pharmacol*. 2010;23(4):1143-1152.
141. Grekas D, Alivanis P, Kiriazopoulou V, et al. Influenza vaccination on renal transplant patients is safe and serologically effective. *Int J Clin Pharmacol Ther Toxicol*. 1993;31(11):553-556.
142. Soesman NM, Rimmelzwaan GF, Nieuwkoop NJ, et al. Efficacy of influenza vaccination in adult liver transplant recipients. *J Med Virol*. 2000;61(1):85-93.
143. Versluis DJ, Beyer WE, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation*. 1986;42(4):376-379.
144. Powles AV, Hardman CM, Porter WM, Cook T, Hulme B, Fry L. Renal function after 10 years' treatment with cyclosporin for psoriasis. *Br J Dermatol*. 1998;138(3):443-449.
145. Gilbert SC, Emmett M, Menter A, Silverman A, Klintmalm G. Cyclosporine therapy for psoriasis: serum creatinine measurements are an unreliable predictor of decreased renal function. *J Am Acad Dermatol*. 1989;21(3 Pt 1):470-474.
146. Altomare G, Ayala F, Bardazzi F, et al. Consensus on the use of cyclosporine in dermatological practice. Italian Consensus Conference. *G Ital Dermatol Venereol*. 2014;149(5):607-625.
147. Ito T, Furukawa F, Iwatsuki K, et al. Efficacious treatment of psoriasis with low-dose and intermittent cyclosporin microemulsion therapy. *J Dermatol*. 2014;41(5):377-381.
148. Reich K, Mrowietz U, Radtke MA, et al. Drug safety of systemic treatments for psoriasis: results from The German Psoriasis Registry PsoBest. *Arch Dermatol Res*. 2015;307(10):875-883.
149. Vena GA, Galluccio A, Pezza M, Vestita M, Cassano N. Combined treatment with low-dose cyclosporine and calcipotriol/betamethasone dipropionate ointment for moderate-to-severe plaque psoriasis: a randomized controlled open-label study. *J Dermatolog Treat*. 2012;23(4):255-260.
150. van de Kerkhof PC, Cambazard F, Hutchinson PE, et al. The effect of addition of calcipotriol ointment (50 micrograms/g) to acitretin therapy in psoriasis. *Br J Dermatol*. 1998;138(1):84-89.
151. Geiger JM, Czarnetzki BM. Acitretin (Ro 10-1670, etretin): overall evaluation of clinical studies. *Dermatologica*. 1988;176(4):182-190.
152. Goldfarb MT, Ellis CN, Gupta AK, Tincoff T, Hamilton TA, Voorhees JJ. Acitretin improves psoriasis in a dose-dependent fashion. *J Am Acad Dermatol*. 1988;18(4 Pt 1):655-662.
153. Lassus A, Geiger JM, Nyblom M, Virrankoski T, Kaartamaa M, Ingervo L. Treatment of severe psoriasis with etretin (RO 10-1670). *Br J Dermatol*. 1987;117(3):333-341.
154. Ling MR. Acitretin: optimal dosing strategies. *J Am Acad Dermatol*. 1999;41(3 Pt 2):S13-S17.
155. Lowe NJ, Lazarus V, Matt L. Systemic retinoid therapy for psoriasis. *J Am Acad Dermatol*. 1988;19(1 Pt 2):186-191.
156. Murray HE, Anhalt AW, Lessard R, et al. A 12-month treatment of severe psoriasis with acitretin: results of a Canadian open multicenter study. *J Am Acad Dermatol*. 1991;24(4):598-602.
157. Olsen EA, Weed WW, Meyer CJ, Cobo LM. A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. *J Am Acad Dermatol*. 1989;21(4 Pt 1):681-686.
158. Torok L, Kadar L, Geiger JM. Acitretin treatment of severe psoriasis. *Acta Derm Venereol Suppl (Stockh)*. 1989;146:104-106.
159. Gollnick H, Bauer R, Brindley C, et al. Acitretin versus etretinate in psoriasis. Clinical and pharmacokinetic results of a German multicenter study. *J Am Acad Dermatol*. 1988;19(3):458-468.
160. Kragballe K, Jansen CT, Geiger JM, et al. A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre study. *Acta Derm Venereol*. 1989;69(1):35-40.
161. Geiger JM. Efficacy of acitretin in severe psoriasis. *Skin Ther Lett*. 2003;8(4):1-3, 7.
162. Buccheri L, Katchen BR, Karter AJ, Cohen SR. Acitretin therapy is effective for psoriasis associated with human immunodeficiency virus infection. *Arch Dermatol*. 1997;133(6):711-715.
163. Ozawa A, Ohkido M, Haruki Y, et al. Treatments of generalized pustular psoriasis: a multicenter study in Japan. *J Dermatol*. 1999;26(3):141-149.
164. Wolska H, Jablonska S, Bounameaux Y. Etretinate in severe psoriasis. Results of double-blind study and maintenance therapy in pustular psoriasis. *J Am Acad Dermatol*. 1983;9(6):883-889.
165. Sevrain M, Richard MA, Barnetche T, et al. Treatment for palmoplantar pustular psoriasis: systematic literature review, evidence-based recommendations and expert opinion. *J Eur Acad Dermatol Venerol*. 2014;28(Suppl 5):13-16.
166. Ozdemir M, Engin B, Baysal I, Mevlitoglu I. A randomized comparison of acitretin-narrow-band TL-01 phototherapy and acitretin-psoralen plus ultraviolet A for psoriasis. *Acta Derm Venereol*. 2008;88(6):589-593.
167. Yelverton CB, Yentzer BA, Clark A, et al. Home narrowband UV-B phototherapy in combination with low-dose acitretin in patients with moderate to severe psoriasis. *Arch Dermatol*. 2008;144(9):1224-1225.
168. Lebwohl M, Drake L, Menter A, et al. Consensus conference: acitretin in combination with UVB or PUVA in the treatment of psoriasis. *J Am Acad Dermatol*. 2001;45(4):544-553.
169. Lebwohl M. Acitretin in combination with UVB or PUVA. *J Am Acad Dermatol*. 1999;41(3 Pt 2):S22-S24.
170. Lowe NJ, Prystowsky JH, Bourget T, Edelstein J, Nychay S, Armstrong R. Acitretin plus UVB therapy for psoriasis. Comparisons with placebo plus UVB and acitretin alone. *J Am Acad Dermatol*. 1991;24(4):591-594.

