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September 2003 "Treatment, Management & Prevention of Psoriasis" 707-000-03-009-H01

THIS MONTH
"Psoriasis Management"

NOVEMBER 30, 2003 IS DEADLINE FOR US TO RECEIVE QUIZZES FOR THIS YEAR.

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Psoriasis is a common, yet complex disease. Our goal in this lesson is to discuss common therapeutic options. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings. The program ID # for this lesson is 707-000-03-009-H01. Pharmacists completing this lesson by September 30, 2006 may receive full credit.

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

Complete List of 2003 Topics: See Page 10.

If you have any comments, suggestions or questions, contact us at the above address, or call toll free 1-800-323-4305. (In Alaska and Hawaii phone 1-847-945-8050). **Please write your ID Number (the number that is on the top of the mailing label) in the indicated space on the quiz page** (for continuous participants only).

The objectives of this lesson are such that upon completion the participant will be able to:

1. Discuss the signs & symptoms associated with different types of psoriasis.
2. List factors to consider for patient education, particularly for elderly & pediatric patients.
3. Define the goal of psoriasis treatment, & outline the concepts presented in a general treatment algorithm.
4. Compare & contrast the benefits & risks of topical psoriasis therapies, phototherapy, & systemic psoriasis therapies.
5. Discuss the advantages & disadvantages of the topical psoriasis therapies.
6. Discuss the advantages & disadvantages of the systemic psoriasis therapies.
7. Discuss the role of phototherapy in the treatment of psoriasis.

INTRODUCTION AND BACKGROUND

Psoriasis is a chronic skin disease that affects up to 3% of Americans (1-4,7-9). Approximately 7 million patients in the USA have psoriasis, with over 1.5 million patients seeking physician treatment (4,5). It is estimated that $3 billion are spent annually for psoriasis management.

The onset may occur at any time; however, the incidence has 2 peaks (4,7). The first occurs at 16-22 years, and is referred to as early-onset psoriasis. The second occurs at 57-60 years, and is referred to as late-onset psoriasis. The highest incidence occurs at 22.5 years. Psoriasis is more prevalent in patients of European ancestry than in Asians or Blacks, and the lowest risk group is indigenous peoples of the Americas. The lifetime risk of inheriting psoriasis, if no parent has it, is 4% (8); with one parent 28% and both parents, 65%.

The etiology is unknown (4-9). The general consensus is that both a genetic predisposition to psoriasis and environmental triggering factors are both needed to precipitate the disease. (8). There is an autoimmune component, wherein specialized T cells are active in the onset and propagation of symptoms (5). These specialized T cells exit skin blood vessels in response to an auto-antigen in the skin (6).

Psoriasis is a papulosquamous skin disease characterized by keratinocyte hyperproliferation and inflammation (1-9). Epidermal cells mature and slough-off in 3 to 4 days in psoriatic skin, versus about 27 days in normal skin. The accelerated epidermal maturation creates a stratum corneum that is not fully keratinized. The epidermal cells build up abnormally to form papules, which grow and unite to create well-demarcated erythematous plaques that are covered with scales having an epidermal thickness up to 5 times greater than a normal stratum corneum. The plaques vary in thickness, size, shape, and pattern. Often lesions on one side of the body will mirror those on the opposite side. If scales are removed, light pink skin is noted. A pinpoint of bleeding may occur with removal, which is referred to as an Auspitz sign. Lesions usually are asymptomatic, but 20% of patients note pruritus or burning during acute flares. The disease typically cycles through periods of remission and acute flare-ups.

Psoriatic lesions often are symmetrical, and most commonly occur on the elbows, knees, lower back, buttocks, scalp, groin or genitalia, and axilla (1-9). Lesions in intertriginous areas often appear glazed, and are not scaly or elevated. Psoriasis of the hands and feet has less erythema, but is well demarcated with white scales. Scalp psoriasis can range from dispersed redness and scaling to thick scaling plaques, and may cause temporary hair loss.

There are several classifications of psoriasis, and each responds differently to therapy (1-9).

Plaque psoriasis is the most common type, and occurs in about 90% of patients (4-9). The raised white scaling plaques described above characterize it.

Guttate psoriasis is the second most common type in pediatric patients. It is characterized by small, red, teardrop-shaped papules dispersed generally over the trunk, extremities, and occasionally the face. Guttate often follows a systemic infection, particularly beta-hemolytic streptococcal pharyngitis. Its onset is quick, and it usually responds to therapy faster than plaque psoriasis.

Pustular psoriasis is a severe form that is either localized to the palms and soles, or generalized over large areas (4,7,8). Pus-like blisters containing noninfectious fluid characterize it. The generalized form is most severe, and typically occurs in middle-aged or elderly patients. Hospitalization may be required because systemic symptoms can be life threatening, and include fever, malaise, tachycardia, shortness of breath, infection, edema, dehydration, and electrolyte shifts. Pustular psoriasis has a high rate of relapse, and most often occurs in patients with a previous history of psoriasis.

