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# The Role of the Specialty Pharmacist in Optimizing the Quality of Care for Patients with Psoriasis and Psoriatic Arthritis

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## **The Role of the Specialty Pharmacist in Optimizing the Quality of Care for Patients with Psoriasis and Psoriatic Arthritis**

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### **Disclosures**

*The following contributors have no relevant financial relationships with commercial interests to disclose.*

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### **Educational Objectives:**

*After completing this continuing education program, the participant will be able to:*

- Identify common comorbidities, focusing on signs and symptoms of psoriasis and psoriatic arthritis and the need for increased recognition
- Demonstrate knowledge of the efficacy and safety of current and emerging treatments for psoriasis and psoriatic arthritis
- Characterize the major barriers to optimal adherence to psoriasis and psoriatic arthritis treatments and describe the role of the specialty pharmacist in overcoming them
- Examine the importance of patient education and awareness in improving treatment outcomes

**Target audience:** Pharmacists

**Type of activity:** Application

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**Estimated time to complete activity:** 1.5 hours

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## Overview

The American Academy of Dermatology defines psoriasis as a “genetic, systemic, inflammatory, chronic disorder that may be altered by environmental factors.” Reportedly, it affects nearly 2% of the population in the United States,<sup>1</sup> and while the disease affects males and females equally, it is seen more commonly in Caucasians than in other racial groups.<sup>2</sup> The strong genetic component of the disease links nearly one-third of those affected with a first-degree relative.<sup>3</sup> This disease has been reported to be responsible for greater than \$50 billion annually in direct health care costs.<sup>4-6</sup> While psoriasis falls under the umbrella of dermatologic disorders, the sequelae are a varied group of immunologic inflammatory conditions that carry significant consequences. The multisystem effects of psoriasis can manifest as psoriatic arthritis, inflammatory bowel disease, and coronary artery disease.<sup>4</sup>

In a recent analysis of survey data collected from more than 5600 patient members of the National Psoriasis Foundation, nearly 49% of the respondents reported going untreated.<sup>7</sup> Equally important, of those undergoing treatment for psoriasis and psoriatic arthritis (PsA), overall dissatisfaction with their treatment was found to be very high.<sup>7</sup> With an increased understanding of the signs and symptoms of psoriasis and PsA, as well as greater insight into patient-specific medication selection and monitoring, specialty pharmacists can help improve patient adherence and treatment satisfaction.<sup>8</sup>

## Comorbidities

In 1974, Farber and Nall published early population-based data linking first- and second-degree relatives with psoriasis.<sup>9</sup> More recent population-based research has found that psoriasis is associated with a greater frequency of chronic pulmonary disease, mild liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease, anxiety disorders, lymphoma, and rheumatologic disease.<sup>5,10</sup> Current genomic research has identified several genetic markers linking psoriasis to an increased incidence of cardiovascular disease, Crohn’s disease, and type 2 diabetes, which also share common genetic markers with moderate to severe psoriasis.<sup>4,11</sup>

The risk associated with development of type 2 diabetes was also dependent on psoriasis severity.<sup>12</sup> Given the increased prevalence of comorbidities in patients with psoriasis, greater surveillance is essential. Those patients with severe psoriasis are at an even greater risk of mortality than those with mild disease.<sup>13-15</sup>

## Types of Psoriasis

Psoriasis is a chronic multisystem disease that manifests predominantly in the skin and joint areas.<sup>16,17</sup> While the cause remains unknown, the abnormal changes in epidermal cells and activation of immune processes are believed to be initiating factors.<sup>17</sup>

For the purposes of this activity the types of psoriasis will be described as cutaneous psoriasis (skin-related disease) and psoriatic arthritis (joint-related disease). Treatment modalities for cutaneous psoriasis are based on the area of involvement and severity of disease. PsA is a chronic inflammatory disease associated with psoriasis. It causes pain and stiffness of affected joints. It is estimated that 4% to 30% of patients with psoriasis have PsA.<sup>18</sup>

Therapies for the cutaneous disease can be both topical and systemic. Due to the immunologic basis of the psoriatic disease, systemic therapies for the cutaneous manifestations of the disease and joint-related disease are common and may overlap.

Classification of cutaneous psoriasis is generally based on morphology; however, patients often present with overlapping categories (**see Table 1**).<sup>4</sup>

**Table 1: Classification of Cutaneous Forms of Psoriasis<sup>4</sup>**

Type	Presentation	Symptoms
Plaque	Scaly knees and elbows	Pruritic painful fissures
Inverse/flexural	Skin folds erythematous plaque	Lacking scales due to moist area
Guttate	Pink/fine-scale lesions Trunk and extremities	Recent history of upper respiratory infection (Group A Hemolytic Strep)
Erythrodermic	Generalized erythema	Almost entire body Fever, chills, malaise
Pustular	Pustules generalized or localized on palms and plantar surface	Can be accompanied by fever toxicity

### Triggers

Factors related to the environment, behavior, and medication have been identified as initiating the immunologic cascade of events resulting in psoriatic flares. Patients should be cognizant of traumatic injury to the skin, physical and psychological stress, and how cold weather affects their disease.<sup>19</sup> Patients should be educated on lifestyle modifications that could contribute to controlling psoriatic flares. These changes include decreasing stress as well as alcohol consumption, smoking cessation, and addressing obesity.<sup>20</sup> Management of hypertension, diabetes, and cholesterol are also believed to play a role in decreasing psoriatic flares.<sup>20</sup>

