

Continuing Education for Pharmacists

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Management of Psoriasis: Focus on Raptiva

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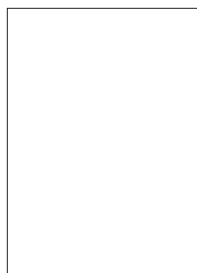
Goals. The goals of this lesson are to provide background information on psoriasis and review the newest drug, Raptiva (efalizumab), approved for its treatment.

Objectives. At the conclusion of this lesson, successful participants should be able to:

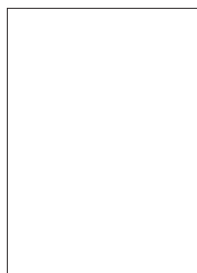
1. explain the etiology and incidence of psoriasis;
2. identify factors associated with its onset;
3. identify the pharmacologic classification and list therapeutic considerations for efalizumab; and
4. select from a list, the indication, mechanism of action, adverse effects and toxicities, drug interactions, and benefits and limitations of efalizumab.

Psoriasis affects 1 to 3 percent of the world's population. Although distressing to the victim, this chronic inflammatory skin disorder is rarely life-threatening.

Psoriasis has an unpredictable course; after onset, it may remain



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confined to an elbow, knee, the scalp, face or nails, or become generalized over much of the body's surface. It occurs rarely on mucosal surfaces, and is not contagious. Silvery scales, which can be easily removed by picking or rubbing with a rough cloth, overlay the lesions. If removed, the scales become brittle and powdery. Lesions may appear at any age, but the average age of onset is 28 years. When psoriasis is diagnosed before age 15, it often involves a greater proportion of body surface, and these patients are less responsive to therapy. Slightly more common in women than men, psoriasis may appear for the first time following childbirth.

A positive family history of the disease is shared by over 50 percent of psoriasis sufferers. If one parent is affected, offspring have a 25 percent greater chance of developing psoriasis; if both parents are affected, the probability increases to 65 percent. Ninety-eight percent of all psoriasis sufferers are Caucasian, but the disease occurs in all races. Psoriasis shows no preference for socioeconomic class or geographic area of residence.

Chronic itching can be severe in some patients with psoriasis. When scales are removed by scratching, rubbing, or picking, a salmon-pink to glassy-red lesion is exposed. The underlying skin may bleed from

small points (Auspitz sign). Some patients suffer from chronic scaling, itching and discomfort; others, however, may remain asymptomatic for long stretches, followed by periods of intermittent flare-ups. Seventy-five percent of people with moderate to severe psoriasis report that their disease has a moderate to large negative impact on their everyday lives. The National Psoriasis Foundation estimates that the overall cost to treating psoriasis in the U.S. may exceed \$3 billion annually.

Plaque psoriasis (psoriasis vulgaris), the most common type of psoriasis, is characterized by stable, slow-developing, usually symmetrical lesions (plaques) appearing typically on the elbows, knees, gluteal region (area of the buttocks) cleft, and scalp. Plaques may wax and wane but tend to be chronic.

Inverse psoriasis is characterized by sharply demarcated plaques in the intertriginous regions (areas of skinfolds), including under the arms, groin, submammary region, and navel. These lesions may also appear on palms, soles, and scalp.

Eruptive psoriasis (guttate psoriasis) develops in patients who lack a prior history of psoriasis or in those with chronic plaque psoriasis. It is most common in children and young adults. Patients usually display multiple small, erythematous, teardrop-shaped lesions that later coalesce into larger plaques. Scaling papules may be precipitated by a variety of conditions, including upper respiratory tract infection with beta-hemolytic streptococci.

Nummular psoriasis presents as lesions that coalesce into large, usually symmetrical, coin-

Table 1
Provoking Factors in Psoriasis

- Contact sports
- Dermal lesions (e.g., cuts, burns, sunburns)
- Systemic infections
- Drugs (e.g., antimalarials, lithium, certain beta-adrenergic blockers, clonidine, potassium iodide, NSAIDs, gold salts)
- Endocrine (e.g., psoriasis can improve or worsen during pregnancy and can flare with menopause)
- Immunologic mechanisms
- Obesity
- Psychological stress
- Alcohol
- Climate change
- Sunlight* and weather extremes
- Low humidity

*Exposure to moderate amounts of sunlight is associated with improvement of psoriasis. Excessive exposure or sunburn is correlated with psoriatic flares.

shaped masses. Appearing predominantly on the elbows, knees and lower back, these lesions do not cause significant itching, but scratching the surface of the plaque produces a waxy trail.

