Psoriasis is a complex and multifaceted chronic skin condition that is subject to an ongoing cycle of remissions and exacerbations. The characteristic scaly red plaques are sometimes thick (the term indurated is used, but this should not be confused with induration of diseases such as cellulitis) and typically vary in size, site, extent of involvement, and associated symptoms. They occur most commonly on the elbows, knees, sacrum, and scalp. Thus, in any given individual, severity fluctuates and with it the impact of psoriasis on quality of life and psychosocial well-being.1 An earlier article reviewed the pathophysiology and etiology of psoriasis, and discussed topical therapies for treatment of this condition.2 This review discusses the scoring system for the evaluation of psoriasis and its treatment with phototherapy and systemic medications.

PURPOSE: To review the scoring, severity, and systemic treatment of moderate to severe psoriasis.

Epidemiology: Psoriasis occurs in 1% to 3% of the US population. In 20% to 25% of these persons, the disease will be more than limited. Approximately 20% of patients with plaque psoriasis will require more aggressive treatment than topical therapy. Plaque psoriasis is more common in individuals with haplotypes HLA-B13, -B17, and -Cw6. It worsens with HIV infection, stress, other infection, and exposure to ultraviolet light.

Review Summary: Psoriasis is a complex and multifaceted chronic skin condition that is subject to an ongoing cycle of remissions and exacerbations occurring most commonly on the elbows, knees, sacrum, and scalp. Severity fluctuates and with it the impact of psoriasis on quality of life and psychosocial well-being. Traditionally, assessments of psoriasis severity are based on clinician appraisal of the visible signs of disease, using the Psoriasis Area and Severity Index (PASI) scoring system. A number of therapies are available to treat moderate to severe psoriasis, including phototherapy and systemic treatment with oral retinoids, methotrexate, and cyclosporine.

Type of Available Evidence: Randomized-controlled trials, retrospective cohort studies, unstructured reviews.

Grade of Available Evidence: Good.

Conclusion: The treatment of psoriasis remains challenging. As advances in biotechnology lead to the development of agents that target specific molecular mechanisms in the pathogenesis of psoriasis, it is the hopeful that the future will provide safer and more effective therapeutic options for patients with this debilitating disease.

severity of psoriasis in order to determine when a patient should be referred for systemic treatment. Because systemic treatments can impact a patient’s other medical problems in a variety of ways (eg, diuretics can sometimes be photosensitizing agents and should be very cautiously given with ultraviolet light therapy; retinoids can raise lipid levels; cyclosporine affects renal function), an understanding of these treatments facilitates comprehensive, safe, and effective care of patients. This is true in particular when the care of patients is shared between a primary care physician and a dermatologist.

**Psoriasis Severity and Scoring**

Objective and accurate evaluation of disease severity in patients with psoriasis is important for designing therapeutic strategies and assessing patient progress, and is invaluable for evaluating and comparing efficacy of new psoriasis treatments in clinical trials.1,5

**Psoriasis Area and Severity Index**

Traditionally, assessments of psoriasis severity are based on the treating physician’s appraisal of the visible signs of disease.1 Using the Psoriasis Area and Severity Index (PASI), a clinician generates a score based on the quantitative assessment of erythema, desquamation, and induration of plaques, combined with the skin surface area involved.4 A numerical value from 0 to 6 is assigned for each of 4 body regions—head, trunk, upper extremities, and lower extremities—based on the percentage of area involved. Each region is then rated from 0 to 4 for erythema, induration, and desquamation. The PASI score is calculated from the total scores of each region in all 4 categories and ranges from 0 to 72, with higher scores representing a greater degree of psoriasis severity (Table 1).1,5

Alternatively, the self-administered PASI (SAPASI) is based on patient assessment of disease severity. The score is computed using the same formula as the PASI and similarly ranges from 0 to 72. A comparison study of PASI and SAPASI scores in 351 patients showed a high correlation between the 2 measures, though SAPASI scores were generally higher and more widely scattered, which may reflect a subjective component in the self-scoring group, influenced by the burden of the disease on their QOL.6

