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Drugs for Psoriasis

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Summary

- Topical corticosteroids are generally used for treatment of mild to moderate disease.
- Topical vitamin D analogs or topical tazarotene can be used as alternatives or in addition to topical corticosteroids.
- UV phototherapy can be used for mild to moderate disease that is widespread or has not responded to topical agents.
- Systemic therapy is recommended for patients with moderate to severe disease.
- Methotrexate is effective for treatment of moderate to severe disease.
- Cyclosporine appears to be at least as effective as methotrexate, but use for more than one year is not recommended.
- Acitretin is effective, but it can cause significant mucocutaneous toxicity.
- Apremilast is an expensive oral alternative.
- Biologic agents appear to be the most effective treatment for moderate to severe disease, but they may lose efficacy over time and they are expensive.
- IL-17A antagonists and IL-23 antagonists have been more effective than some TNF inhibitors or the IL-12/23 antagonist ustekinumab.

Mild to moderate psoriasis can be treated with topical drugs or with phototherapy. Patients with moderate to severe disease generally require systemic therapy.

TOPICAL THERAPY

Ointments are generally the most effective topical formulation for treatment of psoriasis. Foams and sprays can be applied to large areas, but the alcohol base used in many of them can cause burning in patients with sensitive skin.

CORTICOSTEROIDS — Topical corticosteroids are widely used for treatment of psoriasis, both alone and in combination with phototherapy or systemic therapy.

Adverse Effects – Local cutaneous adverse effects such as atrophy of the dermis and epidermis, telangiectasias, and irreversible striae can occur when these agents are used for prolonged periods of time or under occlusion, when too much is applied, or when corticosteroid-sensitive areas such as the face and intertriginous regions are treated, but usually not when they are applied to active psoriatic lesions. Superpotent topical corticosteroids, such as clobetasol propionate 0.05%, can cause adrenal suppression when applied to large areas, but clinically significant adrenal insufficiency is rare.

Pregnancy and Lactation – Mild-to-moderate potency topical corticosteroids appear to be safe for use during pregnancy and in women who are breastfeeding.[1]

CALCIPOTRIENE — The synthetic vitamin D analog calcipotriene (*Dovonex*, and others) is about as effective as a medium-potency corticosteroid for topical treatment of plaque psoriasis. UVA exposure can inactivate calcipotriene.[2]

Adverse Effects – Calcipotriene is generally well tolerated, but burning and itching can occur. Hypercalcemia has been reported rarely.

Pregnancy and Lactation – There are no adequate studies on the use of calcipotriene in pregnant women. Skeletal abnormalities have occurred in the offspring of animals given oral calcipotriene. There are no data on the presence of calcipotriene in human breast milk after topical application or its effects on the breastfed infant or milk production.

Calcipotriene/Betamethasone Dipropionate – This combination (*Taclonex,* and others) is more effective than either component alone for treating plaque psoriasis and has been well tolerated.[3]

Table 1. Some Topical Nonsteroidal Drugs for Psoriasis[1]

Drug	Some Formulations	Cost[2]
Calcipotriene 0.005%[3] –		
generic	60, 120 g ointment, cream; 60 mL soln	$297.60
Dovonex (Leo)	60, 120 g cream	732.10
Sorilux (Mayne)	60, 100 g foam	770.70
Calcipotriene/betamethasone dipropionate 0.005%/0.064%[4,5] –		
generic	60, 100 g ointment	644.30
Taclonex (Leo)	60, 100 g ointment; 60, 120 g susp	1037.00
Enstilar (Leo)	60 g foam	1050.30
Calcitriol 3 mcg/g[6] –		
Vectical (Galderma)	100 g ointment	908.60
Tazarotene 0.05% and 0.1%[7] –		
generic[8]	30, 60, 100 g cream	252.80
Tazorac (Allergan)	30, 60 g cream; 30, 100 g gel	398.50
Tazarotene/halobetasol propionate 0.045%/0.01%[9] –		
Duobrii (Bausch)	100 g lotion	825.00

