Psoriasis is a chronic inflammatory disease that affects 2% to 3% of individuals worldwide. In the United States, it is the most common autoimmune disease [1]. Both men and women are equally affected and disease can occur at any age. Disease onset occurs in a bimodal distribution with the first peak at age 15 to 20 and the second peak at age 55 to 60 [2].

Psoriasis is primarily characterized by skin manifestations. Plaque-type, the most common form, has thickened, erythematous, scaly plaques that can be associated with pruritus and pain and periods of exacerbation and remission [3]. Psoriasis causes a significant decrease in quality of life, comparable to that seen with other major medical conditions [4]. Psoriasis has internal manifestations, as 10% to 30% also develop psoriatic arthritis [1]. Other comorbidities include cardiovascular disease, metabolic syndrome, lymphoma, and other systemic immune diseases. These are more likely to develop in those with more severe skin disease [5–8].

Psoriasis is now classified as an immune-mediated inflammatory disease (IMID). This has brought about a focus on comorbidities and has led to new treatment options. Current treatment for localized disease remains topical therapy, though localized phototherapy can also be used. Patients with more extensive, generalized disease (or involvement of the palms and soles) usually require more intensive treatments such as phototherapy or systemic treatments. Traditional systemic treatments have a wider range and chance of side effects. Biological response modifiers more specifically target the inflammatory pathways that cause psoriasis and show great promise for both improved disease control and better patient quality of life [9].

Referral to a specialist may be appropriate when there is diagnostic uncertainty or for treatment options with which the primary care provider are not familiar. The need for coordination of care is greater than ever with the need to monitor systemic treatments and to monitor for...
and treat comorbid conditions. Patient education about the disease, the comorbidities, and the risks and benefits of the many treatment options is essential.

CASE STUDY

Initial Presentation

A 21-year-old white female soccer player presents to her primary care physician for an annual physical. The patient is overall healthy but is concerned about a red, flaky rash on her elbows and knees. She says this rash is “so ugly” that she dislikes wearing clothing that exposes her arms and legs during practice and that her teammates are concerned about “catching” her “contagious” rash.

• What are the clinical presentations of psoriasis?

Psoriasis is a chronic inflammatory skin disease characterized by skin erythema, thickening, and scaling and often associated with pruritus and pain. In most cases, the diagnosis is clinical and a biopsy is not required. Psoriasis is classified into morphological forms; however, patients may display more than one form simultaneously or many over the course of this life-long, episodic disease. Plaque psoriasis is the most common form (Figure 1), affecting about 80% to 90% of patients. This classic variant has well-defined, erythematous, thick plaques with an overlying silvery scale. Plaques can coalesce into larger lesions and have a symmetrical distribution involving the scalp, trunk, or extensor surfaces of extremities (such as the knees and elbows) [3,6].

The other forms are less common. Guttate psoriasis (Figure 2) occurs mostly in children, often 2 to 3 weeks after an episode of streptococcal pharyngitis. The lesions are erythematous, scaly, tear-shaped papules or plaques in a central body distribution, usually involving the trunk and proximal extremities. Inverse psoriasis involves intertriginous areas, such as the axilla, inframammary fold, perineal area, or other skin folds. Because these areas are moist, the lesions (while still erythematous) are instead thin, smooth, and without scale [3,10]. Erythrodermic psoriasis (Figure 3) is
a generalized form, where 90% to 100% of the skin is erythematous and scaly. Extensive compromise of the skin barrier can cause difficulty in regulating body fluids and temperature and place the patient at increased risk for infection [3,6]. Pustular psoriasis (Figure 4) displays sterile accumulations of neutrophils (pustules) that can be localized or more extensive. The localized form often involves the palmar and plantar surfaces, causing pain and disability. Nail changes (Figure 5), primarily affecting the fingernails, are present in 10% to 80% of cases and include onycholysis, subungual hyperkeratosis, pitting, and discoloration (“oil-drop” phenomenon) [3,11].

- **What is the differential diagnosis of psoriasis?**

Reaching a diagnosis is easier if psoriasis presents in the classic plaque-type form. Close attention to history along with a comprehensive skin examination that includes inspection of the ears, breasts, groin, buttocks, genitalia, and any skin folds will help identify distinguishing features that may lead the clinician to alternative diagnoses (Table 1). Often the more difficult cases are ones that present in the rare forms or show an atypical distribution [11]. The differential includes seborrheic dermatitis, lichen simplex chronicus, tinea corporis, lichen planus, subacute cutaneous lupus erythematosus, pityriasis rosea, pityriasis rubra pilaris, and mycosis fungoides.

Seborrheic dermatitis (Figure 6) may be confused with scalp or facial psoriasis since both display erythema, pruritus, and scaling. Seborrheic dermatitis has greasy, yellow scales versus the silvery scale of psoriasis. Scalp psoriasis can extend beyond the hairline and can be accompanied by lesions on the trunk and extremities. In contrast, seborrheic dermatitis will have lesions just to the hairline with a characteristic facial distribution involving the nasolabial folds, eyebrows, glabella, and retroauricular area. Body distribution is less common and involves intertriginous and sternal areas [12,13].
Lichen simplex chronicus (Figure 7) may also complicate the diagnosis. It results from repetitive mechanical trauma such as rubbing or scratching and can be seen as a result of psoriasis or other conditions such as atopic dermatitis or xerosis. The lesions are thickened and scaly, but unlike psoriasis, are red-brown and usually less scaly and less well demarcated. Lesions are located in areas commonly scratched such as the posterior scalp, neck, wrists, elbows, and knees [14].

