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Systemic and Light Therapies for the Management of Childhood Psoriasis: Part II

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ABSTRACT

The choice of treatment for psoriasis in children, as in adults, is determined by disease acuity, morphology, distribution, severity, and the presence of comorbidities, such as psoriatic arthropathy. Fortunately, most patients present with mild disease that responds adequately to topical medications. A minor subset of children will present with severe, rapidly evolving disease that requires more aggressive interventions. Advanced medical treatment with systemic and phototherapy is challenging and primarily anecdotal, as these modalities are neither well-studied nor approved for use in children. Part II of this 2-part series features an overview of systemic and light therapies including their varying degrees of effectiveness, potential side-effects and applications in clinical practice.

Keywords: antibiotics, biologics, children, cyclosporine, methotrexate, phototherapy, retinoids, UVA, UVB

Systemic Therapy

The 3 most commonly used systemic treatments for psoriasis in children, as in adults, are acitretin, methotrexate, and cyclosporine. None are US FDA labeled for this indication in children nor have they undergone the scrutiny of randomized controlled trials in the pediatric population. Accumulated data regarding the utility, benefits, and risks of these agents for the treatment of psoriasis derives largely from long-term use in children with disorders of cornification (retinoids), juvenile rheumatoid arthritis (methotrexate), and transplanted organs (cyclosporine). Treatment with systemic agents is typically reserved for severe, refractory, widespread or incapacitating disease, pustular or erythrodermic forms, and psoriatic arthropathy. Close clinical and laboratory monitoring for associated toxicity is mandatory for all 3 agents.

Retinoids

Acitretin is a second generation aromatic retinoid that is US FDA-approved for the treatment of severe psoriasis in adults. It is not immunosuppressive and has no formal restrictions on duration of therapy. Acitretin is useful for intermittent rescue therapy in children with generalized pustular flares or longer term treatment of older children with pustular, erythrodermic or severe plaque psoriasis as monotherapy, or in combination with other agents such as topicals and narrowband UVB (NB-UVB) phototherapy.[1,2] There are convincing data, from long-term clinical follow-up of patients with disorders of cornification, that oral retinoids are safe in children, but do require monitoring as in adults.[3] Treatment should be initiated and maintained at dosages at or below 0.5-1mg/kg/day to limit short- and long-term toxicities. The most common adverse events are mucocutaneous (xerosis, cheilitis, skin fragility, epistaxis) and minor reversible alterations in liver enzymes and lipids, which rarely necessitate cessation of therapy.[4] The most feared complications are teratogenicity and effects

on bone. The use of acitretin in females of childbearing potential should be avoided if possible. Pregnancy must be avoided for 3 years following discontinuation of acitretin because of the potential for irreversible esterification to etretinate with ingestion of ethanol. Although effects on bone similar to that observed in chronic vitamin A toxicity have been rarely identified with long-term, high-dose use,[5] available evidence does not substantiate a clear link between radiologic skeletal abnormalities and long-term, low-dose use.[6] In children anticipated to be on long-term retinoid therapy, baseline and serial or symptom-driven radiologic evaluation of the long bones and spine, and close monitoring of growth parameters are appropriate.

Methotrexate

Methotrexate has been used for psoriasis since the 1950s and remains the most widely prescribed drug for severe psoriasis worldwide. Its use in children is reserved for severe, recalcitrant, extensive or disabling disease, psoriatic arthritis, or erythrodermic and generalized pustular forms unresponsive to topical and phototherapy. Methotrexate may be used to gain control in the acute phases or flares of psoriasis followed by transition to more conventional topical or light-based maintenance regimens. In children, 0.2-0.7mg/kg/week is the recommended therapeutic dose range.[7] In nonemergent situations, a test dose of 1.25mg to 5mg, followed in 1 week by laboratory monitoring, is recommended to detect early toxicity. Conservative dose escalations of 1.25-5mg/week are advised until therapeutic effect is obtained, followed by a slow taper to a beneficial maintenance dose. The drug is supplied as 2.5mg scored tablets that can be split or crushed and given with nonmilk food, and as an injectable preparation (2.5mg/mL and 25mg/mL supplied in 2mL vials) that can be given orally. Side-effects, both short- and long-term, are observed in children taking methotrexate for psoriasis, but are much less frequent and severe than in adults, likely because of the relative lack of comorbidities and concurrent medications in children. Regardless of age, methotrexate is associated with a substantial number of potential side-effects and drug interactions and requires vigilant clinical and laboratory monitoring.[7-9] Folic acid supplementation increases tolerability and reduces the risk of pancytopenia, nausea, macrocytic anemia, and liver enzyme elevations without altering efficacy.[10]