Of significant importance to pharmacists, several classes of medication have been implicated as psoriasis triggers. The most common drugs that have been documented to induce psoriatic exacerbations include beta-blockers, lithium salts, and antimalarial agents.<sup>21</sup> There are, however, several other classes of drugs that have also been reported and should not go unrecognized; these include tetracycline-derivative antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting-enzyme (ACE) inhibitors, carbamazepine,  $\alpha$ -interferon, and abrupt withdrawal of systemic corticosteroids.<sup>21-23</sup> Identifying drugs that are reported to induce disease exacerbations, such as psoriatic flares, as well as recognizing those symptoms are fundamental competencies for today's specialty pharmacists.<sup>24</sup> The profession's leading accrediting organizations, namely the American Society of Consultant Pharmacists, the Accreditation Council for Pharmacy Education, and the Center for Pharmacy Practice Accreditation, have identified that performing thorough assessments of patients' medical conditions, as well as drug-related problems, are required competencies for pharmacists today.<sup>24-26</sup> It is essential that pharmacists caring for patients with psoriasis are able to identify the drugs that may trigger psoriatic flares. Pharmacist intervention in this area can facilitate possible adjustments to treatment and most importantly, safe use of medications by patients.<sup>24-26</sup>

### **Pathophysiology of the Disease**

Psoriasis was previously believed to be a result of unchecked proliferation of epidermal keratinocytes,<sup>27</sup> and the resulting inflammatory response was considered to be secondary to the keratinocytes hypertrophy.<sup>28</sup> While there is currently no existing explanation as to what initiates the initial cascade of events that results in this disease process, it is now recognized that once triggered, the epidermis becomes infiltrated with T-cells, which induce the hyperproliferation of dermal keratinocytes.<sup>28,29</sup> This inflammatory process is what leads to the production of various cytokines, such as tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), interferon gamma, and interleukin-12 (IL-12 and IL-23).<sup>29</sup> Recognition of the disease pathways has led to the utilization of many of the biologic therapies used today.

### **Management of Cutaneous Psoriasis**

There are several distinct clinical subtypes of cutaneous psoriatic disease, the most common of which is plaque psoriasis (90%). In terms of assessment of disease, the clinical tool most often used is the Psoriasis Area Severity Index (PASI), which combines severity of erythema, induration, and desquamation with percentage of body surface area affected.<sup>30</sup> The tool, however, does not allow for assessment of the severity of nonplaque psoriasis. In 2014, a new assessment tool, known as the Brigham Scalp Nail Inverse Palmoplantar Psoriasis Composite Index (B-SNIPI), was introduced.<sup>31</sup> This tool measures the severity of plaque psoriasis, as well as all subtypes. It also calculates Patient Reported Outcomes (PRO) and objective physician assessment equally.<sup>31,32</sup> In 2006, researchers also developed and validated a Nail Psoriasis Severity Index (NPSI), the relevance of which will be discussed in greater detail.<sup>33</sup> Proper training of assessment and clinical evaluation of psoriasis is critical for all practitioners who use these tools. For patients with severe psoriasis, progressive disease is reported to produce a measured decline in health-related quality of life indices; reports classify these patients on a similar scale with those suffering from depression, diabetes, and heart failure.<sup>34</sup> The American Academy of Dermatology acknowledges that localized plaque psoriasis is generally diagnosed clinically and may be managed by primary care providers. It does, however, recommend that all other types be referred to a specialist.<sup>1</sup>

There are several factors that impact the type of treatment that patients with psoriasis should receive, including the patient's age, type of psoriasis, site and extent of lesions, previous treatments, and comorbidities.<sup>35</sup> Therapy should be individualized for each patient, and it is important that these goals balance anticipated treatment outcomes with patient expectations. The primary goal for treatment remains control of psoriatic lesions<sup>17</sup>. Prescribed treatment should be evaluated within a predetermined time frame (ie, 6 to 8 weeks), and the selected therapy should produce a minimum of 50% reduction in baseline PASI score. Therapy should also reflect a Dermatology Life Quality Index of less than or equal to 5 (with 0-5 measured as little to no impact on quality of life).<sup>36</sup> If these outcomes are not achieved, patients and providers should consider alternate therapies available.<sup>36</sup> It is vital that any therapy selected should have maximum efficacy with minimal adverse effects. The treatment should improve the patient's quality of life and control the lesions.<sup>17</sup>

Approximately 80% of patients with psoriasis have mild to moderate disease, who generally respond well to topical therapy. Recent studies also show that more than 86% of all patients with psoriasis are treated with topical agents.<sup>37</sup> The following factors should be considered prior to selection of topical agents<sup>35</sup>:

- Choice of vehicle, such as creams, ointments, solutions, and gels. Patient acceptance may affect adherence.
- Occlusion of some topical agents can alter effectiveness of the drug. For example, use of occlusive covering with topical corticosteroids may increase the absorption of the drug.<sup>38</sup>
- Combining certain topical agents can alter efficacy. For example, calcipotriene requires that the skin pH be greater than 8 in order to be effective.<sup>39,40</sup> As a result, it becomes inactive when applied concomitantly with lactic acid or salicylic acid agents.<sup>39</sup> Application time should be separated in patients using both calcipotriene and a lactic acid or salicylic acid agent.
- Patients receiving chronic topical treatment should be evaluated regularly for therapeutic efficacy. Long-term treatments have been reported as affective in achieving relief for the patient with the lowest potency agent needed while providing minimal long-term risk to the patient.