171. Ruzicka T, Sommerburg C, Braun-Falco O, et al. Efficiency of acitretin in combination with UV-B in the treatment of severe psoriasis. *Arch Dermatol*. 1990;126(4):482-486.
172. Iest J, Boer J. Combined treatment of psoriasis with acitretin and UVB phototherapy compared with acitretin alone and UVB alone. *Br J Dermatol*. 1989;120(5):665-670.
173. Spuls PI, Rozenblit M, Lebwohl M. Retrospective study of the efficacy of narrowband UVB and acitretin. *J Dermatolog Treat*. 2003;14(Suppl 2):17-20.
174. Lauharanta J, Geiger JM. A double-blind comparison of acitretin and etretinate in combination with bath PUVA in the treatment of extensive psoriasis. *Br J Dermatol*. 1989;121(1):107-112.
175. Saurat JH, Geiger JM, Amblard P, et al. Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. *Dermatologica*. 1988;177(4):218-224.
176. Tanew A, Guggenbichler A, Honigsmann H, Geiger JM, Fritsch P. Photochemotherapy for severe psoriasis without or in combination with acitretin: a randomized, double-blind comparison study. *J Am Acad Dermatol*. 1991;25(4):682-684.
177. Nijsten TE, Stern RS. Oral retinoid use reduces cutaneous squamous cell carcinoma risk in patients with psoriasis treated with psoralen-UVA: a nested cohort study. *J Am Acad Dermatol*. 2003;49(4):644-650.
178. David M, Hodak E, Lowe NJ. Adverse effects of retinoids. *Med Toxicol Adverse Drug Exp*. 1988;3(4):273-288.
179. US Food and Drug Administration. Acitretin (Soriatane) [package insert]. Stiefel Laboratories, Inc. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019821s028lbl.pdf; 2017. Accessed August 26, 2019.
180. Koo J, Nguyen Q, Gambla C. Advances in psoriasis therapy. *Adv Dermatol*. 1997;12:47-72. discussion 73.
181. Yamauchi PSRD, Kormill T, Patnaik R, Lowe NJ. Systematic Retinoids. In: Gottlieb GWaA, ed. *Therapy of Moderate-to-Severe-Psoriasis*. New York: Marcel Dekker, Inc.; 2003:137-150.
182. Malloy MJ, Kane JP. A risk factor for atherosclerosis: triglyceride-rich lipoproteins. *Adv Intern Med*. 2001;47:111-136.
183. Treewittayapoom C, Singvahanont P, Chanprapaph K, Haneke E. The effect of different pulse durations in the treatment of nail psoriasis with 595-nm pulsed dye laser: a randomized, double-blind, intrapatient left-to-right study. *J Am Acad Dermatol*. 2012;66(5):807-812.
184. Roenigk HH Jr, Callen JP, Guzzo CA, et al. Effects of acitretin on the liver. *J Am Acad Dermatol*. 1999;41(4):584-588.
185. van Ditzhuijsen TJ, van Haelst UJ, van Dooren-Greebe RJ, van de Kerkhof PC, Yap SH. Severe hepatotoxic reaction with progression to cirrhosis after use of a novel retinoid (acitretin). *J Hepatol*. 1990;11(2):185-188.
186. DiGiovanna JJ, Sollitto RB, Abangan DL, Steinberg SM, Reynolds JC. Osteoporosis is a toxic effect of long-term etretinate therapy. *Arch Dermatol*. 1995;131(11):1263-1267.
187. Vincent V, Zabraniecki L, Loustau O, et al. Acitretin-induced enthesitis in a patient with psoriatic arthritis. *Joint Bone Spine*. 2005;72(4):326-329.
188. Okada N, Nomura M, Morimoto S, Ogihara T, Yoshikawa K. Bone mineral density of the lumbar spine in psoriatic patients with long term etretinate therapy. *J Dermatol*. 1994;21(5):308-311.
189. Van Dooren-Greebe RJ, Lemmens JA, De Boo T, Hangx NM, Kuijpers AL, Van de Kerkhof PC. Prolonged treatment with oral retinoids in adults: no influence on the frequency and severity of spinal abnormalities. *Br J Dermatol*. 1996;134(1):71-76.
190. Luthi F, Eggel Y, Theumann N. Premature epiphyseal closure in an adolescent treated by retinoids for acne: an unusual cause of anterior knee pain. *Joint Bone Spine*. 2012;79(3):314-316.
191. Vahlquist A. Long-term safety of retinoid therapy. *J Am Acad Dermatol*. 1992;27(6 Pt 2):S29-S33.
192. Elmets CA, Lim HW, Stoff B, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. *J Am Acad Dermatol*. 2019;81(3):775-804.
193. Carpentieri A, Pacello L, De Marco IM, Loiacono A, Picconi O, Loconsole F. Retrospective analysis of the effectiveness and costs of traditional treatments for moderate-to-severe psoriasis: a single-center, Italian study. *J Dermatolog Treat*. 2016;27(5):399-405.
194. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheumatol*. 2019;71(1):5-32.
195. US Food and Drug Administration. XELJANZ® (tofacitinib) [package insert]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s025lbl.pdf; 2019. Accessed January 8, 2020.
196. Vijayakrishnan L, Venkataramanan R, Gulati P. Treating inflammation with the Janus kinase inhibitor CP-690,550. *Trends Pharmacol Sci*. 2011;32(1):25-34.
197. Papp KA, Menter MA, Abe M, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. *Br J Dermatol*. 2015;173(4):949-961.
198. Papp KA, Menter A, Strober B, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol*. 2012;167(3):668-677.
199. Bachelez H, van de Kerkhof PC, Strohal R, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet*. 2015;386(9993):552-561.
200. A One-Year Study To Evaluate The Efficacy And Safety Of CP-690,550 For Patients With Moderate To Severe Chronic Plaque Psoriasis. Pfizer. Available at: https://clinicaltrials.gov/ct2/show/NCT01309737?term=NCT01309737&draw=2&rank=1; 2014. Accessed January 9, 2020.
201. Zand MS. Tofacitinab in renal transplantation. *Transpl Rev (Orlando)*. 2013;27(3):85-89.
202. Vincenti F, Silva HT, Busque S, et al. Evaluation of the effect of tofacitinib exposure on outcomes in kidney transplant patients. *Am J Transpl*. 2015;15(6):1644-1653.
203. Mrowietz U, Reich K, Spellman M. Efficacy, safety, and quality of life effects of a novel oral formulation of dimethyl fumarate in patients with moderate to severe plaque psoriasis: results of a phase 3 study. *J Am Acad Dermatol*. 2006;54(3 Suppl):AB202.
204. Arbiser JL. Fumarate esters as angiogenesis inhibitors: key to action in psoriasis? *J Invest Dermatol*. 2011;131(6):1189-1191.
205. Meissner M, Valesky EM, Kippenberger S, Kaufmann R. Dimethyl fumarate-only an anti-psoriatic medication? *J Dtsch Dermatol Ges*. 2012;10(11):793-801.
206. Atwan A, Ingram JR, Abbott R, et al. Oral fumaric acid esters for psoriasis. *Cochrane Database Syst Rev*. 2015;(8):CD010497.
207. Altmeyer PJ, Matthes U, Pawlak F, et al. Antipsoriatic effect of fumaric acid derivatives. Results of a multicenter