Cutaneous mycoses (Figure 8) may involve the same areas of psoriasis: the scalp (tinea capitis), the body (tinea corporis), perineal areas (tinea cruris), and feet (tinea pedis). Lesions are asymmetrically distributed and are erythematous with central clearing and scaling at the periphery that gives them an annular appearance. Fungal skin lesions and psoriasis may look very similar both clinically and histologically. A potassium hydroxide preparation of skin scrapings with positive identification of hyphae is a simple way to achieve a diagnosis [15].

Lichen planus (Figure 9) may mimic psoriasis, as these pruritic papules and plaques may coalesce and form after trauma, but the lesions are purplish, flat topped, and polygonal. Half of all patients have lesions in the oral (especially buccal) mucosa (sometimes with fine white lines called “Wickham’s striae”). Skin lesions may be distributed anywhere but are commonly on flexor surfaces of the wrists, forearms, dorsal hands, and anterior shins as well as in areas of skin injury [16].

Subacute cutaneous lupus erythematosus (SCLE) (Figure 10) is a subtype of cutaneous lupus. Patients are photosensitive and lesions commonly appear on the face, neck, and arms after sun exposure. The lesions can be annular with peripheral scaling or erythematous, scaly papules/plaques. Hypo- or depigmentation is also seen. Inquiry into the presence of systemic symptoms such as arthritis, fatigue, and lymphadenopathy should occur. The clinician may want to obtain a blood sample to check for elevated erythrocyte sedimentation rate, anti-ANA, anti-dsDNA, and other autoantibodies if SCLE is suspected [17].

Pityriasis rosea (Figure 11) can be differentiated with the help of the history. It commonly affects adolescents and young adults. The patient may recount an incidence of a single, 2- to 4-cm erythematous oval or round plaque (a “herald” patch) and then a subsequent eruption days to 2 weeks later of similar but smaller lesions that align along cleavage (“Langer”) lines and (if located on the back) have a “Christmas tree” pattern. Palmar, plantar, and facial areas are usually not involved and lesions are gone within 2 to 3 months [18].

Pityriasis rubra pilaris (Figure 12) is often mistaken for psoriasis but is very rare (1 in 5000–50,000). It begins on the scalp, face, or chest and descends downward. The follicular papules are pruritic and salmon-colored and have small, uninvolved “islands of sparing.” Palmar and plantar skin is thickened and takes on a red-orange color [18].
Mycosis fungoides (Figure 13) is the most common type of cutaneous T-cell lymphoma. Early disease may be mistaken for psoriasis, as erythematous patches with fine scales are seen, but lesions then progress to a horseshoe, annular, or polycyclic pattern and are red-brown or dark red in color. Mycosis fungoides is more commonly found on the buttocks, hip, lower trunk, axilla, groin, and breast. A minority of patients will progress to a tumor stage with involvement of skin folds and the face. Tumors are red-violet nodules that may ulcerate. Lymphoma can also occur [19].

**Further Evaluation**

The patient reports that the rash has been present for 1 month and is getting worse. The areas are very itchy, red, and occasionally painful. She constantly “picks” at the lesions on her elbows, which results in bleeding. She noticed some improvement when she spent a weekend at the beach for a family vacation. The rash has since worsened, most notably on her legs where her shin guards and socks rub and irritate her lower legs. She has used moisturizers without relief. On review of systems, she has a dry scalp but denies any nail changes or joint pain (a critical issue in the review of systems of psoriasis patients). To her knowledge, her family history is negative for skin or joint diseases. She has no other medical conditions and takes no medication.

Physical examination reveals discrete, large, erythematous plaques with thick, silvery scales located on the extensor surfaces of the knees and elbow in a symmetrical distribution. There are also similar but smaller plaques on the scalp and behind the ears. The rest of the skin exam and physical exam is normal. Based on the history and skin exam, the physician makes a diagnosis of psoriasis. The physician informs her she has psoriasis.
Psoriasis occurs due to a dysregulation of the inflammatory process in the body that results in keratinocyte hyperplasia and increased angiogenesis. Both the innate and adaptive immune systems play a role [20]. On histology, psoriasis lesions show an infiltrate of myeloid dendritic cells and T-cells (particularly CD8+ cells) into the epidermis not seen in normal skin. Langerhans cells show an abnormal and increased distribution into superficial skin layers in psoriasis plaques [21]. This hyperactive adaptive immune response expresses cytokines of the Th1 pathway (IL-1, IL-12, TNF-α, and INF-γ) and of the Th17 pathway (IL-22 and IL-23) [22]. Neutrophils, natural killer cells, and natural killer T cells are increased in psoriasis plaques along with a higher level of the antimicrobial proteins beta defensins and cathelicidins [20].