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Erythrodermic psoriasis is a severe form often occurring in patients with an existing dermatological condition. Over 90% of the body is affected by exfoliation of fine scales creating large protein losses, problems in temperature regulation, and fluid and electrolyte shifts. It must be treated aggressively, and often requires inpatient management. A number of triggers cause erythrodermic psoriasis. Pharmacological triggers include systemic corticosteroids, overuse of topical corticosteroids, and drug reactions to antimalarials, gold therapy, and lithium.

Inverse psoriasis most commonly occurs in elderly patients. Lesions are glossy, well-defined, erythematous patches in major skin folds, which must be distinguished from other dermatoses, such as candidiasis or dermatophytosis.

Diaper psoriasis is thought to be increasing in frequency due to the use of topical steroids to treat diaper rash, and the withdrawal effects associated with topical steroids. About 17% of infants that exhibit diaper psoriasis develop classic psoriasis.

Extracutaneous manifestations occur in nails and as psoriatic arthritis. Nail psoriasis often alters the nail plate to varying degrees, and leaves nails open to infection. It may be associated with arthritis of the terminal phalangeal joint.

The core of psoriasis prevention and control is patient education (1-8). Being aware of, and avoiding psoriasis triggers is important. Often psoriasis is first noticed after trauma to the skin, known as the Koebner phenomenon. Koebner phenomenon can also occur after sunburn or chemical skin trauma. Cold weather with prolonged periods of low humidity is associated with a higher prevalence of disease, while hot weather and sunlight are reported to be beneficial to psoriasis patients. Systemic or topical bacterial, viral, and fungal infections can aggravate psoriasis. HIV and streptococcal infections are particularly suspect for triggering the onset or worsening of psoriasis. Stress may cause psoriasis exacerbations. Controversy exists regarding the impact of smoking and alcoholism. The incidence of psoriasis is higher than in the general population for patients who smoke, are obese, have chronic tonsillitis, heart failure, hypertension, and type 2 diabetes mellitus. Finally, antimalarials, beta-blockers, quinidine, indomethacin, systemic corticosteroid withdrawal, interferon-alpha, and lithium medications are reported to trigger the disease.

Elderly patients often take antihypertensive medications, which can aggravate psoriasis (7). In addition to drugs listed above, ACE inhibitors and NSAIDs can cause psoriasis flares in elderly patients. Elderly patients have a higher incidence of the more severe forms of psoriasis than younger patients. Many individuals have existing complicated medication regimens, which create pharmacological challenges if systemic anti-psoriatic drugs are needed. If topical medications are indicated, medical professionals must confirm that patients are able to apply the agents as required, or be referred to a day center for assistance.

Patients with childhood psoriasis must receive prompt care to avoid problems in future development and disease complications (8). Parents must understand the clinical aspects of the disease, Koebner phenomenon, that periods of remission are not indicative of cure, the rationale for prescribed treatment, and the therapeutic adverse effects.

The goals of psoriasis therapy are to control its presentation, completely clear lesions at critical times in a patient's social life, and to induce its remission. There is no cure, and patients suffer from chronic recurrent flares and remissions for their lifetime (1-8). Psoriasis is treated primarily as an immunological disorder that leads to a secondary epidermal hyperproliferation (9). Therapies are focused on suppressing the immunity response, exfoliating plaques, and restoring skin function.

GENERAL TREATMENT ALGORITHM

A 3-step treatment approach has been suggested for psoriasis (4). For mild to moderate psoriasis, Step-1 recommends topical therapy with either coal tar or topical corticosteroids. Second line therapies include anthralin, calcipotriene, tazarotene, or intra-lesional injections of corticosteroids. Supplemental therapies to Step-1 agents include moisturizers, keratolytics, and exposure to sunlight.

If symptoms persist, Step-2 therapy is started with PUVA (psoralen plus ultraviolet A) therapy. A Step-1 therapy may be added to PUVA if necessary. Psoriasis conditions that are severe and do not respond to Step-1 or Step-2 treatment require aggressive therapy outlined in Step-3. Step-3 agents are rotated in 12 to 24 month cycles, and include: acitretin, methotrexate, and cyclosporin.

Psoriasis therapy differs from patient to patient as clinicians gauge the patient response (4). When combination therapy is required, drugs with different mechanisms of action must be used to compliment each other. Adverse effects must be monitored, especially for drugs having immunosuppressant actions. The following text outlines important considerations for specific drugs used in psoriasis treatment.

TOPICAL THERAPIES

(NOTE: For complete dispensing information for the specific therapies discussed, please refer to Reference #3).