1. For information about topical corticosteroids, see Comparison Table: Some Topical Corticosteroids. Available at: secure.medicalletter.org/downloads/1520d_table.pdf.
2. Approximate WAC for one tube or bottle of the lowest available strength and size. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2019. Reprinted with permission by First Databank, Inc. All rights reserved. ©2019. www.fdbhealth.com/policies/drug-pricing-policy.
3. Applied twice daily.
4. Applied once daily. Adults should not use more than 100 g of ointment or suspension per week or more than 60 g of foam every 4 days.
5. The ointment and foam can be applied for up to 4 weeks and the topical suspension can be applied for up to 8 weeks.
6. Applied twice daily. Maximum dose 200 g/week.
7. Applied once daily in the evening.
8. Generic is only available in 0.1% strength.
9. Applied once daily. Total dosage should not exceed 50 g/week.

CALCITRIOL — Calcitriol *(Vectical)*, another vitamin D analog, may also be effective for topical treatment of mild to moderate plaque psoriasis in adults.[4]

Adverse Effects – Calcitriol causes less skin irritation than calcipotriene. Skin discomfort, pruritus, and erythema can occur, but are generally mild.

Pregnancy and Lactation – As with calcipotriene, there are no adequate studies on the use of calcitriol in pregnant women. Skeletal abnormalities have been reported in animal studies. There are no data on the presence of calcitriol in human breast milk after topical administration.

TAZAROTENE — The acetylenic retinoid tazarotene (*Tazorac*, and generics) is effective for topical treatment of psoriasis. The therapeutic effect may persist after treatment is stopped; in one 8-week trial, the effect was sustained for at least 4 weeks after treatment was stopped.[5]

Adverse Effects – Erythema, burning, pruritus, peeling, and an increased risk of sunburn can occur with tazarotene. The cream formulation is better tolerated than the gel, but peeling may be more frequent.

Pregnancy and Lactation – Although systemic absorption of tazarotene is minimal after topical application, the drug is tetratogenic and its use is contraindicated during pregnancy. Confirmation that the patient is not pregnant should be obtained before starting treatment. No data are available on the presence of tazarotene in human breast milk or its effects on the breastfed infant or milk production.

Tazarotene/Corticosteroids – Use of tazarotene in combination with a topical corticosteroid may improve its efficacy and tolerability.[6]

CALCINEURIN INHIBITORS — Topical **tacrolimus** (*Protopic*, and generics) and **pimecrolimus** (*Elidel,* and generics) are not FDA-approved for treatment of psoriasis, but they have been shown to be effective for treatment of psoriasis involving the face and intertriginous areas.[7] They can be used as alternatives to topical corticosteroids in such patients.

Adverse Effects – The most common adverse effects of topical calcineurin inhibitors are erythema, burning, and pruritus; they occur less frequently with pimecrolimus. Lymphoma and cutaneous malignancies have been reported rarely in patients who have used topical calcineurin inhibitors; a boxed warning in their labels states that continuous long-term use is not recommended.

Pregnancy and Lactation – There are no adequate studies on the use of topical tacrolimus or pimecrolimus in pregnant women or in women who are breastfeeding. The potential for maternal systemic absorption of these drugs following topical administration is low.[1,8]

PHOTOTHERAPY

UV phototherapy can be used for widespread disease or when psoriasis is unresponsive to topical agents. Narrow-band UVB is safer and more effective than broad-band UVB and has largely replaced it. Oral or topical psoralens combined with UVA radiation (PUVA) is also effective for treating psoriasis, but it can increase the risk of skin cancer. Studies comparing narrow-band UVB with oral or topical PUVA have not shown that either one is consistently more effective than the other for treatment of psoriasis.[9] Excimer laser therapy has been safe and effective for localized disease and is FDA-approved for this indication.[10]

Adverse Effects – Itching, burning, blistering, stinging, dryness, and erythema can occur.