The following topical agents are, by consensus, recommended for treatment of mild to moderate psoriasis: emollients, keratolytics, topical corticosteroids, topical calcineurin inhibitors, topical retinoids, topical D<sub>3</sub> analogs, fixed dose steroids/calcipotriene, and coal tar as well as anthralin.<sup>41</sup>

### **Emollients, Moisturizers, and Keratolytics**

Emollients, moisturizers, and keratolytics are essential adjunctive topical psoriasis therapy. They reduce the "scale load" in these patients.<sup>42</sup> Examples of keratolytic agents include 5% to 10% salicylic acid gel and 12% ammonium lactate. Ammonium lactate is reported to cause transient stinging on application.<sup>43</sup> Keratolytics are generally applied twice daily, while moisturizers and emollients are applied two to three times daily. They are reported to normalize hyperproliferation of the skin cells, as well as serve as a protective barrier to the stratum corneum. They are most effective when applied to moistened skin.<sup>44</sup>

It is recommended that salicylic acid and higher concentration urea products be used as initial keratolytic therapy. During the intermediate and remission phases, moisturizers and emollients should be used. They are most effective when used in combination with bath oils.<sup>42</sup>

## **STAR**

***Unless directed by a provider, which topical therapy should not be occluded?***

### **Topical Corticosteroids**

Topical steroids are considered first-line therapy in the treatment of mild to moderate psoriasis. Their mechanism of action is to modify the intracellular signaling system of the body's immune system and to decrease vascular permeability that allows dissemination of the immune mediated inflammatory response. They effectively decrease local cytokine production, decrease skin inflammation, and inhibit hyper-proliferation of skin cells.<sup>45,46</sup>

The long-term use of corticosteroids in patients with psoriasis is controversial. While older studies report tachyphylaxis occurring with use of topical corticosteroids within two to four months of initiation of therapy, a newer body of literature reports failure to demonstrate this phenomenon.<sup>47,48</sup>

Lower potency topical steroids are recommended if needed for extended periods.<sup>49</sup> There are, however, side effects to these drugs; they can result in striae, pigmentary changes, perioral dermatitis, and purpura.<sup>49</sup> Greater caution should be used with the Class 1 or ultra-high-potency topical steroids such as clobetasol and betamethasone dipropionate.<sup>49</sup>

These agents should have limited treatment use of no more than two consecutive weeks. Additionally, patients should be counseled not to use more than 50 grams (21 capfuls) of cream/ointment in a one-week period. Occlusive dressings should only be used with this class under physician's supervision. Use should also be avoided on the face, groin, or axillae. The FDA has issued a warning that these medications can cause reversible hypothalamic-pituitary-adrenal axis suppression, and that patients should be monitored closely.<sup>38</sup>

### **Topical Calcineurin Inhibitors**

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are believed to inhibit T-lymphocyte activation, by binding to FKBP-12, an intracellular protein, and complexes with calcineurin-dependent proteins to inhibit calcineurin phosphatase activity.<sup>50</sup> They are FDA approved for the treatment of moderate to severe atopic dermatitis in patients who have not responded to first-line agents. Their use in the treatment of psoriasis, however, is currently off-label and should be considered only by specialists. Many specialists consider them an acceptable alternative when corticosteroids cannot be used, such as in areas where steroid use is contraindicated. There are numerous clinical trials demonstrating a 65% clearance of lesions on the face, genitals, and intertriginous areas.<sup>51-53</sup>

### **Topical Retinoids**

Tazarotene is the only topical vitamin A derivative approved for the treatment of psoriasis. Its effects are exhibited through the inhibition of keratinocyte proliferation.<sup>54</sup> While the once-a-day dosing regimen makes tazarotene an attractive therapeutic option, it is generally less effective

when used as monotherapy. This drug is a teratogen and has previously carried the FDA's Category X labeling nomenclature.<sup>55</sup> As of June 30, 2015, due to changes made to the FDA's *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR or final rule)," tazarotene will be required to carry a new labeling stating that it "requires pregnancy testing, and that contraception is recommended before, during, or after drug therapy."<sup>55,56</sup>

### **Topical D<sub>3</sub> Analogs and Fixed Dose Steroids/Calcipotriene**

Calcipotriene is the most widely used topical D<sub>3</sub> analog. This class of drugs has been shown to be safe and effective in combination with other agents or as monotherapy. Topical vitamin D is believed to bind with the vitamin D receptor and inhibit proliferation of keratinocytes.<sup>57</sup> A combination product containing calcipotriene 0.005% and betamethasone dipropionate 0.064% was approved by the FDA in 2006. It is considered by some experts to be first-line topical therapy for patients with mild to moderate psoriasis.<sup>58</sup> A randomized double-blind trial published in 2014 reported superior efficacy of the fixed dose combination agent over the individual active components.<sup>59</sup> Safety and efficacy data for the combination product have been evaluated. The results demonstrate that efficacy was maintained after one year of continued use, while the adverse effects profile was comparable to the individual products.<sup>60</sup> The dosing regimen of this agent is recommended as once daily,<sup>61</sup> in an effort to improve patient adherence.<sup>62</sup>