Internal and external factors initiate this process. Family members of psoriasis patients are at an increased risk.
Table 2. Genes Associated with Psoriasis

<table>
<thead>
<tr>
<th>Function</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin barrier</td>
<td>HBD, LCE, SLC12A8</td>
</tr>
<tr>
<td>Inflammation</td>
<td>HLAC, IL2/IL21, IL12B, IL23A, IL23R, TNFAIP3, TNIP1</td>
</tr>
</tbody>
</table>

Table modified from reference 22.

risk of developing the disease. Genomic wide linkage and association studies have identified many loci involved in psoriasis susceptibility (Table 2). These loci are associated with genes involved in both inflammation and skin barrier function. Loci have been found in genes that encode for human leukocyte antigens, interleukins such as IL-12 and IL-23, and factors in the natural killer cell pathway [22].

Normal histology in uninvolved skin indicates a role for environmental factors. Koebnerization is a well known phenomenon of psoriasis, where direct trauma leads to the delayed response of plaque formation. Bacterial infection (especially streptococcus), HIV, drugs (beta blockers, rapid withdrawal of immunosuppressants, and interferons) and physiological stress are more indirect factors that can lead to psoriasis [21].

Case Continued

The physician explains the causes of psoriasis and what can trigger the disease. The patient confirms she understands this information and asks what course is expected with psoriasis and what treatment options can control the disease. She also asks if she is at risk for developing other diseases.

- What impact does psoriasis have on the patient’s quality of life?

The clinical course of psoriasis is a chronic disease with periods of well-controlled, reduced disease and episodes of flares. Remission occurs in only 5% of cases but can last 5 or more years [3]. As a result, most patients try a number of treatment forms and may require maintenance therapy to avoid flares.

Psoriasis impairs physical, mental, and social functioning similar to that seen with other chronic diseases like diabetes, congestive heart failure, and depression [4]. For patients, it is not only the pruritus, pain, and plaques that cause disability or the time and expense of treatment options, but also the social stigmatization that accompanies the disease. Many psoriasis plaques are in highly visible regions and because of fears of contagiousness or unsightly appearance, patients may be avoided or rejected by other individuals. This can lead to self-esteem issues and social avoidance [23]. People with psoriasis have a high rate of depression and anxiety disorders (about 30%) and 10% have suicidal ideation. Over time, the impact made on a person’s physical, emotional, and social well-being results in a “cumulative life impairment” [24]. The leisure and daily activities, personal relationships, social connections and mental well-being of family members and partners are also affected and are more closely related to the patient’s quality of life rather than the disease severity [25].

The patient’s ability to deal with these psychosocial aspects can be influenced by the physician, family members and friends, or other patients suffering from psoriasis. Various coping strategies are used by patients, such as educating others about the condition, covering the plaques, and telling oneself that others are insensitive [26]. Physicians can show acceptance verbally through discussion of the disease and these psychosocial issues and nonverbally through open body language and touching the skin lesions during the skin examination to stress that psoriasis is not transmissible. A recent survey of psoriasis patients regarding utility of support sources found that the internet was rated higher than physicians, family or friends, or traditional support groups. These online participants also reported improved quality of life regardless of their health status or disease severity [27]. Online resources can be accessed on the patient’s own schedule and allow for anonymous or personalized communication. Patients should be referred to the National Psoriasis Foundation (Table 3),

Table 3. National Psoriasis Foundation Contact Information

| Online: | www.psoriasis.org |
| E-mail: | getinfo@psoriasis.org |
| Mail: | 6600 SW 92nd Avenue, Suite 300 Portland, OR 97223 |
| Phone: | 800-723-9166 |
| Fax: | 503-245-0626 |
Psoriasis is an IMID with consequences beyond skin manifestations. Patients are at a higher risk for other comorbidities, especially autoimmune, metabolic, and cardiovascular disorders [28]. Patients with severe cases of psoriasis are more likely to develop these comorbidities [5,7,8]. Clinicians need to be aware of this connection in order to guide appropriate screening and treatment at both the initial evaluation and follow-up appointments.

The connection between psoriasis and psoriatic arthritis has been well documented, but psoriasis shares risk factors with other autoimmune diseases. Inflammatory bowel disease has an increased prevalence in psoriasis patients, with both Crohn’s and ulcerative colitis affecting these patients more frequently than the general population (0.5% vs. 0.004–0.04% and 0.05–0.07%, respectively) [7]. Patients are also at an increased risk for celiac disease and multiple sclerosis. The cause is multifactorial, but includes both shared gene loci (Table 4) and shared inflammatory pathways [22].