**Body Surface Area Assessment**

The percentage of involved body surface area (BSA) is the basis of many rating methods and is often used to define psoriasis severity in clinical trials and by drug regulatory agencies and pharmaceutical companies.1 In a common technique, the area of 1 side of a flat closed hand not including the fingers represents 1% of BSA affected. In an alternative method, “the rule of nines,” each body region represents 9% BSA (except the genitalia, which represents 1%) and the total area affected is the sum of the percentages assigned to each region.5

Such visual grading methods are based on subjective assessments and therefore are often associated with high interobserver variability and questionable reliability.5,6 In fact, planimetric investigations suggest that a hand area actually represents 0.70% to 0.76% BSA rather than 1%.4 When 4 clinicians assessed the area of involvement in 10 patients, their ranking differed significantly.7

In addition to questionable reliability, BSA estimates may not be an optimal means of defining psoriasis severity because of the complex, multifaceted nature of the disease. Some patients with low BSA involvement have severe psoriasis whereas some with high BSA have mild psoriasis, depending on concomitant symptoms and associated effects on QOL.

**Factoring Quality of Life**

Psoriasis is a widely variable disease that affects each patient differently, so an alternative approach for determining clinically significant improvement, whether in clinical practice or in pharmaceutical trials, is to consider QOL issues in conjunction with estimates of BSA involvement. Specific aspects of QOL include symptomatic discomfort, body anxiety, and the impact of the disease on daily activities as well as social, emotional, and professional well-being.1 The National Psoriasis Foundation (NPF) developed the NPF-Psoriasis Score (NPF-PS) based on a scale of 0 to 30 with scores assigned based on 5 equally weighted components. In a double-blind, placebo-controlled study, the NPF-PS was strongly correlated with PASI and Physician’s Global Assessment (PGA), but better reflected patients’ perceptions.10 Alternatively, the Salford Psoriasis Index (SPI) is a measure of psoriasis severity that incorporates the current clinical extent of psoriasis based on PASI, with scores indicating psychosocial disability

### Table 1. Psoriasis Area and Severity Index Scoring and Formula*

<table>
<thead>
<tr>
<th>Area of Involvement</th>
<th>Erythema</th>
<th>Induration</th>
<th>Desquamation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>0</td>
<td>no involvement</td>
<td>0 no involvement</td>
</tr>
<tr>
<td>Trunk</td>
<td>1</td>
<td>&lt;10%</td>
<td>1 slight</td>
</tr>
<tr>
<td>Upper</td>
<td>2</td>
<td>10% &lt; 30%</td>
<td>2 moderate</td>
</tr>
<tr>
<td>Extremities</td>
<td>3</td>
<td>30% &lt; 50%</td>
<td>3 marked</td>
</tr>
<tr>
<td>Lower</td>
<td>4</td>
<td>50% &lt; 70%</td>
<td>4 very marked</td>
</tr>
<tr>
<td>Extremities</td>
<td>5</td>
<td>70% &lt; 90%</td>
<td>4 very marked</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>90% &lt; 100%</td>
<td>4 very marked</td>
</tr>
</tbody>
</table>

*PASI = 0.1(E₉ + I₉ + D₉)Ah + 0.3(E₉ + I₉ + D₉)At + 0.2(E₉ + I₉ + D₉)Aₐ + 0.4(E₉ + I₉ + D₉)Aₐ —
where E = erythema; I = induration; D = desquamation; A = area.
PHOTOTHERAPY

Ultraviolet B. In combination with coal tar preparations, UVB phototherapy is part of the oldest treatment (the Goeckerman Regimen involved application of crude topical coal tar and exposure to UVB) for moderate to severe psoriasis.26 Whereas this regimen typically leads to remission of psoriasis in 80% of patients within 25 days,13 it has fallen out of favor; hospitalization for phototherapy is no longer economically practical, patients have difficulty with the time and expense of the 25 to 30 outpatient treatments necessary to achieve reasonable benefit, and patients dislike the smell of coal tar preparations.26