Pregnancy and Lactation – Narrow-band UVB and the excimer laser are considered safe for use during pregnancy.[1] Breastfeeding should be avoided for at least 24 hours after PUVA; UVB phototherapy is preferred for women who are breastfeeding.[8]

SYSTEMIC THERAPY

A variety of drugs, including immunosuppressive agents, retinoids, and biologics, are used for systemic treatment of psoriasis. Their effectiveness is usually measured in clinical trials by a PASI 75 or 90 response (≥75% or ≥90% improvement in Psoriasis Area and Severity Index score). Biologic agents appear to be the most effective, but they are also the most expensive and direct comparisons are limited.[11]

METHOTREXATE — For control of moderate to severe psoriasis refractory to topical therapy, low doses of methotrexate (7.5-25 mg/week), given orally or by SC or IM injection, are often used. In a randomized, double-blind trial of SC methotrexate (17.5-22.5 mg/week) in 120 patients, a PASI 75 reponse was achieved at week 16 in 41% of patients who received methotrexate, compared to 10% of those who received placebo.[12]

Adverse Effects – In low doses, methotrexate is usually well tolerated, but it can cause stomatitis, anorexia, nausea, vomiting, abdominal cramps, fatigue, aminotransferase elevations, and hepatic fibrosis. The GI adverse effects associated with oral methotrexate formulations are less likely to occur with parenteral administration. Hepatotoxicity is the most frequent serious adverse effect; the drug is contraindicated in patients with alcoholism. Methotrexate-induced pneumonitis is rare, but can be fatal. Macrocytic anemia, leukopenia, and thrombocytopenia can occur. Decreased renal function and inadvertent overdosing (daily rather than weekly) are common causes of hematologic toxicity.

Methotrexate is immunosuppressive and should not be used in patients with active infections. In an observational cohort study including 107,707 patients who were new users of systemic drugs for psoriasis, the rate of overall serious infection was higher with methotrexate than with apremilast, etanercept, or ustekinumab, but not different from the rates with acitretin, adalimumab, or infliximab, except for a significant increase in the risk of cellulitis with acitretin.[13]

Drug Interactions – Trimethoprim and other drugs that interfere with folate metabolism may increase bone marrow suppression caused by methotrexate. Proton pump inhibitors (PPIs) and drugs that reduce renal function, particularly NSAIDs, may increase serum concentrations of methotrexate and possibly its toxicity. Concurrent use of methotrexate with alcohol or hepatotoxic drugs, such as acitretin, may increase the risk of hepatotoxicity.

Pregnancy and Lactation – Methotrexate is teratogenic and abortifacient; it is contraindicated for use during pregnancy. After stopping the drug, men should wait a minimum of 3 months and women should probably wait 6 months before attempting to conceive. Methotrexate has been detected in human breast milk; it is contraindicated for use in women who are breastfeeding.

CYCLOSPORINE — Low doses (3-5 mg/kg/day) of cyclosporine (*Neoral*, and others) have been at least as effective as methotrexate for treatment of moderate to severe psoriasis.[14,15]

Adverse Effects – The doses of cyclosporine used for psoriasis have generally been safe, but nephrotoxicity and hypertension can occur; use of the drug for more than one year is not recommended. Cyclosporine can also cause GI disturbances, infection, hirsutism, pruritus, headache, paresthesias, hypertriglyceridemia, and musculoskeletal or joint pain. It can increase the risk of skin malignancies in patients previously treated with PUVA.

Drug Interactions – Use of cyclosporine with other nephrotoxic drugs, such as aminoglycosides, can result in additive nephrotoxic effects. Concurrent use of potassium-sparing diuretics such as spironolactone (*Aldactone*, and generics) with cyclosporine may increase the risk of hyperkalemia. Cyclosporine is a substrate and an inhibitor of CYP3A4 and P-glycoprotein (P-gp); use with CYP3A4 and/or P-gp inhibitors may increase its toxicity and use with inducers may decrease its effectiveness.[16]

Pregnancy and Lactation – Cyclosporine appears to be relatively safe for use during pregnancy, but it has been associated with low birth weight and prematurity.[1] Cyclosporine is present in human breast milk and detectable levels have been reported in breastfed infants whose mothers were taking the drug.