Etiology and Pathogenesis

The etiology of psoriasis is poorly understood, perhaps in part because the lack of a reliable animal model has impeded research. Psoriasis is characterized by alterations in the epidermis that permit rapid turnover of cells and inflammation of underlying capillaries, which culminate in rapid epidermal cell growth. Patients with psoriasis are more intolerant to cold weather than normal due to increased vasodilation and capillary proliferation, which promote loss of body heat.

With normal wear and tear of skin and replacement of new cells from underneath, the outermost dead cells are shed continually. The process that normally requires three to four weeks to complete may be shortened to three to four days in psoriasis patients. Accelerated epidermal proliferation is a hall-

mark of psoriasis. The rapid turnover of keratinocytes causes both viable and dead cells to accumulate on the skin's surface forming the characteristically thickened, scaly, silvery patches.

A key point in its etiology seems to be an altered immune function. Immunoglobulin G (IgG) can be detected in psoriatic lesions. One theory is that psoriasis patients cannot form sufficient T-suppressor cells so antibodies form against dermal antigens to promote formation of antigen-antibody complexes and inflammatory lesions.

Some known triggers of psoriasis are listed in Table 1. The Koebner phenomenon (isomorphic phenomenon) occurs when lesions develop on otherwise healthy skin at sites of severe injury (e.g., following cutting or scratching the skin, acute sunburn). This feature of psoriasis appears in 10 to 40 percent of patients and helps distinguish it from other pathologies. The relationship between trauma and subsequent appearance of lesions, usually within two to 18 days of the initial injury, is unclear. Patients should be advised to avoid injury or trauma to their skin, refrain from scratching, rubbing, or picking at the scales, and not apply adhesive tape over lesions.

Complications are uncommon; however, infection has resulted from over-ambitious therapy with corticosteroids applied under occlusive wrappings. Unrelenting itching from excessive scratching, sensitization to topically applied agents, and pus formation may also occur.

Arthritis symptoms are estimated to occur in 10 to 15 percent of patients and can be severe. Classically, the distal interphalangeal joints (i.e., of the fingers or toes) and adjacent nails are affected. Knees, elbows, wrists, and ankles may also be involved.

Differential Assessment

Psoriasis may be mistaken for seborrheic dermatitis and severe dandruff. Cradle cap is a form of seborrheic dermatitis that affects

infants and may also be misdiagnosed as psoriasis. Certain features of each disorder permit a reliable differential assessment (Table 2). This is important since psoriasis requires a different therapeutic approach than dandruff or seborrheic dermatitis. Assessment may be aided by examining the fingernails and toenails for abnormal growth of nail plates and keratin accumulation under the nails with psoriasis. This produces distorted, thick, opaque, crumbly nails that may show pits and ridges. The nail may separate from its bed and be lost completely. Nail changes are noted in about half of all psoriasis sufferers. These changes are suggestive but not entirely diagnostic of psoriasis.

Management

There is no cure for psoriasis at present, only suppressive therapy. The goal of therapy is to decrease epidermal proliferation and dermal inflammation. Treatment depends on the type, location, and extent of disease. Regular use of appropriate medications can help control symptoms. Since psoriasis causes the barrier that normally prevents drug penetration into the skin to be disrupted, psoriatic skin may be more permeable than normal skin to many medications. In early treatment, patients may respond rapidly to a topical agent, with improvement slowing over time as the skin's barrier improves.

Raptiva (efalizumab)

Efalizumab is the newest therapy approved for treatment of psoriasis. It is a humanized immunosuppressive monoclonal antibody obtained by recombinant DNA technology that binds to human CD11a. CD11a is the alpha subunit of leukocyte function antigen-1 (LFA-1). LFA-1 is expressed on all leukocytes, and decreases cell surface expression of CD11a. Efalizumab inhibits the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1), thereby inhibiting adhesion of leukocytes to other cells. The