### **Coal Tar and Anthralin**

Coal tar was the mainstay therapy for psoriasis for many years. It is used in Goeckerman therapy, which is a day-treatment regimen requiring full-body application of coal tar followed by ultraviolet light therapy. The use of coal tar in combination with phototherapy has been investigated in several clinical trials, and superior efficacy with minimal safety concerns were demonstrated.<sup>63</sup> Similarly, anthralin, also known as dithranol, is a topical agent that is derived as an extract from the trunk of a South American tree. Conventional therapy involves overnight application. Although they are both effective treatment options for psoriasis, there are disadvantages to use of both coal tar and anthralin. Adverse effects include discoloration and staining of clothing and skin, as well as photosensitivity.<sup>64</sup>

### **Salicylic Acid/Lactic Acid**

Keratolytic therapies are considered adjunctive treatments to traditional agents. Regimens including salicylic acid with topical corticosteroids are considered to be a safe and effective treatment option when other therapies present a risk of toxicity or the patient has medical conditions that preclude other treatments. Salicylic acid should not be used in combination with ultraviolet B (UVB) because it blocks UVB.<sup>65,66</sup> Lactic acid, an alpha-hydroxy acid, is generally considered to be a second-line agent for recalcitrant scaling and can be used when there is a potential of salicylate toxicity.<sup>67</sup>

### **Phototherapy**

Phototherapy through natural sunlight for the treatment of a variety of skin diseases has been used for centuries.<sup>68</sup> Those patients generally considered candidates for this method of treatment either as monotherapy or in combination with topical therapies have moderate to severe disease.<sup>69</sup> Ultraviolet (UV) light therapy may be considered a treatment option for those patients with as



little as 5% body surface area (BSA) involvement, but whose psoriatic lesions are in difficult areas to treat such as: palms and soles of the feet, scalp and intertriginous areas.<sup>69,70</sup> Both UVA and UVB light therapies are considered to have local immunosuppressive effects directly on Langerhans cells, as well as inhibit epidermal hyperproliferation and angiogenesis.<sup>69</sup> A current review of treatment protocols suggest that narrowband UVB (NB-UVB) has increased efficacy over broadband UVB (BB-UVB) and is safer than psoralen plus Ultraviolet A (PUVA) due to the psoralen toxicity profile as well as an increased risk of developing skin cancer with long-term use.<sup>68 69</sup>

While considered effective therapy, the treatment has fallen out of favor in the last two decades.<sup>71</sup> Patients report phototherapy to be time consuming, inconvenient due traveling to clinics for short therapy several times a week, resulting in missed work days and time away from family.<sup>72</sup>

### **New Oral Agent for Moderate to Severe Plaque Psoriasis**

In September 2014, the FDA approved apremilast, an oral agent, for the treatment of moderate to severe plaque psoriasis for when phototherapy or systemic therapy is appropriate. The drug is a selective inhibitor of phosphodiesterase 4 (PDE4). Apremilast is believed to elevate cAMP levels, which indirectly modulates the production of inflammatory mediators.<sup>73</sup> Both the *ESTEEM 1 and 2* trials reported sustained improvement in difficult-to-treat areas such as nails, soles of feet, and scalp psoriasis.<sup>61,73</sup> One of the adverse effects reported during clinical trials include an increase in depression; this is of concern, as depression is a recognized comorbidity of psoriasis. Initiation of apremilast therapy should be evaluated by skilled providers for risk versus benefit, and patients should be carefully monitored.<sup>74</sup> It is recommended that initial dosing should be step-up therapy beginning at 10 mg daily, increasing to a maintenance dose of 30 mg twice daily by day 6; this reduces risk of GI symptoms. Patients with severe renal impairment taking apremilast should be closely monitored. Pharmacists should also screen for drug interactions with strong CYP 450 inducers.<sup>74</sup>

### **STAR**

***Psoriatic nail disease affects 80% to 90% of patients with psoriasis.***

***In which type is it most commonly identified?***

### **Management of Severe Cutaneous Disease and Psoriatic Arthritis: Systemic Therapies**

The onset of PsA usually presents between the third and fifth decade of life. It affects men and women equally and can lead to destruction of joints if undiagnosed or untreated.<sup>7,75</sup> Generally PsA appears 10 to 15 years after cutaneous psoriasis occurs. It has been reported that in 10% to 15% of patients, PsA appears with no history of skin lesions.<sup>76</sup> Systemic treatments for psoriasis and PsA are generally considered in those patients with greater than 10% body surface area affected or those patients whose disease is debilitating.<sup>4,35</sup>