ACITRETIN — Use of the oral retinoid acitretin (*Soriatane*, and generics) in doses of 25-50 mg/day can reduce the area and severity of psoriasis, but it can cause significant mucocutaneous toxicity. Some expert clinicians recommend using lower doses to avoid adverse effects. Acitretin is often used in combination with UVB radiation or with PUVA.[9]

Table 2. Some Systemic Drugs for Psoriasis

Drug	Usual Adult Dosage[1]	Cost[2]
Retinoid		
Acitretin – generic	10-50 mg PO once/day[3]	$1778.40
Soriatane (Stiefel)		3954.10
Phosphodiesterase 4 (PDE4) Inhibitor		
Apremilast – *Otezla* (Celgene)	30 mg PO bid[4]	10,194.00
Immunosuppressants		
Cyclosporine – generic	2.5-5 mg/kg/day PO in 2 divided doses	1416.20
Neoral (Novartis)		1536.00
Gengraf (Abbvie)		1253.30
Methotrexate, oral – generic	7.5-25 mg/week PO in a single dose or in 3 divided doses over 36 hours	86.30
Methotrexate, injectable – generic	10-25 mg SC or IM once/week	17.50
Otrexup[5] (Antares)	10-25 mg SC once/week	1949.40
Rasuvo[5] (Medac)	10-25 mg SC once/week	1479.00
TNF Inhibitors		
Adalimumab – *Humira*[6,7] (Abbvie)	80 mg SC at week 0, 40 mg at week 1, then 40 mg q2 weeks[8]	15,522.30
Certolizumab pegol – *Cimzia* (UCB)	400 mg SC q2 weeks[9]	25,964.60
Etanercept – *Enbrel*[10] (Amgen)	50 mg SC twice/week x 12 weeks, then once/week	15,522.20
Infliximab – *Remicade* (Janssen)	5 mg/kg IV at weeks 0, 2, and 6, then q8 weeks[11]	9342.60[12]
Infliximab-abda – *Renflexis*[13] (Merck)		5843.10[12]
Infliximab-dyyb – *Inflectra*[13] (Pfizer)		7570.20[12]
IL-12/23 Antagonist		
Ustekinumab – *Stelara* (Janssen)	45 mg or 90 mg[14] SC at weeks 0 and 4, then q12 weeks	11,002.30
IL-17A Antagonists[15]		
Brodalumab[16] – *Siliq* (Bausch Health)	210 mg SC at weeks 0, 1, and 2, then q2 weeks	10,500.00
Ixekizumab – *Taltz* (Lilly)	160 mg SC at week 0, then 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg q4 weeks	16,104.00
Secukinumab – *Cosentyx* (Novartis)	300 mg[17] SC at weeks 0, 1, 2, 3, and 4, then q4 weeks	15,534.00[18]
IL-23 Antagonists		
Guselkumab – *Tremfya* (Janssen)	100 mg SC at weeks 0 and 4, then q8 weeks	21,718.90[12]
Risankizumab-rzaa – *Skyrizi* (Abbvie)	150 mg SC at weeks 0 and 4, then q12 weeks	14,750.00
Tildrakizumab-asmn – *Ilumya* (Sun)	100 mg SC at weeks 0 and 4, then q12 weeks[19]	13,256.00

1. Dosage adjustment may be needed for renal or hepatic impairment.
2. Approximate WAC for 3 months' treatment at the lowest usual adult maintenance dosage (cost of starting doses are not included). Cyclosporine and infliximab costs calculated for a patient weighing 80 kg. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. June 5, 2019. Reprinted with permission by First Databank, Inc. All rights reserved. ©2019. www.fdbhealth.com/policies/drug-pricing-policy.
3. Some expert clinicians recommend not exceeding 25 mg/day to avoid adverse effects.
4. The recommended starting dose is 10 mg, which should be titrated over 5 days to 30 mg to reduce the risk of GI adverse effects. Following the titration, the maintenance dosage is 30 mg bid, which should be reduced to 30 mg once/day in patients with severe renal impairment (CrCl <30 mL/min).
5. Available as single-dose auto-injectors.
6. Three biosimilars, adalimumab-atto *(Amjevita)*, adalimumab-adbm *(Cyltezo)*, and adalimumab-adaz *(Hyrimoz)*, are FDA-approved, but not yet available.
7. *Humira Citrate-free* does not contain citrate buffers, which have been associated with injection-site pain (P Nash et al. Rheumatol Ther 2016; 3:257). Other differences compared to original *Humira* include a smaller needle and smaller injection volume.
8. Some patients may require a dose of 40 mg per week for adequate disease control.
9. An alternative regimen for patients weighing ≤90 kg is 400 mg SC at weeks 0, 2, and 4, then 200 mg q2 weeks.
10. Two biosimilars, etanercept-szzs *(Erelzi) and* etanercept-ykro *(Eticovo)*, have been approved by the FDA, but are not yet available.
11. Some patients may require more frequent dosing (every 4 or 6 weeks) and/or a higher dose (10 mg/kg) for adequate disease control.
12. Cost based on two 400-mg doses for infliximab and two 100-mg doses for guselkumab.
13. Biosimilar of infliximab.
14. Dose is 45 mg for patients weighing ≤100 kg and 90 mg for those weighing >100 kg.
15. Brodalumab targets the IL-17A receptor. Ixekizumab and secukinumab target IL-17A.
16. Brodalumab is only available through a REMS program because suicidal ideation and behavior, including completed suicides, have occurred in patients treated with the drug.
17. For some patients, 150 mg may be sufficient.
18. A carton containing a 300-mg dose (two 150 mg/mL pens or syringes) costs the same as a carton containing a 150-mg dose (one 150 mg/mL pen or syringe).
19. The labeling recommends that tildrakizumab be administered by a healthcare professional.