Psoriasis patients are more likely to have metabolic syndrome, a constellation of hypertension, central obesity, dyslipidemia, and hyperglycemia [5]. Psoriasis patients in clinical trials have a higher average weight when compared to the average weight of the US population [9]. Children with psoriasis have a higher age-adjusted BMI percentile than both atopic dermatitis and non-inflammatory skin disease patients. Also, overweight pediatric psoriasis patients are more likely to be obese in severe cases versus moderate cases [29]. Psoriasis patients have a 48% to 59% prevalence of non-alcoholic fatty liver disease versus 20% to 30% in the general population [7]. Shared inflammatory pathways triggered by both genes and the environment are the link [5]. Increased leptin and decreased adiponectin, adipokines that play a role in the inflammatory (especially Th1) response, are strongly linked to obesity and also associated with psoriasis. Hyperleptinemia is seen in psoriasis independent of obesity. Adiponectin is anti-inflammatory through its antagonization of TNF-α, IL-1, and IL-6 but is decreased in psoriasis patients. In some patients, weight loss can reduce or cause remission of psoriasis as well as improve response to psoriasis treatment [28].

Psoriasis is also associated with an increased risk of cardiovascular disease, such as atherosclerosis and thromboembolic events [5]. The correlation between psoriasis and cardiovascular risk factors such as metabolic syndrome, diabetes, obesity, and hypertension may explain this. In addition, psoriasis patients are at risk due to higher levels of smoking and alcohol consumption [8]. However, psoriasis and several other chronic autoimmune inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus, show an increased risk of coronary artery disease [30]. Psoriasis may be an independent risk factor based on a study that showed increased risk of myocardial infarction in spite of controlling for known risk factors [5]. This has led to a new theory of a “psoriasis march” where genetic and environmental triggers that cause inflammation and development of psoriasis plaques cause similar inflammation in endothelial cells and contribute to cardiovascular disease [20,28,30].

### Table 4. Shared Loci Between Psoriasis and Other Diseases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL2/IL21</td>
<td>Celiac disease, Crohn’s disease, multiple sclerosis, psoriatic arthritis, ulcerative colitis</td>
</tr>
<tr>
<td>IL12B</td>
<td>Crohn’s disease, multiple sclerosis, psoriatic arthritis</td>
</tr>
<tr>
<td>5q31</td>
<td>Crohn’s disease, psoriatic arthritis</td>
</tr>
<tr>
<td>IL23R</td>
<td>Crohn’s disease, psoriatic arthritis</td>
</tr>
<tr>
<td>CDKAL1</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>PTPN22</td>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>TNFAIP3</td>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>COG6</td>
<td>Ulcerative colitis</td>
</tr>
</tbody>
</table>

Table modified from reference 22.

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### What other diseases is this patient at risk for?

Psoriasis is an organization whose goal is to provide education, promote research, and improve patient and family quality of life. The Psoriasis Foundation has an extensive website with information in both English and Spanish and can be followed on social networking and multimedia sites.

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### What is the approach to selecting therapy?

Both objective disease severity and subjective patient preference guide therapy. There are a number of ways
to classify disease severity. The simplest way is by the percent body surface area (BSA) involved. A general rule is that a patient’s palm (with closed fingers and thumb) represents about 1% of his/her total BSA. From the sum percentage, the National Psoriasis Foundation categorizes psoriasis into 3 groups: mild (< 3%), moderate (3–10%), and severe (> 10%). About 25% of psoriasis patients have moderate to severe disease [1]. There are other classifications more appropriate for use in clinical trials. These include the Psoriasis Area and Severity Index (PASI) which considers BSA and lesion severity, the Psoriasis Global Assessment (PGA) which rates overall severity on a 7-point scale, and the Lattice System Physician’s Global Assessment (LS-PGA) which looks at BSA and plaque qualities rated on an 8-point scale [2]. Severity then guides the 2 main strategies: local therapy or generalized therapy. For mild disease, local therapy with topical or targeted phototherapy is recommended. For moderate to severe disease, generalized therapy with phototherapy, traditional systemic, or biologic medications—or some combination of these—is recommended [6].

Patient preference is a major consideration, since both the disease and the treatment regimen affect a patient’s and family’s quality of life [25]. Plaque location is important, as topical treatment may not be realistic in less accessible areas without the aid of another individual. A small area that nonetheless significantly impairs a patient’s activities of daily living should be treated more aggressively with a systemic agent. Involvement of the palms or soles results in more pain and disability, so oral medications are indicated [3]. Patient goals for treatment should also be addressed and education about appropriate expectations should occur, as complete clearance may not be a realistic goal [31]. Patient behavior can impact disease course, so clinicians should emphasize that vigorous scrubbing and shampooing, scratching, and picking can worsen lesions. Some patients prefer the minimal treatment available while others wish more aggressive combination therapy in order to achieve the best outcomes [31].

- What therapies are used to treat local disease?