Nail disease associated with psoriasis (psoriatic onychodystrophy) is reported to affect 80% to 90% of this population at some point during their disease.<sup>77</sup> It can be painful and debilitating, affecting job performance and activities of daily living.<sup>78</sup> Studies suggest that psoriatic nail disease is most often seen in patients with PsA (53-86%), the severity of the nail involvement also correlates with the degree of joint involvement.<sup>78,79</sup> Failure to recognize nail involvement as part of the PsA could result in delay of treatment with destructive and permanent changes to untreated joint.<sup>80</sup>

## **STAR**

***Patients taking high-dose methotrexate therapy should be counseled to avoid which class of OTC drugs?***

### **Immunomodulatory Drugs and Cyclosporine**

For more than 30 years, methotrexate has been an effective agent for systemically treating psoriasis. It has also been proven effective in psoriatic nail disease. It is believed that the immunosuppressive effects of methotrexate suppress the activated T-cells associated with psoriasis.<sup>20</sup> Once-weekly dosing beginning at 7.5 mg per week and increasing to a maximum of 25 mg per week has been used as long-term therapy and is generally well tolerated. In a 16-week, randomized, placebo-controlled trial comparing methotrexate to placebo, 36% of patients receiving methotrexate achieved a 75% improvement in symptoms score when compared to placebo.<sup>81</sup> Guidelines recommend that patients should be monitored for hepatic toxicity.<sup>35</sup> Folic acid supplementation is advised due to the drug's inhibition of folic acid and subsequent adverse effects. Caution should also be used when combining the high doses of methotrexate used for the treatment of psoriasis with NSAIDs, as methotrexate toxicity has been reported.<sup>35</sup>

Cyclosporine, a calcineurin inhibitor, is considered to be safe and effective for the treatment of psoriasis. It is useful in the management of psoriatic crises, treating patients with psoriasis who are unresponsive to other modalities, and as a bridge to other therapies. It can be used within a rotational regimen of other medications. Oral dosing of 2.5 mg to 4 mg/kg/day have been shown to decrease PASI up to 70%. Doses greater than 5 mg/kg/day do not show greater benefit. Renal toxicity and hypertension can occur in long-term use of cyclosporine; therefore, patients should be monitored closely.<sup>82-84</sup>

### **Biologic Agents**

Biologic agents play a major role in the treatment of moderate to severe psoriasis and PsA. These are recommended for those patients who are on more traditional systemic agents who have not responded adequately to current therapy, those who have comorbidities affecting therapy, or those who have had adverse effects resulting in intolerance to the medication.<sup>4</sup> These agents block the pathways initiated through the T-cell inflammatory response.<sup>29</sup> Currently approved biologic agents inhibit tumor necrosis factor-alpha (TNF $\alpha$ ) or interleukins (IL), namely IL17-A, or a combination of IL-12 and IL-23. These cellular proteins play a major role in the pathophysiology associated with psoriasis and PsA.<sup>85</sup>

### **TNF $\alpha$**

Tumor necrosis factor-alpha (TNF $\alpha$ ) plays an important role in the inflammatory process through stimulation of pro-inflammatory cytokines (interleukins), facilitating leukocyte migration, the activation of neutrophils and eosinophils, and the induction of acute phase reactants and tissue-degrading enzymes. Elevated TNF $\alpha$  levels have been found in tissues/fluids of patients with rheumatoid arthritis, ankylosing spondylitis, PsA, plaque psoriasis, Crohn's disease, and ulcerative colitis.<sup>86</sup>

TNF $\alpha$  inhibitors bind to TNF $\alpha$  receptor sites and interfere with cytokine-driven inflammatory processes.<sup>86</sup> These agents, while effective in the treatment of moderate to severe psoriasis and PsA, have been linked with malignancies, demyelinating disorders, cardiovascular events, reactivation of latent tuberculosis, herpes zoster, and hepatitis B.<sup>87,88</sup>

## **TNF $\alpha$ Inhibitors**

### *Etanercept*

Etanercept is approved for the management of PsA in patients with moderate to severe plaque psoriasis. Standard dosing of etanercept in adults is subcutaneous injection of 50 mg twice weekly for the initial three months of therapy, followed by a 50-mg injection once weekly for maintenance therapy.<sup>89</sup>

A randomized trial involving patients with stable plaque psoriasis, who were selected to receive either 25 mg or 50 mg subcutaneous etanercept twice weekly for 12 weeks. The results demonstrated the regimen was efficacious, with a 75% improvement PASI score, and was well tolerated.<sup>90</sup>

### *Infliximab*

Unlike etanercept, infliximab is administered as IV therapy. Therapy is started at 5 mg/kg at weeks 0, 2, and 6 with maintenance therapy beginning week 8. The infusion of this drug takes from two to three hours and is given in a clinic or institutional setting.<sup>86</sup> In clinical trials, this dosing regimen has demonstrated a rapid patient response rate. A trial involving 249 patients reported that 80% of the subjects saw a decrease in symptoms after just three infusions.<sup>91</sup>

### *Adalimumab*

Adalimumab is indicated for patients with moderate to severe PsA who have failed treatment with etanercept.<sup>92,93</sup> The initial dose is 80 mg subcutaneously, followed by 40 mg every other week starting 1 week after the initial dose. In a 12-week clinical trial, 53% of patients taking adalimumab every other week, and 80% of patients taking adalimumab weekly showed a 75% improvement in PASI scores.<sup>94</sup> There have been reports of formation of antibodies against adalimumab in 6% to 50% of patients treated with adalimumab for psoriasis. Patients who have been found to be positive for antibodies to adalimumab have shown decreased clinical response to therapy.<sup>95</sup>