Adverse Effects – Like other oral retinoids, acitretin can cause dose-related cheilitis, hair loss, dry skin, and desquamation. Increases in aminotransferase levels occur in about one-third of patients; levels usually return to normal even when treatment is continued, but symptomatic retinoid hepatitis can occur and rarely progresses to cirrhosis. Decreases in HDL cholesterol, hypertriglyceridemia, skeletal hyperostosis, conjunctivitis, corneal erosions and opacities, iritis, and decreased visual acuity can also occur.

Drug Interactions – Concurrent use of alcohol and acitretin can lead to formation of etretinate, a teratogenic retinoid that has a longer elimination half-life

than acitretin; women of childbearing potential should not consume alcohol while taking acitretin and for 2 months after stopping the drug. Acitretin decreases the efficacy of oral progestin-only contraceptives (mini-pills); these contraceptives are not recommended for use in women taking acitretin. Concurrent use of acitretin and methotrexate can increase the risk of hepatotoxicity and is contraindicated. Concurrent use of acitretin and tetracyclines can increase intracranial pressure and the risk of pseudotumor cerebri and is contraindicated. Coadministration of acitretin and supplements containing vitamin A can increase the risk of vitamin A toxicity.

Pregnancy and Lactation – Acitretin is a long-lasting teratogen; patients should not become pregnant or donate blood while taking the drug and for at least 3 years after stopping it. Acitretin is secreted into human breast milk and should not be used in women who are breastfeeding.

APREMILAST — The phosphodiesterase 4 inhibitor apremilast *(Otezla)* is FDA-approved for oral treatment of moderate to severe plaque psoriasis in adults. In 2 randomized, double-blind trials in a total of 1257 patients, significantly more patients achieved a PASI 75 response after 16 weeks with apremilast than with placebo (33% and 29% vs 5% and 6%).[17,18] In an extension study, 45.9% of patients who continued taking apremilast maintained a response after 2 years of treatment.[19]

Adverse Effects – The most common adverse effects of apremilast in clinical trials were diarrhea, nausea, upper respiratory infection, and headache. These effects occurred most frequently during the first 2 weeks of treatment and tended to resolve with continued use of the drug; initial titration of the dose can improve tolerability. Apremilast can increase the risk of depression. Loss of 5-10% of body weight has been reported.

Drug Interactions – Apremilast is metabolized primarily by CYP3A4; concomitant use of apremilast with strong CYP enzyme inducers such as rifampin or carbamazepine can reduce the efficacy of apremilast and is not recommended.[16]

Pregnancy and Lactation – There are no adequate studies of apremilast use in pregnant women. Spontaneous abortions, skeletal abnormalities, dystocia, and reduced birth weights have been reported in animals given apremilast at doses higher than the recommended human dose. Apremilast has been detected in the milk of lactating mice. There are no data on the presence of apremilast in human breast milk or its effects on the breastfed infant or milk production.