Topical therapies are the safest approach to psoriasis treatment. They often are effective for treating patients with lesions covering less than 20% of their body.

Dithranol (Anthralin) has been used since the mid 1800's in India and Brazil (4). It is a derivative of chrysarobin, which comes from the Brazilian tree *Andira araroba*. It is considered one of the safest therapies because it has no systemic side effects. Its mechanism is under study, and is believed to slow cellular proliferation, inhibit epidermal growth enzymes, modify the activity of numerous skin chemical messengers, reduce inflammation, and decrease epidermal growth factor binding. Dithranol is very effective for scalp psoriasis. It should not be used in sensitive areas such as the face or genitalia, and is not recommended for inverse psoriasis therapy.

Despite good efficacy and low adverse effects, skin, hair, nail and clothing staining to a brown/purplish color have limited dithranol acceptance in the U.S. (4, 7-9).

Topical Corticosteroids stop epidermal growth by inhibiting DNA synthesis and mitotic activity (4,7,9,10). They have anti-inflammatory and anti-pruritic effects that result from inhibiting phospholipase A_2. They also cause vasoconstriction. The outcome from corticosteroid therapy is flatter, less inflamed psoriasis plaques. The benefits are temporary, since topical steroids rarely induce psoriasis remission, and are associated with tachyphylaxis. Most sources agree that corticosteroids are best when used as adjunctive therapy. Regimens typically have an induction phase where the drug is applied twice daily for up to 4 weeks, followed by applications 3 times weekly for 12 hour intervals to maintain control or clear the lesions. Outcomes are variable.

Low potency corticosteroids are best for treating the delicate skin areas of the face, genitals, and flexures (9). Mid-potency products are used to treat lesions on the torso and extremities. High potency steroids are often needed to achieve therapeutic benefits for resistant lesions, and for those on the palms and soles. Ointment products work better for more severe lesions. Some rules-of-thumb for topical corticosteroid use include (7):

1. daily use of potent corticosteroids should be limited to a 6 week maximum,
2. potent corticosteroids should only be applied a maximum of once a day,
3. corticosteroid therapy needs to alternate with other topical antipsoriatic drugs,
4. a maximum of 100 grams per month of a moderately potent corticosteroid should be used,
5. patients should be evaluated monthly by a healthcare professional.

High potency steroids used over a period of time also can cause acne, irreversible skin atrophy, capillaries to surface as localized spots or "spider veins," or irreversible epidermal restructuring into layers (called straie) (4,7,9,10). Typically, pain and burning sensations precede skin atrophy. If steroid products are used near the eyes, cataracts may form. Discontinuing use of a high potency steroid can cause psoriasis plaques to flare-up. Topical steroids should not be used if a topical bacterial or fungal infection is present. References 3 and 4 have detailed topical steroid product and dispensing information.

Vitamin D and Vitamin D Analogues. Vitamin D is made in the skin when it is exposed to UVB radiation. It undergoes a number of biochemical modifications to form 1-alpha, 25-dihydroxy-D_3, also called active vitamin D_3 or calcitriol (4). Calcitriol is useful in treating psoriasis because it increases cellular differentiation, inhibits proliferation, and modifies immune system activity. Oral preparations have a narrow therapeutic range for safety, but are effective in psoriasis treatment. Topical treatments have been ineffective due to lack of a good drug delivery system. As a result, vitamin D analogues have been used. Hypercalcemia, hypercalciuria, nephrocalcinosis, nephrolithiasis, and lower bone mineral density are the major systemic side effects of vitamin D therapy.

Calcipotriene (also called calcipotriol, or Dovonex®) is a vitamin D_3 analogue that has a 100 to 200 fold reduced effect on systemic calcium and bone metabolism than calcitriol (4). It binds keratinocyte receptors to enhance epidermal shedding, inhibit epidermal growth, and modify immune regulator cells (4,7,9,10,11). Calcipotriene at a strength of 50 mcg/g is applied twice daily for up to 8 weeks, and maintenance therapy may continue up to 1 year. Effects are noticed in about 2 weeks, and a ring of scaling around the lesions may be a sign of initial improvements and clearing. Sustained effects and no lesion rebound are advantages to calcipotriene. Outcomes indicate either complete clearing or significant lesion improvements occurring in more than half of patients. About 20% of patients do not respond to therapy. Calcipotriene was found to be safe for use in pediatric patients; however, serum calcium levels should be monitored to insure hypercalcemia does not occur. It is contraindicated in pregnancy and lactation.

About 15% of patients report localized skin irritation with calcipotriene use, especially if it is used on the face or intertriginous areas (4,7,9,10,11). Systemic absorption occurs, if over 100 grams per week are used. It should not be used in erythrodermic or pustular psoriasis due to an increased risk of systemic absorption and hypercalcemia.