Another combination regimen, the Ingram method, is based on the substitution of anthralin for coal tar. However, in addition to poor patient acceptance of anthralin, 2 bilateral paired comparison studies in 11 and 15 patients showed little additional benefit.27,28 By the 1970s, it was shown that lubricating base was as effective as crude coal tar and that outpatient treatment 3 times per week was as effective as an equal number of inpatient treatments. Most current regimens involve outpatient treatment 3 times per week with topical application of mineral oil or petrolatum.16

Narrowband UVB (NB UVB) encompasses the sunburn spectrum wavelength of 311 ± 2 nm and has been shown to offer a significant therapeutic advantage over broadband UVB (BB UVB, 300 - 320 nm). In a bilateral comparison study in which 22 patients were treated with NB UVB on one side and BB UVB on the other, faster clearing and more complete resolution of
Psoriasis occurred on the side treated with NB UVB. However, the erythema response to treatment was significantly more intense and persistent on this side. In histopathologic sections, considerably more necrotic keratinocytes were observed in skin treated with NB UVB after a single 2.0-minimum erythema dose exposure. As a result, treatment with NB UVB should be coupled with obligate minimum erythema dose testing and close clinical observation during dose increases.29

Concomitant use of calcipotriene with both NB and BB UVB has been shown to enhance PASI score reductions.30 The combination of tazarotene with UVB is similarly effective. Patients treated with tazarotene and BB UVB achieved faster and significantly greater reductions in plaque elevation and scaling with a significantly lower median cumulative UVB exposure than with vehicle gel plus UVB light or UVB phototherapy alone.31 No significant difference was detected between NB UVB combined with topical calcipotriol vs tazarotene gel.32

Though in many instances combining UVB with various agents achieves better results, special caution must be taken with combined therapies; unwanted results may include increased photosensitivity and burning, shortened duration of therapy,33 and

<table>
<thead>
<tr>
<th>Table 2. Treatment Options for Management of Psoriasis*19</th>
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<tbody>
<tr>
<td>Treatment</td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>Phototherapy</td>
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<tr>
<td>UVB</td>
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<tr>
<td>NB UVB</td>
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<tr>
<td>PUVA</td>
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<td>Systemic Agents</td>
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<td>Acitretin</td>
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<tr>
<td>Methotrexate</td>
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<td>Cyclosporine</td>
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*UVB = ultraviolet B; NB = narrowband; PUVA = psoralen with ultraviolet A; BB = broadband. **
decreased efficacy. For example, salicylic acid should not be used with phototherapy because it acts as a sunscreen and blocks therapeutic light, and duration of remission is shortened when UVB is administered in conjunction with topical corticosteroids.

The major drawbacks of UVB phototherapy are time commitment and accessibility. Short-term side effects mimic the effects of sunburn and include erythema, vesiculation, and skin dryness, while long-term therapy can lead to cutaneous aging, wrinkling, and actinic keratoses. Current evidence suggests that the risk of UVB-induced skin cancer is minimal.

The xenon-chloride gas excimer laser offers a means for local monochromatic 308-nm UV phototherapy of skin and therefore holds considerable advantages over current phototherapy treatments. It can deliver high-intensity UVB energy at 308 nm—a wavelength similar to that used in NB UVB—via a flexible handpiece, thereby leaving the adjacent unaffected skin unexposed. Since psoriatic lesions often can withstand much higher UV exposures, this localized delivery of UVB energy allows higher doses to be used initially on the psoriasis plaques, resulting in faster clearing and fewer exposures. It has been shown that as little as 1 high-dose excimer laser treatment can be effective for localized plaque-type psoriasis and that multiple treatments or other irradiation schedules may prove even more efficacious with longer-lasting remissions. In a recent multicenter trial, 72% (66 of 92) of patients achieved at least 75% clearing in an average of 6.2 treatments. Eighty-four percent reached improvement of 75% or better after 10 or fewer treatments and 50% reached improvement of 90% or better after 10 or fewer treatments. The treatments were generally well tolerated. Common side effects included erythema, blisters, hyperpigmentation, and erosions.

**Psoralen With UVA.** The second form of ultraviolet therapy combines the photosensitizing drug methoxypsoralen (psoralen) with ultraviolet A in the range of 320 to 400 nm. Methoxypsoralen is administered in a dose of 0.6 mg/kg of body weight 2 hours prior to UVA exposure. The dose of UVA is determined by the patient’s skin type and sensitivity to ultraviolet radiation.