Cyclosporine

Cyclosporine is an immunosuppressant that is US FDA-approved for severe, recalcitrant psoriasis in non-immunocompromised adults and for prevention and treatment of transplant rejection in children >6 months of age. In carefully selected and closely monitored patients, cyclosporine can produce relatively rapid clinical effects and can be effectively combined with topical and systemic therapies to increase efficacy and reduce toxicity. Its use is limited by the risk of nephrotoxicity, hypertension, and immunosuppression, and close laboratory and blood pressure monitoring prior to and throughout the treatment period is required.[11] Maximum dosing by US guidelines is 4mg/kg/day and total duration of therapy should not exceed 1-2 years.[11,12] Onset of effect is rapid (4-8 weeks) and gradual tapering should start after a 1-3 month period of stability and adjusted according to clinical response. Rebounds during taper or after withdrawal are not uncommon. Sequential therapy (i.e., the addition of a second, less potentially toxic agent, such as acitretin) in select situations allows gradual tapering of cyclosporine and reduced total dose and duration of both medications in an effort to maximize efficacy and minimize toxicity.[13] The risk of malignancy, skin cancer, and lymphoproliferative disorders, as observed in the transplant population, are a concern in children; however, evidence suggests that risk is minimal if using 5mg/kg/day or less in patients who are not on concomitant immunosuppressive medications.[14] Cyclosporine is available as 25mg and 100mg soft gelatin capsules and as a clear yellow liquid supplied in 50mL bottles containing 100mg/mL.

Biologics

As the complex molecular mechanisms underlying the pathogenesis of psoriasis become increasingly clear, targeted therapies aimed at specific components of the inflammatory cascade, such as tumor necrosis factor, are gaining popularity and are in widespread use among adults with psoriasis and psoriatic arthritis. Experience with their off-label use in children with psoriasis is limited, and critical evaluation of the potential risk of these agents in children with psoriasis is difficult because of the small number of children treated and the short follow-up period. No specific guidelines exist for dosing and laboratory monitoring in pediatric patients. Enthusiasm for the efficacy, short-term safety, and ease of use of anti-tumor necrosis factor alpha agents in children is reasonably tempered by concerns about the risk of infection, lymphoma, demyelinating disorders, and cost.[15]

Phototherapy

Phototherapy is an excellent, safe, and appropriate treatment for carefully selected patients with refractory plaque, guttate and pustular disease, diffuse (>15%-20% body surface area) involvement, or focal debilitating palmoplantar psoriasis. To avoid burns and other light-associated complications, it is essential to utilize a phototherapy unit with experienced and well-trained personnel who are comfortable working with children. Three main types of therapeutic light options exist: broadband UVB (BB-UVB, 280-320nm), NB-UVB (311-313nm) and UVA (320-400nm). BB-UVB encompasses the most biologically active radiation in sunlight and guttate psoriasis responds best, but plaque psoriasis in children tends to be thinner and will respond to higher doses and a longer duration of treatment. One of the greatest advances in phototherapy for psoriasis is the use of NB-UVB, which, at therapeutic doses, is less erythemogenic than other wavelengths in the UVB range.[16] Centered on 311-313nm, NB-UVB is safe and effective for a number of photoresponsive dermatoses in children,

including psoriasis.[17-19] Short-term side-effects of UVB phototherapy are usually mild and consist of xerosis, erythema, pruritus, and photoactivation of herpesvirus. Potential long-term effects include premature photoaging and cutaneous carcinogenesis.[20]