double-blind study in 100 patients. *J Am Acad Dermatol*. 1994;30(6):977-981.
208. Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. *Trends Mol Med*. 2005;11(1):43-48.
209. Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: results and side effects of 2 years of treatment. *J Am Acad Dermatol*. 1992;27(5 Pt 1):769-771.
210. Raschka C, Koch HJ. Longterm treatment of psoriasis using fumaric acid preparations can be associated with severe proximal tubular damage. *Hum Exp Toxicol*. 1999;18(12):738-739.
211. Bomprezzi R. Dimethyl fumarate in the treatment of relapsing-remitting multiple sclerosis: an overview. *Ther Adv Neurol Disord*. 2015;8(1):20-30.
212. Gollnick H, Altmeyer P, Kaufmann R, et al. Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. *Dermatology*. 2002;205(1):46-53.
213. Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. *Br J Dermatol*. 1998;138(3):456-460.
214. Peeters AJ, Dijkmans BA, van der Schroeff JG. Fumaric acid therapy for psoriatic arthritis. A randomized, double-blind, placebo-controlled study. *Br J Rheumatol*. 1992;31(7):502-504.
215. Kimball AB, Gladman D, Gelfand JM, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. *J Am Acad Dermatol*. 2008;58(6):1031-1042.
216. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract*. 2004;17(1):59-67.
217. *Administrative Regulation-Evidence-Based Clinical Practice Guidelines*. American Academy of Dermatology; 2014. Available at: https://server.aad.org/Forms/Policies/Uploads/Members/AR%20-%20Evidence-Based%20Clinical%20Practice%20Guidelines.pdf. Accessed March 27, 2020.