Topical Retinoids. Increased understanding about retinoid receptors and their genes has allowed the development of receptor-selective agents (4). Whereas tretinoin generally has been ineffective as a psoriasis therapy, tazarotene has been studied, and found to be safe and effective in the treatment of mild to moderate plaque psoriasis, including facial and scalp lesions, involving up to 20% of body surface area (4,7,9,10). Tazarotene is quickly metabolized in the skin after application to the active metabolite tazarotenic acid. It selectively binds to retinoid nuclear receptor subtypes b and g to modulate inflammation, hyperproliferation, and abnormal keratinocyte differentiation.

A 0.5% or 0.1% gel is applied sparingly once daily to dry lesions for up to 3 months (4,7,9,10). Initially, erythema may appear, and is considered a sign that the healing process is starting. If itching occurs, a topical steroid should be started to avoid scratching that can cause skin damage and Koebner's phenomenon. Once psoriasis lesions are pink and flat, either maintenance doses of tazarotene or alternate drug maintenance regimens can be initiated. Studies indicate that using a medium to high potency topical steroid in an emollient base in combination with tazarotene helps reduce irritation, does not reduce tazarotene efficacy, minimizes steroid induced skin atrophy, manages skin inflammation, and does not compromise the long-term benefits of tazarotene. The steroid should be slowly discontinued once lesions are pink and flat.

Tazarotene is associated with long-term psoriasis improvements, and does not cause rebound flares when therapy is reduced or stopped. The most notable side effect is local irritation, particularly to healthy skin areas. Topical laboratory studies indicate tazarotene is not mutagenic, carcinogenic, or teratogenic. Tazarotene can be used in children older than 11 years who have resistant lesions (3,8).

Coal tar. Heating organic substances such as wood, shale or coal in the absence of oxygen makes tars (4). The tar that is most effective relative to its irritation potential to treat dermatological conditions is coal tar. Coal tar consists of thousands of hydrocarbons. It is found in a variety of over-the-counter products at a concentration of 2 to 20%. Treatment is initiated between 0.5% and 2%, and gradually increased (7). The 5% preparations are said to be the most effective (4). Although the official mechanism of action is unknown, tar products inhibit epidermal cell mitosis, reduce sebum production, and have anti-inflammatory effects (4,9).

Monotherapy with coal tar is effective for treating mild to moderate psoriasis (4,7,8,9). In combination with UVB radiation, called the Goeckerman regimen, it can successfully clear refractory psoriasis. Coal tar preparations are applied once or twice daily and allowed to dry for about 15 minutes. It is then either removed using mineral oil and bathing, allowed to remain on the lesions throughout the night, or exposed to UVB radiation. Tar shampoo products may be used overnight if needed to treat psoriasis of the scalp. Coal tar products are particularly effective in patients that suffer from severe itching, and for guttate psoriasis (4). It is second line therapy for erythrodermic and pustular psoriasis because skin irritation may cause Koebner's phenomenon.

Coal tar products are irritating (4,7,8,9). They should be applied to well separated lesions of limited size (4). Reported dermatological side effects include photosensitivity, acne eruptions, contact dermatitis, folliculitis, and irritation. Patients do not like using coal tar products due to their messiness, smell, and purple-brown skin staining. They stain clothing and bedding also. The messiest preparations contain crude coal tar. Yet they are

most effective (7). The more esthetic preparations have reduced efficacy. Coal tar products should be avoided on the face or genitalia. The overall toxicity of topical tar products is less than that from anthralin or topical steroids.

Emollients are helpful to most psoriasis patients (4,7-9). They are safe, affordable, and make patients more comfortable. Often they are used to pretreat plaques prior to therapy with topical drugs.

Keratolytic drugs, such as alpha-hydroxy acids or salicylic acid, often leave mild to moderate psoriasis plaques smooth and pink. If applied 2 to 3 times daily, they may enhance the absorption of other topical medications. Some patients may find keratolytic agents irritating. Salicylic acid agents should not be applied extensively over the body, as they can cause salicylism, particularly in children.

SYSTEMIC THERAPIES

(NOTE: For complete dispensing information for the specific therapies discussed, please refer to Reference #3).

Anti-Infectious Therapy (1)**.** The Problem Psoriasis Clinic at the University of Tennessee in Memphis studied about 3000 psoriasis patients that underwent antimicrobial therapy or surgery. Up to 50% of patients treated were almost completely, or completely, cleared of their psoriasis; about 30% of patients were greatly improved; and about 20% of patients did not respond to therapy. The researchers strongly feel that the therapies they recommend are safer, and no more costly than traditional psoriasis treatments, and that the benefit to risk ratio is best for patients who can be controlled or cleared by antibiotics relative to traditional approaches. The specific findings follow.