In patients with mild or moderate psoriasis, topical therapy is the first-line treatment. Use of topical corticosteroids is one option. Steroids are classified into 7 levels of potency, with the most potent class (class I) used initially for control of psoriasis [9,32]. Class I steroids include clobetasol and one of the forms of betamethasone and are applied twice daily for 2 to 4 weeks. A systematic review of the efficacy of class I steroids showed a clearance rate from 58% to 92% [33]. Possible local side effects include skin atrophy, striae, and telangiectasia [34]. Systemic side effects like Cushing’s syndrome or adrenal suppression are rare and are more likely to occur with higher-potency options applied over a larger area under occlusion [33]. Lower-potency classes should be used in sensitive areas such as the face and intertriginous areas [32,34]. After reduction of plaques or control is reached, use should be tapered to avoid rebound disease. The patient should be switched to a low-potency form or to weekend-only dosing, and non-steroid therapy may be added with a later transition to non-steroid monotherapy [35]. Tachyphylaxis—reduced efficacy with use of medication—has been observed clinically but has not been shown in clinical trials and may be due to poor adherence to long-term treatment [9,33]. Patients are often dissatisfied with topicals because the application process is time-consuming and messy [9]. Physicians should explain the various vehicle forms to patients. Often, patients prefer lighter creams and foams over thicker ointments [34,36]. The best vehicle is generally the one the patient wants to use.

Topical vitamin D analogs can be used alone or in combination with corticosteroids. Ointments offer the benefit of moisturizing the plaques, and calcitriol (the “all-natural vitamin D”) and calcipotriene (a synthetic vitamin D analog) ointment preparations are available. A single agent used only once a day is available that contains the vitamin D derivative calcipotriene and the class II steroid betamethasone propionate [32]. Combination therapy reduces the risks associated with corticosteroid use and is more effective than monotherapy [35]. Steroids are anti-inflammatory and vitamin D decreases keratinocyte proliferation, so combination therapy targets 2 main processes in the progression of psoriasis. Topical vitamin D products are applied twice daily and available as an ointment, cream, or solution. Side effects include skin irritation and photosensitivity, but no clinical effect on calcium homeostasis is seen unless high doses of the drug (greater than ~200 g/month) are used [37,38].

A number of other treatment options are available.
daily and usually in combination with corticosteroids. However, these derivatives are less effective than vitamin D topicals and are more irritating [32]. Side effects include skin irritation, drying, and sun sensitivity [32,39]. Pregnancy is to be avoided as tazarotene is pregnancy category X. Reports of non–skin-related adverse effects have not been substantiated [39]. Topical anti-inflammatory drugs from the calcineurin inhibitor family (tacrolimus and pimecrolimus) are not particularly effective for plaque psoriasis, but can be useful for facial or inverse psoriasis where the skin is thinner [40]. There is an FDA black box label warning about increased risk of lymphoma for topical calcineurin inhibitors, but the warning is controversial and appears unwarranted [33]. Options such as anthralin or coal tar have fallen out of popularity given lower efficacy rates but may be used in combination with phototherapy [9,32]. Both agents cause staining and tar has an unpleasant odor.

Over-the-counter options such as salicylate acid (a keratinolytic), tar, emollients, moisturizers, and bath salts are available for patients. Use of a keratinolytic increases efficacy of other medications via increased penetration, but makes the treatment regimen more complicated and can reduce adherence [9]. Moisturizers are generally safe and can be used many times a day [33].

Initiation of Topical Therapy

Because the patient has localized disease, the physician prescribes her combination therapy with a potent topical corticosteroid and a vitamin D analog initially, with plans for use of the vitamin D analog alone after 1 month. She is also referred to the National Psoriasis Foundation for additional information and support. The patient shows some concerns for the daily application of a topical given her rigorous academic and athletic schedule. She asks the physician if there is a pill she can take instead.

**What steps can be taken to improve patient adherence?**

Finding and prescribing a treatment regimen is of no value if the patient does not use it. Adherence to topical treatment is often very poor. A recent open prospective study of 200 patients prescribed topical and/or oral medication for psoriasis found that 40% reported nonadherence (and many of the other 60% may have been nonadherent, too). Medication adherence was decreased in chronic users of medication, those with facial involvement, severe disease, oral therapy (alone but not in combination), and twice daily dosing and those experiencing adverse drug events [41].

Providers can play an important role in increasing adherence. Of utmost importance is the patient-physician interaction. Patients who are more satisfied with their appointment are more likely to adhere to treatment regimens. A doctor’s interpersonal skills are crucial to establishment of a rapport with the patient [42]. Physicians should actively listen to a patient, carefully examine and touch a patient’s skin, avoid use of medical jargon, and express empathy. Patient education that takes place in the office and through provision of information for use in the home is also important [42,43]. The National Psoriasis Foundation has a number of brochures that are useful for patient education. Patient preference should influence dosing schedule and delivery method to ensure a practical treatment solution. Patients are more likely to adhere to treatments around the time of an appointment. Follow-up in the form of an appointment (preferable), phone call, or email within the first week is advised to discuss patient concerns. Often increased adherence results in disease improvement that positively reinforces medication use [43,44].

**What are options for treatment of generalized disease?**

For more generalized (moderate to severe) psoriasis, topical therapies are not sufficient. Applying topicals over large body surface areas can be messy and time consuming. This makes adherence unlikely. Patients who have generalized disease may require referral to a dermatologist. Systemic therapy—particularly for methotrexate and cyclosporine—requires close follow-up with blood tests and monitoring for adverse events.