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APPENDIX 1

Method

A multidisciplinary work group of recognized psoriasis experts, consisting of dermatologists (including private practitioners), a rheumatologist, a cardiologist, and representatives from patient advocacy organization, was convened to identify important clinical questions with regards to psoriasis. Work group members completed a

disclosure of interests that was updated and reviewed for potentially relevant conflicts of interest throughout guideline development. If a potential conflict was noted, the work group member recused himself or herself from the discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.

An evidence-based model was used, and evidence was obtained using a search of the PubMed and MEDLINE databases from January 1, 2011, through December 31, 2017, for clinical questions addressed in the previous version of this guideline published in 2008-2011. Searches were limited to publications in the English language. Medical Subject Heading terms/search terms used in various combinations in the literature search included psoriasis (palmoplantar, pustular, guttate, inverse, genital, plaque, scalp, nail) methotrexate, cyclosporine, acitretin, tofacitinib, fumaric acid ester, apremilast, hydroxyurea, mycophenolate mofetil, leflunomide, tacrolimus, thioguanine, and systemic.

After removal of duplicate data, 134 studies were retained for final review based on relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these studies and used by the work group in developing recommendations. The Academy's prior published guidelines on psoriasis were evaluated, as were other current published guidelines on psoriasis.[194,215]

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT) developed by editors of the United States family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*).[216] Evidence was graded using a 3-point scale based on the quality of methodology (eg, randomized control trial, case-control, prospective/retrospective cohort, case series, etc) and the overall focus of the study (ie, diagnosis, treatment/prevention/screening, or prognosis) as follows:

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life)
II. Limited-quality patient-oriented evidence
III. Other evidence, including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes)

Clinical recommendations were developed on the best available evidence tabled in the guideline. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence
C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence

In those situations in which evidence-based data were not available, expert consensus was used to generate our clinical recommendations.

This guideline has been developed in accordance with the American Academy of Dermatology (AAD)/AAD Association Administrative Regulations for Evidence-based Clinical Practice Guidelines (May 2014),[217] which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors. Additionally, this guideline is developed in collaboration with the National Psoriasis Foundation, and as part of the review process; the National Psoriasis Foundation medical board members provided their feedback. This guideline will be considered current for a period of 5 years from the date of publication unless reaffirmed, updated, or retired before that time.