### *Certolizumab*

In October 2013, the approved indication for certolizumab pegol was extended to include treatment of adults with active PsA, when the response to previous disease modifying antirheumatic drug (DMARD) therapy has been inadequate.<sup>96</sup> Compelling evidence was presented based on a 24-week, double-blind, placebo-controlled part of the RAPID-PsA study, in which certolizumab pegol was compared with placebo. American College of Rheumatology criteria (ACR) was used to assess and verify improvement in tender and swollen joints. This assessment is combined with evaluation of improvement in 3 out of 5 of the following: sedimentation rate, patient assessment, physician assessment, pain scale, disability/functional questionnaire.<sup>97</sup>

The certolizumab pegol study results demonstrated a statistically significant increase in the number of people achieving an ACR20 (20% response) at week 12 (primary clinical end point),

and a statistically significant increased physical function from baseline at week 24. Also seen in this study were improvements in inflammation of the fingers and associated bone pain, psoriatic skin involvement, and nail disease (in people with evidence of these at baseline).<sup>98</sup> The recommended dosing schedule for adult patients with PsA is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week. For maintenance, 400 mg every 4 weeks can be considered.<sup>96</sup>

There are several adverse reactions that are common to the TNF $\alpha$  inhibitors. They may vary in degree of intensity. The following are commonly associated with TNF $\alpha$  inhibitors<sup>86,89,93,96</sup>:

- Pain at injection site; may appear with rash
- Infusion reactions include shortness of breath, chest pain, hypertension, and rarely anaphylaxis
- Upper respiratory infections

### **Interleukin**

Medical science has discovered that certain immune responses are linked to the activities of Type 1 T-cells, which are strongly implicated in the pathology of psoriasis.<sup>85</sup> More specifically, Type 1 T-cells and interferon- $\gamma$ , which are responsible for the inflammatory response seen in psoriasis, are strongly regulated by IL-12 and IL-23, which are related cytokines.<sup>85</sup>

### **Interleukin Inhibitors**

#### *Ustekinumab*

Ustekinumab is a human monoclonal antibody that inhibits IL-12 and IL-23. It was approved in 2009 for the treatment of patients with moderate to severe psoriasis. Dosing of ustekinumab is weight based, and standard dosing for ustekinumab for adults  $\leq 100$  kg is 45 mg given at weeks 0, 4, and every 12 weeks thereafter. A 90-mg dose given in the same regimen is recommended for adults who weigh more than 100 kg.<sup>99</sup> A randomized trial reported superior efficacy of ustekinumab over etanercept for the treatment of psoriasis. After 12 weeks of treatment, 75% improvement in the PASI score was observed in 73.8%, 67.5%, and 56.8% of patients receiving 90 mg ustekinumab, 45 mg ustekinumab, and etanercept groups, respectively.<sup>100</sup>

#### *Secukinumab*

Secukinumab, an IL-17A blocking inhibitor, was approved by the FDA in January 2015 for the treatment of moderate to severe PsA.<sup>101</sup> Secukinumab was found to be effective in treating psoriasis in 2 randomized trials.<sup>102</sup> The end point was a PASI score of 75% in each trial. At week 12 in the ERASURE study, scores were higher with secukinumab than the placebo. The response rates were 81.6% with 300 mg of secukinumab, 71.6% with 150 mg of secukinumab, and 4.5% with placebo. The FIXTURE study reported response rates of 77.1% with 300 mg of secukinumab, 67.0% with 150 mg of secukinumab, 44.0% with etanercept, and 4.9% with placebo. The rates of infection were higher with secukinumab than with placebo in both studies and were similar to those with etanercept.<sup>102</sup>

As with the TNF $\alpha$  inhibitors, the IL inhibitors also report similar adverse effect profiles<sup>99,101</sup>: These include:

- Nasal pharyngitis
- Infection
- Fatigue
- Headache

### **Emerging Therapies**

Janus Kinase (JAK) pathways are key mediators in the immune response associated with psoriasis. JAK inhibitors have previously been approved as targeted therapy for rheumatoid arthritis and stand ready to take a role in treatment of psoriasis and PsA. JAK inhibitors are believed to block specific components of the psoriasis pro-inflammatory cascade.