**Phototherapy**

Many patients notice that their disease improves with sun exposure. There are a number of well-studied phototherapy options done at a dermatology office or prescribed for the home such as broadband ultraviolet B light (BB-UVB), narrowband UVB (NB-UVB),
PUVA (UVA combined with psoralen photosensitizer), and home phototherapy devices. Less controlled UV exposure can be achieved through tanning beds (controversial) or natural sun exposure. UV light works via cutaneous immunosuppression, which reduces inflammation in the skin [45]. NB-UVB is administered 3 times a week (BB-UVB up to daily) and can be used in combination with other treatments such as tazarotene, vitamin D derivatives, and acitretin, an oral retinoid [32]. A home UVB device is cost-effective and shows high patient adherence; however, a number of barriers such as insurance coverage, provider unfamiliarity, and upfront costs to patients often hinder its use [9,46]. UVB phototherapy is also a first-line treatment in pregnant patients [48]. PUVA therapy is another option in which psoralen can be topically applied or taken orally to increase sensitivity to UV exposure. Oral psoralen can cause nausea, vomiting, and headache, however [45]. With all UV exposure, side effects include burns, photaging, and increased risk of skin cancer, so careful use and close follow-up should occur when treating with these modalities [32,47]. Patients with more localized disease, particularly scalp, palmar, and plantar psoriasis, can benefit from phototherapy. The use of a 308-nm excimer laser allows for more targeted therapy that spares uninvolved skin [9,48].

**Traditional Systemic Agents**

Systemic agents such a methotrexate, cyclosporine, and acitretin are mainstays of treatment for generalized psoriasis but are complicated by a number of side effects and the potential for drug-drug interactions [49]. Cyclosporine works by inhibiting T-cell activation. The medication can be given as short-term therapy lasting 12 to 16 weeks [50]. Reduced disease has been seen in 80% to 90% of patients [49]. If disease recurs, a second short-term course at the previous effective dose can be given. Cyclosporine is approved for up to 1 year in the United States, so maintenance therapy is another option if the patient is young and healthy [50]. Longer use is usually avoided because cyclosporine can cause renal dysfunction and hypertension. Monitoring involves blood pressure readings, serum BUN and creatinine levels, liver function tests (LFTs), blood counts, magnesium levels, and triglyceride levels. Hypertension can be controlled with calcium channel blockers, but diuretics are not recommended due to concerns for added nephrotoxicity [49]. A 5-year cohort study of patients using cyclosporine for an average of 2 years found a 6-fold increase of non-melanoma skin malignancies. This risk was predominantly in patients who had previously undergone PUVA therapy. Regular skin screenings are recommended for patients [51,52]. Patients are at increased risk for infection, so tuberculosis testing is a prerequisite. Live vaccines are contraindicated, but killed vaccines may be given [53]. Cyclosporine is a P-450 inhibitor, so drug-drug interactions can occur [54].

Methotrexate inhibits dihydrofolate reductase and impairs DNA synthesis, controlling psoriasis via reduced proliferation of leukocytes and immunosuppression. It was approved for use in psoriasis in 1972 and comes in oral, intramuscular, and subcutaneous (least costly) forms. It generally is prescribed as a once-weekly dose that takes about 1 month to work and can be tapered off [49]. Two studies have compared methotrexate to cyclosporine. Methotrexate achieved PASI-75 (a 75% improvement in the Psoriasis Area and Severity Index) in 58% and 60% of patients when given over 12 and 16 weeks, respectively, whereas cyclosporine led to disease reduction in 72% and 71% [55,56]. Compared to biologics, methotrexate was less effective than adalimumab, but the addition of etanercept to patients taking methotrexate can enhance response [57,58]. Common side effects include nausea, anorexia, and fatigue and can be reduced by coadministration of a folate supplement. Toxic effects include myelosuppression and hepatotoxicity and require regular laboratory monitoring with blood counts and LFTs (and possibly liver biopsy if abnormal LFTs). Patients should not become pregnant while on the drug [32,49]. There is a high potential for drug-drug interactions that can lead to elevated serum levels and the potential for fatal consequences. Commonly prescribed drugs that have this potential are NSAIDs and sulfonamides [54].

Acitretin is a retinoid that alters keratinocyte differentiation and moderates hyperproliferation by changing gene transcription. As monotherapy, acitretin is most useful in the treatment of palmoplantar, pustular, and erythrodermic psoriasis. In plaque psoriasis, combination therapy with UVB or PUVA is highly effective. Combination allows UV dosage and exposure time to be reduced [59]. Acitretin has a long half-life and is highly teratogenic; consumption of alcohol extends the half-life of metabolites. Birth control for women of child-bearing age is required during therapy and for 3 years
thereafter. Dose-related mucocutaneous side effects are common and include chelitis, xerosis, nail dystrophy, and alopecia. Less commonly, hyperlipidemia, osteoporosis, skeletal abnormalities, and hepatotoxicity can occur [32]. Monitoring of lipids (especially triglycerides) and LFTs is indicated. Given the teratogenicity, use in women of child-bearing potential should be avoided.