Table 2
Differentiating Psoriasis from Other Skin Disorders

Characteristic	Psoriasis	Dandruff	Cradle Cap	Seborrheic Dermatitis
Site	Scalp & body	Scalp	Scalp	Scalp, face, body
Borders	Very sharp	Indistinct	Indistinct	Indistinct
Inflammation	Yes	No	Yes	Yes
Appearance of scales	Silvery scales that flake off in layers	Dry, grayish-white	Yellowish-brown, greasy	Greasy
Age at onset	Young adulthood usually, but can occur at any age	Puberty	1-2 weeks after birth, up to end of infancy	Puberty
Itching	Variable	Variable	Not known	Usual
External factors that worsen condition	Stress, mechanical irritation	Cold weather	Improper cleaning	Stress, poor health
Rate of epidermal turnover	Greatly increased over the norm (10-20X)	Twice the norm	Not demonstrated	More than twice the norm
Duration	Can persist for life; exacerbations & remissions	Can persist for life, diminishing in middle & old age	Usually clears in 3-4 weeks; can last up to 2 months	Can persist for life; frequent exacerbations & remissions

interaction between LFA-1 and ICAM-1 initiates and maintains multiple biological processes, including activation of T lymphocytes, adhesion of T lymphocytes to endothelial cells, and migration of T lymphocytes to sites of inflammation including psoriatic skin. Activation of lymphocytes and their migration to skin is a prime function in the pathology of chronic plaque psoriasis. In psoriatic skin, ICAM-1 cell surface expression is upregulated on endothelium and keratinocytes. As a side note, CD11a is also expressed on the surface of B lymphocytes, monocytes, neutrophils, natural killer cells, and other leukocytes. It is, therefore, feasible that efalizumab affects the activation, adhesion, migration, and count from cells other than T lymphocytes.

Efalizumab was evaluated in a series of four randomized, double-blind, placebo-controlled studies in adults with stable plaque psoriasis present for ≥ 6 months. All patients

had a minimum body surface area involvement of psoriasis of 10 percent and were candidates for, or had previously received, systemic therapy or phototherapy (PUVA) for their disorder. Patients with clinically significant flares and patients with lesions other than plaque psoriasis were excluded from the trials. Patients received doses of 1 mg/kg SC or 2 mg/kg SC of efalizumab or placebo once a week for 12 weeks; patients receiving efalizumab were administered 0.7 mg/kg as the first dose. Patients could receive concomitant low-potency topical steroids as needed, but no other concomitant psoriasis therapies were permitted.

Patients were evaluated using a standardized index that took into consideration both the fraction of body surface area affected and the nature and severity of the psoriatic changes within the affected regions. Compared with placebo, more patients assigned to efalizumab

experienced a significant improvement in their condition than those receiving placebo. The efalizumab 2 mg/kg dose was not superior to efalizumab 1 mg/kg.

Adverse Effects. The most common adverse reaction associated with efalizumab noted in clinical trials was a reaction complex to the first dose that included headache, chills, fever, nausea, and muscle pain (myalgia). These reactions were largely mild to moderate in severity when the first dose of Raptiva was limited to 0.7 mg/kg. Twenty-nine percent of patients treated with Raptiva 1 mg/kg developed one or more of these symptoms following the first dose compared with 15 percent of patients receiving placebo. After the third dose, the numbers had dropped to 4 percent and 3 percent of patients receiving Raptiva 1 mg/kg and placebo, respectively. Fewer than 1 percent of patients discontinued drug treatment

because of the reaction complex. Other adverse events (as percent) resulting in discontinuation of Raptiva treatment were worsening of psoriasis (0.6), pain (0.4), arthritis (0.4), and arthralgia (0.3).

Additional adverse events have been observed. The most notable during clinical trials were serious infections, malignancies, thrombocytopenia and psoriasis worsening and variants.

Raptiva has the potential to increase the risk of infection and reactive latent, chronic infections because it is an immunosuppressant. The drug should not be administered when clinically significant infection is present. Caution is advised when the use of Raptiva is considered in patients with a chronic infection or history of recurrent infections. The drug should be discontinued if a patient develops a serious infection.

Of 2762 psoriasis patients who received Raptiva at any dose, 31 patients were determined to have developed 37 malignancies. The malignancies included non-melanoma skin cancer, non-cutaneous solid tumors, Hodgkin's lymphoma and non-Hodgkin's lymphoma, and malignant melanoma. The occurrence and incidence of non-cutaneous solid tumors and malignant melanoma were within the range anticipated for the general population.

Platelet counts dropped to <52,000 cells per μL in 0.3 percent of Raptiva-treated patients during clinical trials compared with no cases among those on placebo. Thrombocytopenia resolved in the patients receiving adequate follow-up. Assessment of platelet counts with observation for signs and symptoms of thrombocytopenia (e.g., bleeding from the gums, bruising, or multiple petechiae [pinpoint hemorrhages] on the lower legs especially) is recommended during treatment with Raptiva and the drug should be discontinued if thrombocytopenia develops.