In recent clinical trials, these agents have been proposed to represent important alternatives for patients with inadequate responses to currently available agents.<sup>103</sup> Oral tofacitinib, which is currently FDA approved for treatment of moderate to severe rheumatoid arthritis, is now in clinical trials for use in the treatment of psoriasis.<sup>104,105</sup> Phase 2b trial data reported that patients with moderate to severe plaque psoriasis showed significant improvement with short-course oral therapy. The improvement response was higher for all patients in the twice-daily dosing groups. PASI 75 response rates of 25%, 41%, and 67% were seen, respectively, in the 2-mg, 5-mg and 15-mg dosing regimens.<sup>104</sup>

Another group of therapeutic agents on the horizon are the Interleukin 17-A (IL-17A) inhibitors. IL-17A is a pro-inflammatory cytokine implicated in the inflammatory process in moderate to severe psoriasis, and PsA. IL-17A is believed to stimulate keratinocytes to increase production of cytokines and other markers of inflammation that have been found in psoriatic lesions.<sup>106</sup> This leads to a continuous loop production of IL-17A affecting keratinocytes producing a chronic inflammatory response.<sup>106</sup>

Results of a recent phase 3 study comparing safety and efficacy of ixekizumab, an IL-17A inhibitor, to placebo with etanercept therapy versus placebo, in patients with moderate to severe psoriasis, have been published.<sup>107</sup> Participants were randomly assigned to receive subcutaneous placebo, etanercept (50 mg twice weekly), or one injection of 80-mg ixekizumab every 2 weeks, or every 4 weeks after a 160-mg starting dose in the UNCOVER-2 trial. In the UNCOVER-3 study, patients received placebo, etanercept, or ixekizumab every 2 weeks, or ixekizumab every 4 weeks. Primary end points of the study were measured as the proportions of patients achieving sPGA score 0 or 1 (indicating skin clearing) and 75% or greater improvement in PASI at week 12. The results for UNCOVER-2 demonstrated that 71% of patients receiving ixekizumab every 2 weeks achieved a PASI 90, and 41% achieved PASI 100. The four-week ixekizumab group resulted in 60% PASI 90 and 31% a PASI 100. Patients in the etanercept portion of the study recorded only 19% PASI 90 and 5% a PASI 100.<sup>107</sup> UNCOVER-3 results showed that in the two-week ixekizumab arm, 68% achieved a PASI 90 and 38% a PASI 100. The four-week ixekizumab group reported 65% PASI 90 and 35% a PASI 100. Patients receiving etanercept saw just a 26% PASI 90 and a 7% PASI 100.<sup>107</sup> These studies demonstrated not only that ixekizumab had greater efficacy than etanercept, but that IL-17A inhibitors have a promising role in the treatment of psoriasis.

Other emerging therapies being researched are the IL-23 inhibitors. A recent phase 2 trial compared the IL-23 blocker guselkumab with adalimumab, a recognized TNF $\alpha$  inhibitor, in

patients with moderate to severe plaque psoriasis. The study reported that guselkumab reached its primary end point of reductions in sPGA scores from  $\geq 3$  to either 0 or 1 after 16 weeks of treatment in 34.1% to 87.5% (dose range 5 mg-200 mg) of patients, compared with 7.1% of those in the placebo, and 58.1% of those in the adalimumab treatment arms.<sup>108</sup> Secondary end points of the trial were considered a PASI 75 score at week 16. The guselkumab cohort saw PASI 75 responses in 43.9% of the 5-mg arm, 75.6% of the 15-mg, 81% of the 50 mg, 78.6% of the 100-mg, and 81% of the 200-mg arm. PASI 75 responses were seen in 4.8% of the placebo arm and 69.8% of the adalimumab arm.<sup>108</sup> These early results indicate that blocking IL-23 with agents such as guselkumab may be an important step in the treatment of moderate to severe plaque psoriasis.

The preliminary study results seen for these emerging therapies offer much hope for patients suffering from moderate to severe psoriasis. These new systemic therapies have a commonality, in that they have been shown to work at the intracellular level by inhibiting the production of cytokines, the markers of inflammation.<sup>104 106,108</sup> Therapies that target IL-17A, IL-23 (pro-inflammatory cytokines) or JAK enzymes (which are activated by extracellular cytokines) offer new possibilities for an intracellular mechanism to halt the biologic pathway leading to psoriasis and psoriatic arthritis.

### **Pharmacist's Place in Psoriasis and Psoriatic Arthritis Therapy**

Pharmacists today have an opportunity to have a positive impact on patient outcomes in the management of psoriasis and PsA. It has been reported that provider training in evaluation of psoriasis severity is non-standardized and inconsistent.<sup>109,110</sup> Non-treatment and under-treatment of patients with psoriasis is well established in the literature.<sup>7</sup> Under treatment of psoriasis and PsA leads to disseminated disease, pain and discomfort, and permanent joint destruction.<sup>7</sup> Additionally, it is well documented throughout the literature that patient dissatisfaction with prescribed psoriasis therapies leads to nonadherence.<sup>111</sup> Survey data collected through the National Psoriasis Foundation, which was collected from 2003-2011, reported that 52.3% of the patients surveyed with psoriasis and 45.5% of those surveyed with PsA were dissatisfied with their treatment.<sup>7</sup>

Patients with psoriasis and PsA report a variety of barriers to therapy. Adverse events and lack of effectiveness are oftentimes the primary reasons for discontinuation of the biological medication.<sup>7</sup> Patients also reported inadequate insurance coverage among the top reasons for medication discontinuation.<sup>7</sup> Many patients on biologic therapies report concerns over medication safety.<sup>111</sup> Other studies reported patient non-adherence was due to messiness of the topical treatment.<sup>112</sup> This is of particular concern since 80% of psoriasis patients have mild to moderate disease that can be effectively treated with topical therapies.<sup>82</sup>

Pharmacists must be observant of medication-related clues to advancing disease. Recognition that overutilization of high-potency topical corticosteroids (greater than 50 Gm/week) may signal disease advancement. For patients with greater than 10% BSA coverage with lesions, systemic therapy is recommended, and guidelines recommend that trained specialty providers prescribe systemic therapies for these patients. Pharmacists have the training to clinically monitor these systemic therapies.