Ketoconazole 200 to 400 mg per day for 4 months will clear scalp psoriasis. Two percent ketoconazole shampoo or 2.5% selenium sulfide lotion are used to maintain a healthy scalp.

Patients younger than 30 years of age with limb or trunk psoriasis, often are carriers of beta-hemolytic streptococcus. Culturing the skin lesions of these patients was not very helpful; thus, it is believed a circulating microbial antigen may be the cause of many psoriasis outbreaks. Patients identified as carriers should be treated to eliminate their carrier state. Clindamycin 300 mg 4 times daily for 10 days was found to be the most effective treatment. Less effective medications that were evaluated were penicillin plus rifampin, and erythromycin. Over half of patients who failed therapy or relapsed were completely cleared following a tonsillectomy. Tonsillectomy was not beneficial in patients whose infections were related to *Entercoccus fecalis* infections.

Oropharyngeal candidiasis was linked to patients having psoriasis of the hands and feet. Patients testing positive for *oropharyngeal candidiasis* were treated with fluconazole 200 mg daily for 2 to 4 weeks, or nystatin 500,000 units 4 times daily for 1 to 3 months. Dental plates were also tested, and if a positive culture was found, patients were advised to clean their dentures every night using an ultrasonic cleaning device. This regimen greatly improved most patients.

Middle-aged to older patients experiencing sudden flares of scattered lesions should be examined for an undetected urinary tract infection or group-B beta-hemolytic streptococcus infection, and treated according to culture and sensitivity results. Patients with patch psoriasis over the sacrum, or axial psoriatic arthritis often have changes in bowel pathology, sometimes due to diverticulosis. Such patients are improved or cleared after sulfasalazine 500 mg four times a day for 3 months, or metronidazole therapy.

Tacrolimus is a macrolide antibiotic that has potent immunosuppressant activity. It demonstrated significant improvements in psoriasis versus placebo in clinical studies (4). Therapy is started at 0.05 mg/kg/day, and the daily dose may be increased every three weeks as needed by 0.05 mg/kg/day to a maximum of 0.15 mg/kg/day. Tacrolimus should not be used in patients with kidney or liver conditions. Adverse effects include diarrhea, abdominal pain, nausea, paresthesia, tremor, and hypertension.

Systemic Corticosteroids have not been clinically evaluated for the treatment of psoriasis (1). Experience with their use, however, supports the following generalizations: Systemic corticosteroids should not be used in plaque psoriasis because severe, stubborn flare-ups often occur when they are discontinued. They may be helpful in generalized pustular psoriasis or severe psoriatic arthritis, if other therapies have failed. When used, prednisolone, every morning, or every-other-morning, is the preferred treatment.

Methotrexate (MTX) is considered one of the most effective treatments for moderate to severe psoriasis that does not respond to topical therapy, retinoids, or phototherapy (4). It is effective for patients who have severe erythrodermic psoriasis, psoriatic arthritis, pustular psoriasis, and plaque psoriasis affecting more than 20% of skin surfaces. MTX is considered for patients affected by emotional or physical problems, or who cannot afford other therapies. It is contraindicated in patients with kidney or liver conditions, in pregnancy and lactation, patients trying to conceive, alcoholics, patients with severe anemia, leukopenia, thrombocytopenia, active peptic ulcer disease, and with compromised immune function with active infection.

MTX inhibits dyhydrofolate reductase to prevent DNA, RNA and protein synthesis. Hence, epidermal cell division is stopped, and lymphocyte action is reduced (4,7). MTX value is diminished due to its adverse effects, including bone marrow suppression, nausea, diarrhea, and stomatitis. The side effects of anemia and nausea are reduced if folic acid 1 to 5 mg per day is taken on the days when MTX is not taken. Long term MTX use can cause liver fibrosis. Liver toxicity is more progressive with alcohol consumption, and incidence increases in patients who are obese, or have diabetes mellitus. In the past, patients were required to have periodic liver needle biopsies after a cumulative dose of 1.5 grams of MTX. Historical data indicate that this invasive procedure is not necessary for all patients. A treatment algorithm presented by the American College of Rheumatology recommends rigorous prescreening of patients, followed by monitoring liver function tests and albumin levels every 4 to 8 weeks after MTX is started (4). Persistent deviation of these values from normal necessitates a liver biopsy.

MTX dosing for psoriasis is much lower than used in previous years (4,7). A 5mg oral test dose may precede therapy to confirm that the blood count remains stable for 1 week. A popular dosing regimen suggests, for a healthy 70 kg patient, start with a 2.5mg to 5mg oral dose every 12 hours for 3 doses for the first week. The dose can be increased by 2.5 mg per week to a maximum of 30 mg per week; provided lab tests remain normal and adverse effects are tolerable. Most patients respond to weekly doses of 7.5 to 15 mg. Since renal function is decreased in many elderly patients, doses of 2.5 mg per week have been reported to be effective in patients over 80 years old (7).