BIOLOGIC AGENTS

Updated guidelines for treatment of psoriasis with biologic agents have recently been published.[20] Biologic agents appear to be the most effective treatment for moderate to severe psoriasis, but they may lose efficacy over time and data from head-to-head trials with careful dosage adjustments are limited.[11,21] In patients who have an inadequate response to monotherapy, combining a biologic agent with phototherapy or traditional systemic therapy may improve outcomes, but data are limited and the long-term safety of such combinations is unknown. Switching from one biologic agent to another when the response to the first one is inadequate has been effective in some patients.

TNF INHIBITORS — Four TNF inhibitors, **etanercept** (*Enbrel*, and biosimilars), **infliximab** (*Remicade*, and biosimilars), **adalimumab** (*Humira*, and biosimilars), and **certolizumab pegol** *(Cimzia)*, are FDA-approved for treatment of moderate to severe plaque psoriasis. In one review of randomized, double-blind trials comparing their efficacy for this indication, PASI 75 response rates with infliximab, adalimumab, and etanercept within a 12-week period were 78.6%, 70.5%, and 48.1%, respectively.[22] In two randomized trials, PASI 75 response rates with certolizumab pegol were 66.5% and 81.4% compared to 6.5% and 11.6% with placebo.[23] Use of methotrexate in combination with TNF inhibitors may improve efficacy and reduce the risk of anti-drug antibody formation.[20]

Adverse Effects – Serious infections, including bacterial infections (particularly pneumonia and cellulitis), histoplasmosis, and reactivation of hepatitis B virus and tuberculosis (TB), have been reported with all of the TNF inhibitors, particularly during the first 2-7 months of treatment.[24] These drugs should not be given to patients with active localized or chronic infections. Patients should be screened for TB before starting anti-TNF therapy and annually thereafter. Lymphoma and other malignancies have been reported in patients with rheumatoid arthritis receiving a TNF inhibitor, but a causal relationship has not been established. TNF inhibitors generally should not be used in patients with a recent malignancy. Exacerbations and new onset of heart failure, pancytopenia, and demyelinating disorders such as multiple sclerosis have been

reported.[25] Anti-TNF drugs have been associated with development of auto-antibodies and induction of a lupus-like syndrome. A review of clinical studies found that anti-drug antibodies reduced the efficacy of infliximab and adalimumab, but not of etanercept.[26]

IL-12/23 ANTAGONIST — Ustekinumab *(Stelara)*, a human monoclonal antibody directed against the p40 subunit shared by interleukin (IL)-12 and -23 cytokines, is FDA-approved for treatment of moderate to severe plaque psoriasis.[27] In a randomized, double-blind trial, PASI 75 responses occurred in 66.7% of patients who received ustekinumab 45 mg and in 75.7% of those who received ustekinumab 90 mg, compared to 3.7% who received placebo.[28] In another randomized trial, ustekinumab was more effective than etanercept (PASI 75 response rates with ustekinumab 45 mg and 90 mg were 67.5% and 73.8%, respectively, vs 56.8% with etanercept).[29]

Adverse Effects – The most common adverse effects of ustekinumab reported during clinical trials in patients with psoriasis were nasopharyngitis, upper respiratory infection, and headache. Ustekinumab has been associated with serious infections (including TB) and malignancies, but long-term safety evaluations have found no increased risk.[30] Patients should be screened for TB before starting treatment. Hypersensitivity reactions (including pneumonitis) and (in one patient) reversible posterior leukoencephalopathy have been reported. Anti-drug antibodies have developed; they may reduce the efficacy of ustekinumab.

IL-17A ANTAGONISTS — Three IL-17A antagonists, **secukinumab** *(Cosentyx)*, **ixekizumab** *(Taltz)*, and **brodalumab** *(Siliq)*, are FDA-approved for treatment of moderate to severe plaque psoriasis in adults. Secukinumab, a human IgG1 antibody, and ixekizumab, a humanized IgG4 antibody, target IL-17A. Brodalumab, a human IgG2 antibody, binds to the IL-17A receptor. There are no head-to-head comparisons of these 3 agents for this indication, but their PASI 75 response rates have been similar: 77-87% with secukinumab; 87-89% with ixekizumab; and 83-86% with brodalumab.[31-33] In clinical trials, secukinumab and ixekizumab were more effective than etanercept and all 3 IL-17A antagonists were more effective than ustekinumab.[34-38]

Adverse Effects – IL-17A antagonists have been associated with an increased risk of mucocutaneous candidiasis.[39,40] More serious infections have also been reported with use of IL-17A antagonists. Patients should be screened for TB before starting treatment. Onset and exacerbations of Crohn's disease and ulcerative colitis have been reported with these agents.