With advanced knowledge of appropriate medication selection and medication-related factors affecting patient adherence, pharmacists should regularly monitor prescription refills for timeliness. There are indications of higher adherence levels among patients with access to specialty pharmacists due to their ability to focus on one single disease state. Specialty pharmacists are in a unique position to directly work with these patients and have documented, though medication refill analysis greater patients adherence.<sup>113</sup>

Pharmacists should make opportunities to speak with their patients to discuss their satisfaction with the therapy or any adverse effects they may be experiencing with their current drug regimen.<sup>8</sup> One such opportunity is the in the area of self-administration. Several of the current treatments for psoriasis are administered via self-injection or infusion. There is clearly a distinct need for patient education and instruction on injection technique that specialty pharmacists can provide.

Specialty pharmacists should also be prepared to recommend alternate therapies for these patients. They can increase their patients' awareness of the value of lifestyle modifications as it pertains to their particular disease state. Specialty pharmacists can also provide additional resources that range from helping patients manage their disease to recognizing the emotional distress that comes with chronic disease, and referring patients to various support groups.

Today, many of the patients that we, as pharmacists serve, have challenging medical problems that requires pharmacists to deliver complex care. Specialty pharmacists stand poised to serve as a link between provider and patient for effective patient-specific drug selection that will result in positive patient outcomes for their patients suffering with psoriasis and PsA.

### **Additional Resources**

- National Psoriasis Foundation  
[www.psoriasis.org](http://www.psoriasis.org)
- American Academy of Dermatology: Dermatology A-Z  
[www.aad.org/dermatology-a-to-z](http://www.aad.org/dermatology-a-to-z)
- Arthritis Foundation: Psoriatic Arthritis  
<http://www.arthritis.org/about-arthritis/types/psoriatic-arthritis/>
- MedlinePlus Psoriasis or Psoriatic Arthritis  
[www.nlm.nih.gov/medlineplus](http://www.nlm.nih.gov/medlineplus)

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## Post test Questions

1. Crohn's disease and type 2 diabetes are considered comorbidities of psoriasis because:
  - a. They appear in the same decade of life
  - b. They have dermatologic manifestations
  - c. They share a genetic link**
  - d. They are directly a result of poor diet
2. Proper training in the recognition and assessment of psoriatic disease is important because:
  - a. Psoriasis cannot be cured without proper assessment
  - b. Patients can experience a decline in quality of health**
  - c. Psoriasis can spread to family members if unchecked
  - d. Patients will attempt self-treatment
3. Which of the following has been shown to be trigger for psoriasis?
  - a. Stress**
  - b. Sun exposure
  - c. Increased exercise
  - d. Spicy foods
4. What is the selection of topical medications for treatment of psoriasis based on?
  - a. Cost of medication
  - b. Patient ethnicity
  - c. Thickness of plaques
  - d. Amount of body surface area to be treated**
5. A common adverse effect seen with patients using TNF- $\alpha$  inhibitors is
  - a. Hair loss
  - b. Upper respiratory infection**
  - c. Increased appetite
  - d. Somnolence
6. A 34-year-old patient who has well-controlled plaque psoriasis should be screened for signs and symptoms of:
  - a. Crohn's disease
  - b. Pulmonary involvement
  - c. Joint pain and swelling**
  - d. Nasal pharyngitis
7. JS is a 65-year-old woman with a long history of moderate to severe plaque psoriasis. She and her dermatologist recently discussed changing her medication to a new oral agent (apremilast) recently approved by the FDA. She has been placed on step-up therapy, starting with 10 mg daily, increasing to 30 mg twice daily by day 6. Step-up therapy is recommended in this patient in order to
  - a. Watch for symptoms of depression.

- b. Screen for drug interactions with strong CYP 450 inducers.
  - c. Observe efficacy of treatment on affected nails
  - d. Decrease risk of GI symptoms**
8. Studies have demonstrated that patients with moderate to severe psoriatic disease who are treated with the newer biologic agents, etanercept, and adalimumab:
- a. Have demonstrated a decrease in thickness of psoriatic plaques
  - b. Have seen a reduction of 75% in the PASI score**
  - c. Have been able to switch to oral corticosteroid therapy after 12 weeks
  - d. Have reduced infection rates
9. The following oral therapy has been shown to be successful in treating difficult areas to treat such as scalp, nails, and soles of the feet in patients with psoriasis:
- a. Oral prednisone pulse therapy
  - b. Vitamin A 50,000 units weekly
  - c. Adalimumab 80 mg every other week
  - d. Apremilast 10 mg on day 1 increasing to 30 mg twice daily by day 6**
10. A pharmacist can have an impact on the progression of psoriatic disease by:
- a. Evaluating percentage of BSA affected by disease
  - b. Distributing copies of guidelines for treatment to patients
  - c. Recommending cheaper OTC products as initial treatment of psoriasis
  - d. Examining medication refills to assess patient adherence**