**Biologics**

Biologic response modifiers are the latest treatment option. These drugs have more convenient dosing regimens and target key steps in the inflammatory process that causes psoriasis and psoriatic arthritis and therefore avoid many of the unwanted side effects of traditional systemic medications. Infliximab is given intravenously while the rest are given as injections, either subcutaneously (adalimumab, etanercept, ustekinumab) or intramuscularly (alafacpet) [9]. Use of biologics improves clinical disease and patient quality of life [60]. However, there is no consensus or guideline detailing screening and monitoring with biologics [61]. These innovative new compounds do not have long-term studies regarding safety but have been studied up to 5 years in psoriasis and over 10 years in other chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease [6]. In 2009, the biologic efalizumab was withdrawn from the market after 3 confirmed cases and 1 possible case of progressive multifocal leukoencephalopathy in patients who had been using the drug for at least 3 years [9].

Three of the 5 biologics approved for psoriasis inhibit TNF-α, a key cytokine in the pathogenesis of psoriasis. As a group, TNF inhibitors do have safety concerns. Because TNF inhibitors target the immune system, a user may be at increased risk for both bacterial and viral infections. Patients should be screened for latent tuberculosis infection and hepatitis B infection prior to initiation of treatment (and possibly at intervals during treatment) as TNF inhibitors can lead to reactivation of disease. Live vaccines should be avoided. Patients are also at increased risk for development or worsening of demyelinating diseases, so caution should be used in patients with a personal or family history of these diseases. The effect of TNF inhibitors on patients with congestive heart failure (CHF) is still unclear, as studies evaluating the use of TNF inhibitors in treating CHF have shown improvement, worsening, and no change. Clinicians may not want to prescribe these drugs to patients with more severe, NYHA class III or IV disease, and patients with milder disease need to be monitored for worsening of CHF symptoms [6].

Etanercept is a human fusion protein that binds both soluble and membrane-bound TNF-α. It is given as a subcutaneous injection twice a week for 3 months followed by maintenance therapy of a reduced dose given twice a week or the same dose once weekly [62]. The response is dose-dependent over a 12-week treatment course, as PASI-75 has been seen in 49% of patients given 50 mg biweekly and 33% of patients given 20 mg biweekly [63]. Modest injection site reactions are the most common adverse event [6].

Infliximab is a mouse-human chimeric antibody that also binds soluble and membrane-bound TNF-α [63]. It is given intravenously at week 0, 2, 6 and then every 4 to 8 weeks after for maintenance therapy [9]. Psoriasis rapidly responds to infliximab treatment. PASI-75 was seen in 80% by week 10 and 61% of patients maintained this response to week 50 [64]. Infusion reactions such as blood pressure instability, nausea, sweating, headache, and shortness of breath can occur with administration but can be combated by acetaminophen and antihistamines. Formation of antibodies against the mouse portion of the compound can occur and diminish response, so clinicians may consider giving a low dose of methotrexate to suppress this response [62].

Adalimumab is a human recombinant protein that binds TNF-α. It is administered as a subcutaneous injection given weekly for 2 weeks and then twice a month afterwards [62]. PASI-75 was achieved in 80% at 12 weeks and 68% at 60 weeks in 1 study, and a later phase III trial showed a PASI-75 in 71% at week 16 with a sustained response to week 33 [65,66]. The most common side effect is injection site pain [62].

The previous 3 TNF inhibitor drugs mentioned are approved by the FDA for both plaque psoriasis and psoriatic arthritis. The latest drug in this category, a human monoclonal antibody called golimumab, was approved in 2009 for psoriatic arthritis. The once monthly injection regimen is more convenient. The GO-REVEAL trial found that PASI-75 was achieved at 14 weeks in 40% and 58% with a dose of 50 mg and 100 mg, respectively, and the response increased at 24 weeks with a PASI-75 in 56% and 66% with a 50-mg or 100-mg dose [67].

Alefacept was approved in 2003 for plaque psoriasis and is a fusion protein that blocks the costimulatory pathway between LFA-3 on the antigen presenting cell and CD2 on the T-cell. As a result, T-cell activation
and replication are decreased along with an important decrease in the number of memory T-cells [62]. The drug is given as an intramuscular injection once weekly for 12 weeks. Alefacept is a reasonable option if TNF-α antagonists are contraindicated. It has a good safety profile but is significantly less effective than the other 4 currently approved biologic agents [9]. Only 21% of alefacept-treated patients had a PASI-75 after a 12-week course [68]. Some patients may show a long remission response, and a repeat 12-week treatment course is an option if a patient showed a previous response. Side effects include reduction in CD4 T-cells, so biweekly T-cell counts are required, and use in patients with HIV is contraindicated [6].

Ustekinumab is the most recently approved biologic (September 2009). It is a human monoclonal antibody that binds a p40 subunit present in both IL-12 and IL-23, so both the Th1 and Th17 responses that are upregulated in psoriasis are controlled [9,22]. The dosing is convenient, as injections are given at week 0, 4 and then every 12 weeks. Two multicenter trials (PHOENIX I and II) found that PASI-75 was reached at week 12 in about two-thirds of patients [69,70]. The ACCEPT trial showed ustekinumab to be more effective than etanercept [71]. Injection site reactions can occur, but less frequently than with etanercept. Another drug, briakinumab, also targets p40 and had shown promise and efficacy in clinical trials [9]. Phase II trials showed a few cases of major adverse cardiovascular events in patients treated with this drug. Briakinumab was withdrawn from the FDA application process in January 2011 due to the need for further studies [72].