Neutralizing antibodies have developed in patients treated with secukinumab, but do not appear to be associated with loss of efficacy. Formation of neutralizing antibodies associated with loss of effectiveness has been reported with ixekizumab and brodalumab.

The most common adverse effects of **secukinumab** in clinical trials were nasopharyngitis, diarrhea, and upper respiratory infection. The most common adverse effects of **ixekizumab** were nasopharyngitis, upper respiratory infection, and injection-site reactions, which occurred in 10-15% of patients. Common adverse effects of **brodalumab** included arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection-site reactions, influenza, neutropenia, and tinea infections. Suicidal ideation and behavior, including four completed suicides, occurred during clinical trials of brodalumab in patients with plaque psoriasis. Because of this risk, brodalumab is only available through a Risk Evaluation Mitigation Strategy (REMS) program. No association between use of ixekizumab or secukinumab and suicidal behavior has been reported to date.[41]

IL-23 ANTAGONISTS — Guselkumab *(Tremfya)*, a human IgG1 antibody, **tildrakizumab** *(Ilumya)* and **risankizumab** *(Skyrizi)*, both humanized monoclonal IgG1 antibodies, are FDA-approved for treatment of moderate to severe plaque psoriasis in adults. They selectively bind to the p19 subunit of IL-23, inhibiting it from binding to the IL-23 receptor and preventing downstream release of pro-inflammatory cytokines (such as IL-17A) and chemokines.[42-44]

Guselkumab has been more effective than placebo, ustekinumab, or adalimumab in randomized, double-blind trials. In one trial, after 16 weeks, significantly more patients had achieved a PASI 90 response with guselkumab (73.3%) than with adalimumab (49.7%) or placebo (2.9%).[45] In another trial in patients whose psoriasis had not adequately responded to ustekinumab, switching to guselkumab was significantly more effective than continuing ustekinumab.[46] Guselkumab has also been effective in patients who did not respond to adalimumab.[47]

In 2 double-blind, randomized trials, significantly more patients achieved a PASI 75 response after 12 weeks with **tildrakizumab** than with placebo (64% and 61% vs 6%) or etanercept (61% vs 48%).[48]

In clinical trials, **risankizumab** has been more effective than placebo, ustekinumab, or adalimumab. In 2 randomized, double-blind trials, significantly more patients achieved a PASI 90 response after 16 weeks with risankizumab (75.3% and 74.8%) than with placebo (4.9% and 2%) or ustekinumab (42.0% and 47.5%).[49] In another trial, significantly more patients achieved a PASI 90 response after 16 weeks with risankizumab than with adalimumab (72.4% vs 47.4%). In patients who initially had an intermediate response (PASI 50-<90) to adalimumab after 16 weeks, switching to risankizumab was more effective than continuing adalimumab.[50]

Adverse Effects – The most common adverse effects of **guselkumab** have included tinea infections, herpes simplex infections, and gastroenteritis. Serious hypersensitivity reactions and serious infections, including deep fungal infections, have occurred in patients treated with the drug. Antibody formation has been reported with use of guselkumab; whether it reduces the effectiveness of the drug is unknown.

In clinical trials, the most common adverse effects of **tildrakizumab** were upper respiratory infection, injection-site reactions, and diarrhea. Hypersensitivity reactions (angioedema and urticaria) occurred rarely. Neutralizing antibodies developed in 2.5% of patients treated with tildrakizumab for up to 64 weeks; whether they reduce the drug's effectiveness is unknown.

The most common adverse effects reported with **risankizumab** were upper respiratory infection, fatigue, injection-site reactions, and tinea infections. By week 52, neutralizing antibodies had developed in 14% of patients treated with risankizumab; in some patients, high antibody titers were associated with low drug concentrations and reduced clinical response.

Patients should be screened for TB before starting an IL-23 antagonist.