Although PUVA therapy has the potential to induce long-term remission in just a single course, the implementation of a maintenance regimen, consisting of 1 treatment every 1 to 3 weeks, further improves remission rates significantly.

PUVA therapy is highly acceptable to patients because of its efficacy and the freedom from use of topical medications between treatments. The therapeutic schedule is simple, consisting typically of 2 to 3 outpatient treatments per week for 10 weeks followed by a maintenance regimen that can be as infrequent as once every 2 to 4 weeks with tapering eventually. Short-term side effects include nausea, burning, and pruritus in 10% to 20% of patients. The major long-term concern is photocarcinogenicity. The incidence of skin cancer depends on the cumulative dose of UVA received. Compared with patients who had fewer than 160 PUVA treatments, patients who received more than 160 treatments had an 11-fold increase in squamous cell carcinomas. In addition, a single, prospective trial of 1380 patients first treated with PUVA from 1975 to 1976 reported an increased risk of melanoma after 15 years, especially among patients who received more than 250 sessions.

Increased awareness of the risks of skin cancer has led to regimens that minimize the cumulative dose of PUVA. Patients now receive lower doses, and less frequent, shorter courses of UVA therapy. Though combining PUVA with therapeutic agents that reduce the UVA dose required for clearance of psoriasis may be of benefit in reducing the long-term risk of cutaneous malignancy, both methotrexate and cyclosporine have been shown to contribute to the risk of nonmelanoma skin cancer in patients receiving phototherapy.

A bilateral comparison study of 13 patients with chronic plaque psoriasis found that concomitant use of calcipotriene enhances the response of psoriasis to PUVA. Another observer-blinded comparison in 31 patients found that tacalcitol ointment and tazarotene gel were both comparably effective at accelerating treatment response to PUVA and, by virtue of their UVA dose-sparing effect, might also be useful in reducing the possible long-term hazards of PUVA treatment.

Data regarding the combination of PUVA and corticosteroids have yielded conflicting results, with some claiming that it results in faster clearing without shortening the duration of remission, and others claiming that the addition of topical corticosteroids to a regimen of PUVA results in shorter remissions. Overall, the most ideal combination seems to be PUVA with oral retinoids.

**FOODS AND MEDICATIONS THAT ARE PHOTOSENSITIZERS**

A variety of foods and medications are photosensitizers (ie, they make the skin more sensitive to ultraviolet light—usually to UVA but sometimes to UVB or both). Photosensitizing foods (usually to UVA) include limes, figs, parsley, parsnips, mustard, carrots, and celery (eg, those that contain furocoumarins). Nonsteroidal anti-inflammatory drugs, amiodarone, and phenothiazines can cause phototoxic drug reactions. Some examples of photosensitizing medications (mostly to UVA) include antidepressants (eg, amitriptyline, imipramine); antihistamines (eg, cyproheptadine); antibiotics (eg, tetracyclines); sulfa drugs (eg, sulfamethoxazole, trimethoprim); antipsychotic drugs (eg, chlorpromazine); diuretics (eg, furosemide); hypo-
glycemics (eg, chlorpropamide, tolbutamide); anti-inflammatory drugs (eg, piroxicam); and others (captopril, quinidine sulfate). These medications are much less phototoxic than psoralen. Before referral to a dermatologist, primary care clinicians should be aware of the medications that can be photosensitizing before agreeing that patients should get phototherapy.

**SYSTEMIC THERAPIES**

**Acitretin.** Etretinate and its active metabolite, acitretin, are oral retinoids for the treatment of moderate-to-severe forms of psoriasis. Etretinate was withdrawn from the US market and replaced by acitretin in March 1998 because its long half-life (120 days) and persistence in tissue posed a long-term risk of teratogenicity in women of childbearing potential. Acitretin is less lipophilic than etretinate, and its lack of sequestration into “deep” fatty storage sites is reflected in a comparatively short terminal elimination half-life of 50 to 60 hours.