**Case Continued**

In an effort to encourage adherence, the clinician gives the patient a close follow-up appointment. One week later, the patient is asked about her ability to comply with the current regimen. She reports that she missed a few doses over the weekend while at a soccer tournament but has been able to incorporate the topical applications into her daily routine. More importantly, she is pleased with how the plaques have decreased and thinned out with treatment. Over the next 2 months, the patient further improves and is scheduled for visits every 6 months. For the next several years, she is able to combat flares with increases in the dosing regimen.

### What follow-up is necessary?

Decreased quality of life, poor medication adherence, and the presence of comorbidities make close follow-up of this chronic disease important. Due to the psychological stress of psoriasis, physicians should regularly address the emotional needs of the patient. Patients are at an increased risk for depression, which can cause exacerbations of the disease and decreased use of medication [44]. Stress can also exacerbate disease [73]. This makes early recognition and treatment important [74]. Additional known environmental triggers, such as medication use or infection, should also be reduced if possible [21].

Assessing patient adherence can be difficult and obvious clinical signs such as very thick, scaly skin (coral reef plaques) may not be present, causing providers to rely on the established rapport with the patient and use of a nonjudgmental approach. Follow-up appointments should delve further into reasons for nonadherence, with adjustment in therapy as needed [43,44]. If decreased medication response is seen despite adherence, consideration should be given to combination therapy or rotational therapy.

Concurrent medical conditions should also be addressed. Use of treatment modalities such as PUVA, tar, cyclosporine, methotrexate, and other immunosuppressive drugs increase the risk of squamous cell carcinoma, so patients require intermittent full skin examinations. If plaques in the groin or buttocks region are suspicious looking or unresponsive to traditional therapies, biopsy or referral may be indicated [19,74]. In addition, regular screening for cardiovascular, metabolic syndrome, autoimmune diseases (especially psoriatic arthritis), and substance abuse should occur with appropriate treatment or referral [74].

### 10-Year Follow-up

The patient arrives for an office visit 10 years after the initial diagnosis was made. She has been seen at least twice a year for refills, flares, and adverse event monitoring. She has noticed new lesions arising more frequently that are less responsive to her current regimen. In addition, she has noticed joint pain and stiffness, especially in her left knee and fingers of her right hand. Physical examination reveals large,
scaly, erythematous plaques that have extended down onto her forearms and fingers as well as her back and lower legs. Her nails have deep pits with separation and discoloration. There is boggy edema in the most distal finger joints of her right hand.

- How frequently does psoriatic arthritis occur in patients with psoriasis?

Joint pain and stiffness is seen in up to 60% of patients with psoriasis [75]. Approximately 10% to 30% of psoriasis patients develop an erosive, debilitating version known as psoriatic arthritis [1]. Psoriatic skin disease precedes arthritis in about 80% of patients and typically manifests 12 years after skin symptoms are seen [76].

There is a shared pathogenesis between psoriasis and psoriatic arthritis involving T-cell driven inflammation. However, the severity of skin disease does not correlate with joint disease. Joint disease is most commonly an asymmetrical mono- or oligoarthritis that affects the digits, knees, or ankle. Spine or symmetric arthritis is less common. Clinical findings that help distinguish psoriatic arthritis from rheumatoid arthritis include distal finger or toe joint involvement, dactylitis, and (later on) new bone formation near joints. Joints may have adjacent nail involvement and skin lesions [77]. Radiographic changes showing bony erosion can been seen in 40% of patients [75].

Early identification of psoriatic arthritis is crucial to managing this progressive disease. Clinicians treating patients for psoriasis have a unique opportunity to screen for its onset. Patients should be asked about joint pain, stiffness on awakening lasting more than 30 minutes, swelling, and fatigue at follow-up visits. NSAIDs can be initiated for pain, but if the patient shows no improvement or has disabling symptoms, referral to a rheumatologist should be prompt [75].

CONCLUSION

As the most common autoimmune disease in the United States, physicians are likely to encounter patients with psoriasis. While usually presenting as erythematous papules and plaques, the disease can present in less typical forms and should be differentiated from a number of other skin disorders. Disease onset is triggered by both genetic and environmental factors that result in a dysregulation of the body’s immune response. The inflammation is systemic, so patients can develop psoriatic arthritis and are at increased risk for other comorbidities. This life-long disease significantly impacts a patient’s quality of life and patient education and support is essential. For localized disease, topical medication or localized phototherapy can be prescribed. Patients with generalized disease require a more aggressive approach with phototherapy, systemic medications, or biologics. Referral to a specialist may be appropriate when there is diagnostic uncertainty or for treatment options with which the primary care provider is not familiar. The need for coordination of care is greater than ever with the need to monitor systemic treatments and to monitor for and treat comorbid conditions.

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REFERENCES