DRUG INTERACTIONS — Patients being treated with **biologic agents** should not receive live vaccines. Proinflammatory cytokines can alter the formation of CYP enzymes. Starting treatment with an inhibitor of TNF, IL-17A, IL-12, or IL-23 may normalize CYP enzyme formation and could alter metabolism of CYP substrates; dosage adjustments of substrates with narrow therapeutic indices such as warfarin or cyclosporine may be needed. **Ustekinumab** may decrease the protective effect of allergen immunotherapy.

PREGNANCY AND LACTATION — TNF inhibitors are generally considered safe for use during pregnancy. Placental transfer of anti-TNF antibodies is higher in the late second trimester and in the third trimester, especially with infliximab and adalimumab. Placental transfer is minimal with certolizumab pegol. Human IgG antibodies cross the placenta (especially in the third trimester). There are no adequate data on the use of **ustekinumab**, **IL-17A antagonists**, or **IL-23 antagonists** in pregnant women.[1]

TNF inhibitors are generally considered safe for use in women who are breastfeeding; serum concentrations of TNF inhibitors in human breast milk are expected to be minimal.[8] **Ustekinumab** has been detected in the milk of lactating monkeys. No data are available on the presence of **ustekinumab**, **IL-17A antagonists**, or **IL-23 antagonists** in human breast milk or their effects on the breastfed infant or milk production. ■

Additional Content Available Online

Comparison Table: Some Topical Corticosteroids
http://medicalletter.org/TML-article-1520d
Expanded Table: Some Drugs for Psoriasis
http://medicalletter.org/TML-article-1574b

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In addition to the Principal Faculty above, the following have also contributed to this activity:
Jeffrey Weinberg, M.D., has disclosed that he has received clinical research grants from, participated in speakers' bureaus for, and/or served on advisory boards for Abbvie, Amgen, Boehringer Ingelheim, Celgene, Galderma, Leo, Lilly, Novartis, and Valeant.

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Upon completion of this activity, the participant will be able to:

1. Explain the current approach to the management of plaque psoriasis.
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Issue 1574 Questions

(Correspond to questions #111-120 in Comprehensive Exam #80, available July 2019)

Drugs for Psoriasis

1. For treatment of plaque psoriasis, the most effective topical formulation is generally:
   a. an ointment
   b. a cream
   c. a foam
   d. a spray

2. For topical treatment of plaque psoriasis, calcipotriene is about as effective as a:
   a. low-potency corticosteroid
   b. medium-potency corticosteroid
   c. high-potency corticosteroid
   d. super-high-potency corticosteroid

3. Tazarotene:
   a. has a therapeutic effect that may persist after treatment is stopped
   b. may be better tolerated when used with a topical corticosteroid
   c. is contraindicated for use during pregnancy
   d. all of the above

4. In one clinical trial, a PASI 75 response was achieved with SC methotrexate after 16 weeks in about what percentage of patients?
   a. 40%
   b. 60%
   c. 75%
   d. 90%

5. Cyclosporine:
   a. is at least as effective as methotrexate for treatment of moderate to severe plaque psoriasis
   b. can cause nephrotoxicity
   c. is considered relatively safe for use during pregnancy
   d. all of the above

6. In clinical trials, a PASI 75 response was achieved with apremilast after 16 weeks in about what percentage of patients?
   a. 30%
   b. 45%
   c. 60%
   d. 75%

7. Use of methotrexate with a TNF inhibitor:
   a. significantly decreases the risk of infection
   b. increases the risk of developing Crohn's disease
   c. may decrease the risk of anti-drug antibody formation
   d. all of the above

8. In clinical trials, the IL-17A antagonists were shown to be more effective for treatment of moderate to severe plaque psoriasis than:
   a. phototherapy
   b. apremilast
   c. guselkumab
   d. ustekinumab

9. Which of the following biologic agents has been associated with an increased risk of suicidal ideation and behavior?
   a. adalimumab
   b. brodalumab
   c. guselkumab
   d. ustekinumab

10. Which of the following statements about the use of biologic agents during pregnancy is true?
    a. TNF inhibitors are generally considered safe
    b. placental transfer of anti-TNF antibodies is highest during the first trimester
    c. human IgG antibodies do not cross the placenta
    d. all of the above

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