MTX is best as monotherapy. If it must be combined, calcipotriene or dithranol are the best choices for companion therapies (7,12). Studies evaluating MTX plus calcipotriene indicated that the lower MTX doses were needed to achieve and maintain remission; hence MTX toxicity and side effects were minimized (12). Toxicity is increased if taken concurrently with salicylates, sulfonamides, probenecid, penicillin, phenytoin, barbiturates, NSAIDs, colchicine, trimethoprim-sulfamethoxazole, dipyridamole or furosemide.

Cyclosporin is an immunosuppressant whose action includes inhibition of interleukin-2, interleukin-4 and T-cell production (4,7). In psoriasis patients, it is contraindicated with abnormal renal function, uncontrolled hypertension, and malignancies. Elderly patients are very sensitive to cyclosporin toxicity, thus it often is reserved for those suffering from erythrodermic or severe progressive psoriasis.

Dosing is started at 2.5 to 3mg/kg/day of ideal body weight per day (4,7). If no improvement is noted after 1 month, the daily dose is increased by 1 mg per kg per month to a maximum dose of 5 mg/kg/day of ideal body weight. Remission may take up to 10 weeks, and then the dose is decreased by 0.5 mg per kg every 2 weeks. Most patients relapse within 4 months of ending therapy. Topical agents are started to augment remission. Studies evaluated the use of calcipotriene and cyclosporin, and indicated that the combination was safe and very effective for treating severe psoriasis, and that cyclosporin doses could be reduced by using the combination, decreasing the probability for toxicity (12). Cyclosporin cannot be used with phototherapy, MTX, acitretin, or coal tar. Cyclosporin is very lipophilic. The original formulation (Sandimmune®) has variable bioavailability. A microemulsion formulation (Neoral®) has more consistent bioavailability.

The most significant adverse effects to cyclosporin for psoriasis treatment are nephrotoxicity and hypertension. (3,4,7). Both are dose dependent and develop over time. Patients should be monitored before and throughout therapy for kidney function, liver function, electrolyte abnormalities, uric acid levels, and lipid levels. General guidelines suggest (7):

1. a complete examination precede therapy,
2. a thorough pre-treatment screening of drug interactions,
3. cyclosporin therapy should be limited to 12 weeks,

4. baseline serum creatinine levels should be made by averaging 3 pre-treatment measurements, and therapy decreased or stopped if levels increase over 130% from baseline,
5. baseline blood pressure determination should be made by averaging 2 separate readings, and antihypertensive therapy started for previously normotensive patients.

Consult references 1 or 3 for a complete discussion about the numerous drug interactions that accompany cyclosporin use. In addition to the cost of cyclosporin therapy, lab fees may be considerable.

Acitretin is a second-generation aromatic oral retinoid (4,7). It is the active metabolite of etretinate, which was withdrawn from the US market in 1998 due to toxicity. Acitretin enhances the epidermal turnover rate, and regulates immune function. It is used for all types of psoriasis, and is very effective for pustular and erythrodermic types. It can be combined with PUVA or UVB phototherapy to treat plaque psoriasis, requiring less radiation and fewer treatments than with phototherapy alone. Studies evaluated acitretin and calcipotriene combination therapy (12). It was reported that acitretin doses could be decreased while maintaining therapy effectiveness and reducing toxicity.

The daily dose of acitretin is 0.5 mg/kg/day for plaque psoriasis; up to 0.4 mg/kg/day for erythrodermic psoriasis; and up to 1 mg/kg/day for pustular psoriasis (4). The daily dose is divided into 2 doses. Pustular psoriasis typically responds within 10 days, and erythrodermic psoriasis within a month. Maintenance doses range from 0.125 to 0.5 mg/kg/day for up to 6 months. For plaque psoriasis, topical therapy is started during maintenance therapy.

Retinoids are teratogenic; hence, they are contraindicated during pregnancy. Also, pregnancy should be avoided for 2 years after therapy (3,4,7). It should not be used in patients with kidney, or liver conditions, or in alcoholics. Adverse effects include dry and peeling skin, alopecia, nail changes, muscle pain, chelitis, sticky skin, calcification of ligaments, and alterations in triglycerides, lipids, and liver enzymes. Concurrent tetracycline or vitamin A use is contraindicated, and concurrent use with cyclosporin is not recommended. Concurrent MTX therapy may increase the risk of hepatotoxicity.

Hydroxyurea is often used in cancer chemotherapy regimens, and stops DNA synthesis by inhibiting ribonucleotide reductase (1,3). About 60% of patients who failed other psoriasis therapies have improvement with hydroxyurea at 1 to 1.5 grams a day. At higher doses, hematological toxicity, cutaneous reactions and other side effects occur. Bone marrow suppression is reversible after a few weeks of stopping therapy.