Used alone, the efficacy of either in chronic plaque psoriasis is modest, with just 50% to 60% of patients showing at least a 50% improvement in PASI scores after 8 weeks of treatment and 70% to 75% improvement after 12 weeks. Though oral retinoids are not as effective as UVB, PUVA, or methotrexate, they are highly beneficial when combined with PUVA or UVB. Not only are they synergistic, but they reduce one another’s side effects. Addition of acitretin in doses of 10 to 25 mg to a regimen of PUVA or UVB dramatically decreases the number of treatments required for clearing, reduces the total exposure to ultraviolet light, and minimizes the side effects associated with retinoid use. In a randomized, double-blind comparative study of 60 patients with severe, widespread marked psoriasis, complete clearing occurred in 96% of patients who received acitretin in addition to PUVA, compared with 80% of patients who received placebo. Moreover, the mean cumulative UVA dose given to patients in the acitretin-PUVA group was 42% less than that required for patients in the placebo-PUVA group. Likewise, patients treated with acitretin-UVB achieved a greater degree of disease clearing with fewer treatments and less UVB radiation than patients treated with either placebo-UVB or acitretin alone.

The most common side effects associated with acitretin are mucocutaneous and include cheilitis, conjunctivitis, hair loss, nail plate abnormalities, dry skin, and sticky skin. Periungual pyogenic granulomas can develop but usually resolve with dose reduction. Sometimes pyogenic granulomas develop in other locations. An interesting systemic cutaneous side effect is the development of eruptive xanthomas.

Systemic side effects may include osteoporosis, calcification of ligaments, and skeletal hyperostosis (much rarer than with isotretinoin). However, a recent study found that acitretin at low doses did not appear to cause significant long-term side effects after 1 year of treatment. In addition, laboratory abnormalities, such as elevation of serum lipids (particularly triglycerides) and liver function tests (LFTs), can occur and should therefore be monitored. Elevation of triglycerides levels above 800 mg/dL can lead to pancreatitis.

Although acitretin has a shorter half-life than etretinate, it is still highly teratogenic and contraindicated in pregnant women. Furthermore, in the presence of ethanol, acitretin is esterified to etretinate, creating great concern that birth defects might result if acitretin-treated women inadvertently ingest alcohol, a frequent ingredient in a variety of foods and over-the-counter medications. It is therefore not recommended for women of childbearing potential to become pregnant within 3 years of using acitretin. For these women, isotretinoin, which is the retinoid used to treat acne, can be used if appropriate pregnancy precautions are taken. Isotretinoin has no affinity for lipids and is cleared within a month of usage.

**Methotrexate.** Methotrexate is indicated for moderate to severe psoriasis that is unresponsive to topical or phototherapies. It is particularly beneficial in patients with psoriatic arthritis as well as in patients with severe forms of psoriasis, including psoriatic erythroderma and pustular psoriasis. The other therapies—UVB, PUVA, and retinoids—are not effective for psoriatic arthritis. Methotrexate is the gold standard for oral therapy.

During the course of 22 years, 113 patients with severe psoriasis were treated with low-dose methotrexate (maximum weekly dose of 15 mg; mean cumulative dose of 4803 mg) for an average of approximately 9 years. Of these patients, 81% achieved prolonged, complete, or near-complete clearance and 73% experienced side effects—most frequently abnormal LFTs, nausea, and gastric complaints. Seventy-one patients discontinued therapy. Thirty-three patients discontinued therapy due to side effects and, of the 55 patients who had 1 or more liver biopsies, 13% had fibrosis and 4% had cirrhosis.

Side effects associated with methotrexate have led to the development of guidelines for its usage. Methotrexate is renally excreted, immunosuppressive, hepatotoxic, and teratogenic. Therefore, patients must have normal hematologic status and normal renal and liver function before initiation of therapy, and the drug must be avoided in alcoholic patients as well as in pregnant women. Bone marrow toxicity is the most serious short-term side effect and can result from concomitant use of the antibiotic trimethoprim-sulfamethoxazole or medications that reduce renal clearance of methotrexate. Other side effects include mucosal ulceration or stomatitis, nausea, macrocytic anemia, and pulmonary toxicity. The most concerning, and most common, long-term problem is hepatotoxicity. Retrospective studies have indicated that cirrhosis develops in 3% of patients.
psoriasis patients who have received a cumulative dose of methotrexate ≥1.5 g and 20% to 25% of patients who have received ≥4 g.\cite{22} As a result, American Academy of Dermatology guidelines recommend a liver biopsy at the onset of therapy and at 1.5-g intervals of cumulative dose for the duration of treatment.\cite{23} Miscarriages and birth defects can occur if methotrexate is taken during pregnancy and it has been suggested that men taking the drug discontinue treatment several months before conception.\cite{24}