Symptomology of psoriasis can worsen during or following discon-

tinuation of Raptiva. These events took the form of psoriatic erythroderma (abnormal redness of the skin) or pustular psoriasis in some patients, and some required hospitalization and alternative antipsoriatic therapy.

The safety and efficacy of vaccines administered to patients being treated with Raptiva have not been adequately evaluated. In one small investigation with Raptiva administered IV, a single dose of 0.3 mg/kg (0.3 mg/kg IV has similar pharmacodynamic activity as 1 mg/kg SC) given before primary immunization with a vaccine decreased the secondary immune response; a dose of 1 mg/kg almost completely eliminated it.

Drug Interactions. Formal studies have not been conducted with Raptiva to evaluate the possibility of drug interactions. Raptiva should not be administered with other immunosuppressive drugs, and acellular, live and live-attenuated vaccines should not be used concurrently with Raptiva treatment.

Indications and Uses. Raptiva is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. It is the first biologic therapy designed specifically for continuous control of the disease.

Dosage and Administration. The recommended initial dose of Raptiva is 0.7 mg/kg SC followed with weekly doses of 1 mg/kg SC. A maximum single dose should not exceed a total of 200 mg. Raptiva is to be administered under the guidance and supervision of a physician; if appropriate, patients may self-inject Raptiva after proper training.

Patients should be told that their physician may monitor platelet counts during therapy. They should be advised to seek medical attention at once if they develop any of the signs and symptoms (discussed earlier in this lesson) associated with severe

thrombocytopenia. Patients should understand that Raptiva is an immunosuppressant that may increase their chances of developing an infection or a malignancy. They should be advised to call the prescribing physician promptly if they develop any new signs of, or receive a new diagnosis of, infection or malignancy while undergoing treatment with Raptiva.

It is not known whether Raptiva can cause fetal harm when given to pregnant women. Women should be advised to contact their physician if they become pregnant while taking Raptiva or within six weeks of discontinuing it.

Patients and/or their caregivers should be instructed how to avoid infection and how to measure the correct dose. They should also receive the manufacturer's Raptiva Patient Package Insert and be instructed to read it carefully. In addition, patients should be instructed not to reuse syringes and needles and how to dispose of them properly.

Raptiva is supplied as a lyophilized, sterile powder that when reconstituted provides 125 mg of efalizumab per single-use vial. Vials of lyophilized powder must be refrigerated at 36-46°F and be protected from exposure to light.

Continuing Education Quiz

Management of Psoriasis: Focus on Raptiva

1. All of the following statements about psoriasis are true EXCEPT:
 - a. it is contagious.
 - b. it occurs rarely on mucosal surfaces.
 - c. it is rarely life-threatening.
 - d. it can be confined to one area or generalized over the body.
2. The average age of onset of psoriasis is:
 - a. 14.
 - b. 28.
 - c. 42.
 - d. 56.
3. Psoriasis is most prevalent in:
 - a. Asians.
 - b. African-Americans.
 - c. Caucasians.
 - d. Polynesians.
4. When psoriasis affects intertriginous regions, it refers to areas of:
 - a. exposed skin.
 - b. nails.
 - c. scalp.
 - d. skinfolds.
5. The hallmark of psoriasis is:
 - a. accelerated epidermal proliferation.
 - b. excessive formation of dihydrotestosterone.
 - c. infection by tinea versicolor.
 - d. malfunction of the sebaceous glands.
6. Which of the following statements is true?
 - a. Treatment of psoriasis and seborrheic dermatitis is the same.
 - b. Borders of psoriatic lesions are very sharp rather than indistinct.
 - c. Psoriasis affects the body, but not the scalp.
 - d. Cradle cap is a form of psoriasis.
7. Which of the following best describes the appearance of psoriatic scales?
 - a. Grayish-white
 - b. Greasy
 - c. Silvery
 - d. Yellowish-brown
8. Raptiva is a(n):
 - a. anti-epithelial cell stimulant factor.
 - b. enzyme inhibitor.
 - c. keratin stem cell inhibitor.
 - d. monoclonal antibody.
9. Raptiva is currently approved to be administered:
 - a. intravenously.
 - b. orally.
 - c. subcutaneously.
 - d. topically.
10. Prior to administration, raptiva must be stored:
 - a. at room temperature.
 - b. under refrigeration.