Alefacept (Amevive®), was approved for use in early 2003 for patients whom are refractory to existing plaque psoriasis therapies (3,16). It works by binding to CD2 receptors to stop lymphocyte activation. It is dosed weekly via IM or IV in an office setting. It is contraindicated in patients with suppressed CD4+ T lymphocyte counts, and adverse effects include chills, myalgia, injection site pain and inflammation, dizziness and nausea. Post marketing surveillance will give efficacy insights, and reveal additional adverse effects and use precautions.

PHOTOTHERAPY

(NOTE: For complete dispensing information for the specific therapies discussed, please refer to Reference #3).

Phototherapy is most effective if patients remove plaque scales, and apply emollients prior to therapy (1,4,7,13). Only the affected areas should be exposed to phototherapy. The intensity of therapy must be monitored, since skin burns can cause a psoriasis flare-up. Resort-type spas may provide psoriasis phototherapy treatments. Spa treatments are more expensive than outpatient phototherapy centers, but have therapeutically equivalent outcomes.

The risks to sun exposure and ultraviolet radiation are well documented (1,4,7,13). They include sunburn, photoaging, and skin cancer. There is controversy over the risk involved with UVB phototherapy in the treatment of psoriasis. It is generally agreed that younger patients have higher risk, and risk is increased for all patients using phototherapy in genital or facial areas. With careful use, and protection, the benefits are thought to outweigh risks for patients having moderate to severe psoriasis.

Ultraviolet-B (UVB) Phototherapy inhibits DNA synthesis to stop epidermal growth, and decreases the number of intraepidermal T-cells in the areas of psoriasis plaques (1,4,7,13). Therapy is typically 3 days

per week, and 25 treatments can clear about 80% of moderate to severe psoriasis areas. Some patients obtain clearing after 3 weeks. After clearing, therapy is stopped.

Studies evaluated the outcomes of applying calcipotriene to lesions with UVB therapy (13). It is reported that lower cumulative UVB doses are needed to achieve clearing when calcipotriene is applied up to 2 hours prior to or within 1 hour after UVB exposure. It should not be applied immediately before exposure. More studies are needed to confirm these results.

Oral Psoralen-Ultraviolet-A Photochemotherapy (PUVA). UVA therapy, defined as irradiation from 320 to 400 nm, is ineffective as monotherapy for treating psoriasis (1,4,7,13). About 25 years ago, it was found that taking oral psoralens prior to UVA therapy could rapidly clear severe psoriasis. 8-Methoxypsoralen (also called methoxsalen, or 8-MOP) is the only psoralen used in the USA. The psoralens are only photoactivated after UVA stimulation. Photoactivation results in the inhibition of DNA synthesis and epidermal proliferation, and maximal immunomodulary effects by inhibiting cytokine release, and decreasing epidermal and dermal T-cells.

PUVA is much more effective than UVB therapy (1,4,7,13). It takes about 10 weeks to achieve an effect, and therapy is stepped down over 2 to 3 months to avoid a relapse. It is used to treat very severe, disabling plaque psoriasis. More than 80% of patients report psoriasis clearing after a maximum of 20 treatments that are given within a 1 to 2 month period of time. Treatments usually start at 2 to 4 times weekly, and then are reduced according to response. Once cleared, typically 2 treatments per month are needed to remain plaque free.

Oral methoxsalen is dosed at 0.6 mg/kg two hours prior to UVA exposure (4,7). Adjustments in UVA are made according to response, and a minimum phototoxic dose (MPD) determined for each patient. Initially treatments should be spaced every 48 to 72 hours because that is the amount of time for phototoxic reactions to occur. Patients with higher concentrations of psoralen need less UVA exposure for a response. Methoxsalen deposits into the eyes, and patients should avoid UV exposure for 6 hours after treatment. Common adverse effects include nausea, constipation, diarrhea, itching, and delayed-onset erythema. Patients are susceptible to cataract formation after long-term use.

Topically, methoxsalen is very photosensitizing (4). Absorption is decreased in palmar and plantar locations. Typically 0.1% methoxsalen is applied to localized plaques at least 20 minutes before irradiation. The UVA dose is reduced to about 20% of the dose used for oral therapy. Psoralen baths are well tolerated in patients that have extensive disease (4,7). For patients needing a psoralen bath, 5 capsules of 50 mg methoxsalen are dissolved in about 50 ml (or about 2 ounces) of very hot water. The concentrate is added to about 100 liters (or about 25 gallons) of water. The patient soaks in the solution for 30 minutes, dries, and is exposed to UVA within 30 minutes.