Methotrexate also can induce a hypersensitivity syndrome. The authors have seen this syndrome twice, once in a woman who took methotrexate to induce an abortion and once in a patient taking methotrexate for treatment of choriocarcinoma. Notably, both patients had erosions on their lips and genitals, along with fever and malaise. The authors have not seen this syndrome in psoriasis patients, despite contact with more than 100 patients who have take methotrexate for psoriasis. Most dermatologists administer a test dose of 5 mg and wait 2 weeks before instituting continuous therapy.

**Cyclosporine**. Cyclosporine is an immunosuppressive agent indicated for the treatment of recalcitrant plaque psoriasis. It is usually indicated in patients who have failed to respond to other systemic therapies or for whom other therapies, such as acitretin or methotrexate, are contraindicated or intolerable,\cite{25} and may be useful in women planning pregnancy.\cite{26} Cyclosporine is listed in the Food and Drug Administration pregnancy category C. A recent randomized trial of 88 patients found no significant differences in efficacy between methotrexate and cyclosporine after 16 weeks of treatment for moderate to severe psoriasis.\cite{27}

Cyclosporine is of particular benefit when psoriasis must be cleared quickly (one of the authors cleared severe psoriasis in a patient who had never been treated before and who was to be married in 5 weeks).

In a multicenter US study of 181 patients with extensive or disabling psoriasis, cyclosporine at approximately 5 mg/kg per day produced a reduction in BSA of ≥70% in 86% of the patients. These patients were then entered into a placebo-controlled study of maintenance therapy in which cyclosporine at 3 mg/kg per day adequately and safely maintained 58% of patients with psoriasis for a 6-month period.\cite{28} However, without maintenance therapy, psoriasis relapses soon after the cessation of cyclosporine.\cite{29,30}

A common side effect of cyclosporine is paresthesias in the hands and feet after the medication is taken. Less common side effects, which only occur with continuous use, include hypertrichosis, gastrointestinal disturbances, gingival hyperplasia, hypertension, hyperlipidemia, nephrotoxicity, and electrolyte disturbances. With long-term therapy, nephrotoxicity is the major concern.\cite{31} Of 122 patients treated with cyclosporine for an average of 22 months, 28% discontinued its use due to renal failure and 19% due to hypertension. The risk of toxicity increases with age, duration of therapy, preexisting hypertension, or elevated serum creatinine.\cite{32}

**CONCLUSION**

The treatment of psoriasis remains challenging. Combination, rotational, and sequential therapy regimens, by decreasing the total cumulative doses, aim to enhance efficacy while reducing toxicities associated with individual therapies. Phototherapy and systemic treatments have opened new pathways for the treatment of psoriasis. Though phototherapy with NB UVB light appears to be the current gold standard for the treatment of psoriasis with the efficacy of PUVA but fewer side effects, methotrexate remains an excellent and cost-effective treatment option. In all, the appropriate therapeutic regimen must be tailored to the needs, expectations, underlying health, and schedule of individual patients. Current systemic treatments offer patients a number of effective options in this regard. Patients who experience toxicity or fail to respond to acitretin, methotrexate, and cyclosporine have been treated with a variety of other systemic agents including oral tacrolimus, mycophenolate mofetil, hydroxyurea, 6-thioguanine, sulfasalazine, thioureylenes propylthiouracil, PPAR-γ inhibitors, and parathyroid hormone-related peptide.\cite{33,34} As advances in biotechnology lead to the development of agents that target specific molecular mechanisms in the pathogenesis of psoriasis, it is the hope that the future will provide safer and more effective therapeutic options for patients with this debilitating disease.

**REFERENCES**