PUVA therapy has substantial risks. Phototoxic effects of erythema, blistering, and edema may occur, and can be prevented by carefully controlling the UVA dose. Itching, nausea, vomiting, and headache also are common after therapy. If the patient is using topical steroids when therapy starts, they should be continued until PUVA therapy is controlling the psoriasis, and then gradually withdrawn. While undergoing PUVA therapy, and throughout the entire treatment period, patients must protect themselves from additional UV exposure with sunscreens, protective clothing, and UV filtering sunglasses. The face and genitalia should be protected during therapy.

Oral methoxsalen is known to cause cataract formation, mutagenicity, and is a potential carcinogen. A maximum of 200 treatments are recommended. After 250 high-dose PUVA exposures, there is a large increase in squamous cell carcinoma incidence, and after 15 years of therapy, the incidence of melanoma increases. PUVA therapy should be reserved for patients failing other therapies, and those patients choosing this therapy should comply with a thorough annual examination for skin cancer. PUVA therapy is contraindicated in patients with photosensitivity disease (e.g. lupus erythematous), allergy to psoralens, and skin cancer.

Goeckerman Therapy. In the 1920's, coal tar therapy was combined with UVB therapy, and called the Goeckerman regimen. The advantage of this combination therapy over either therapy alone is questionable. The Mayo clinic provides continuous, 24 hour per day Goeckerman therapy. These clinicians are specially trained in tar application and radiation techniques. Patients must be hospitalized for 2 to 3 weeks for Mayo clinic continuous therapy.

MONOTHERAPIES VERSUS COMBINATION THERAPIES

Monotherapies may clear psoriasis lesions within an average of 4 to 16 weeks (4). The most effective monotherapies that clear existing lesions include calcipotriol, topical corticosteroids, PUVA, methotrexate, and cyclosporin. Acitretin and methotrexate are the most effective monotherapies that maintain resolved lesions.

Using more than one therapy concurrently to treat psoriasis is defined as combination therapy (4). The most effective combination therapies include: acitretin + calcipotriol or PUVA, cyclosporin + calcipotriol, calcipotriol + PUVA, calcipotriol + topical corticosteroids, anthralin + coal tar.

Combinations that should **NOT** be used included: PUVA + cyclosporin or methotrexate or coal tar, methotrexate + cyclosporine, cyclosporin + acitretin.

CONCLUSION

Before recommending a therapy to treat psoriasis, the goals of the patient must be identified. Psoriasis therapies vary in cost, benefit/risk ratio, and treatment time. Since psoriasis is a chronic disease, and patients commonly require repeated treatments, they need to decide what arrangement will work best for them. Pharmacists are in the position to help patients consider all of their options prior to deciding on psoriasis therapy.

Patients should be warned that Internet listings about psoriasis often encourage the use of therapies that are not scientifically tested. Reliable information can be obtained from the National Psoriasis Foundation at 6600 SW 92nd, Suite 300, Portland, OR 97223, or via the Internet at www.psoriasis.org.

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5. Do you have any further comments about this lesson? _____

_____

Please Select the Most Correct Answer

1. Which of these may require "in-patient" management?
   A. Palm & sole
   B. Erythrodermic
   C. Guttate
   D. Pustular
   E. Both B & D
2. Antihypertensive medications can aggravate psoriasis.
   A. True
   B. False
3. Which statement is FALSE?
   A. Topical therapies are the first step for psoriasis treatment
   B. Systemic antimicrobial therapy may clear psoriasis in 50% of patients
   C. No psoriases treatment protocols exist
   D. PUVA phototherapy has substantial identified patient risks
4. The following drug combination pairs are all acceptable, except:
   A. Acitretin + calcipotriol
   B. Methotrexate + cyclosporin
   C. Anthralin + coal tar
   D. Cyclosporin + calcipotriol
5. This agent may require needle biopsies to monitor for toxicity, if liver function tests and albumin levels deviate from normal.
   A. Methotrexate
   B. Tacrolimus
   C. Cyclosporin
   D. Etretinate
6. The topical therapy that will stain the skin is:
   A. Anthralin
   B. Coal tar
   C. Calcipotriene
   D. Both A & D
   E. A, B, & C
7. How do topical corticosteroids stop epidermal growth?
   A. Inhibit DNA synthesis
   B. Inhibit mitotic activity
   C. Promote epidermal replacement
   D. A & B
   E. None of these
8. Step-1 of the psoriasis treatment algorithm suggests use of:
   A. Coal tar
   B. Topical corticosteroids
   C. PUVA
   D. Cyclosporin
   E. A & B
9. Which psoralen is used most?
   A. Phenoxsalen
   B. Methoxsalen
   C. Crysoxsalen
   D. Uroxsalen
   E. Mioxsalen
10. Coal tar therapy combined with UVB therapy is known as:
    A. Koebner management
    B. PUVA
    C. Goeckerman therapy
    D. Reactivated therapy

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