Photochemotherapy (psoralen plus ultraviolet A, [PUVA]) is based on the interaction between UVA radiation and psoralen, a photosensitizing chemical. In children less than 12 years, oral PUVA is rarely used and if so, is done with extreme caution and should be restricted to psoriasis and phototherapy centers staffed by well trained, experienced physicians and nurses. Many authors consider oral psoralen relatively contraindicated in children less than age 12 and prefer topical PUVA because of the many short- and long-term toxicities associated with psoralen ingestion (e.g., nausea, vomiting, headache, hepatotoxicity, generalized photosensitization requiring 24 hours of photoprotection, ocular toxicity, acute risk of burning, and long-term risk of skin cancer).[21] In children, NB-UVB is more convenient and may be less carcinogenic. Given the downsides of using psoralens in children and adults, NB-UVB is now considered first-line phototherapy.[22]

Antibiotics and Tonsillectomy

Ample clinical and laboratory evidence exist suggesting precipitation, exacerbation, and persistence of guttate and other forms of psoriasis by pharyngeal and perianal streptococcal infections. Dermatologists often prescribe empiric systemic antibiotics for recurrence or flares of guttate psoriasis and occasionally recommend tonsillectomy in patients with refractory psoriasis and recurrent tonsillitis. Two recent exhaustive reviews assessed the evidence for such interventions in the management of childhood psoriasis and concluded that available evidence does not support the efficacy of oral antibiotics or tonsillectomy.[23,24]

Conclusion

Treating children with psoriasis is both rewarding and challenging. It requires a current, comprehensive knowledge of available therapies including the mechanism of action, clinical action spectrum, potential toxicity, and appropriate monitoring. Combination, rotational, and sequential therapy as introduced by Menter, Weinstein and White, and Koo, respectively, are time honored methods which aim to improve overall efficacy while reducing the individual toxicity of the chosen medications.[25] Management also requires continued education and support of the patient and the family. Advocacy and education groups such as the National Psoriasis Foundation (www.psoriasis.org; 800-723-9166) are excellent resources and can serve as an extension of your comprehensive care.

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The Role of the Dermatologist in Identification and Treatment of the Early Stages of Psoriatic Arthritis

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ABSTRACT

Early diagnosis of psoriatic arthritis (PsA) is essential for preventing disease progression and joint destruction. The majority of patients develop PsA years after the onset of their skin disease. Therefore, dermatologists are in a strategic position to make the diagnosis of PsA, and either manage it or refer the patient to a rheumatologist in order to prevent the potentially irreversible destruction of the affected joints. We will review the presentation and temporal relationship of psoriasis and PsA, the diagnosis, classification, and management, in addition to the role of the dermatologist in the early detection of PsA.

Key Words: Distal interphalangeal joint (DIP), metatarsophalangeal joint (MTP), psoriasis, psoriatic arthritis, PsA

Psoriatic arthritis (PsA) is often described as a chronic, inflammatory arthropathy affecting the distal interphalangeal joints (DIP) of the hands, metatarsophalangeal joints (MTP) of the feet, and spine in association with psoriasis.[1] One to three percent of the world population has been diagnosed with psoriasis.[2] Estimates of the prevalence of PsA within the psoriasis population range from 6%-39%.[3] The Psoriasis Foundation 2001 Benchmark Survey estimated the prevalence of PsA in patients with psoriasis to be as high as 23%.[4] PsA is often under diagnosed or misdiagnosed, and therefore, statistics may be misrepresented.

Clinical Presentation

There appears to be great variability in the case definition for PsA. One such definition, proposed by Moll and Wright, defines PsA as "an inflammatory arthritis associated with psoriasis and usually with a negative serological test for rheumatoid arthritis."[5] Due to the broad spectrum of PsA there has been a need to create subgroups (Table 1).

Characteristic features of psoriatic arthritis include: swelling, erythema, warmth, and inflammation of the affected joint. PsA can present with asymmetrical joint distribution, involving more joints over time and progressing as an oligoarticular/polyarticular disease. Almost any joint can be involved including peripheral (e.g., the DIPs) and/or axial joints (e.g., spine and sacroiliac joints). PsA can also manifest with involvement of periarticular structures such as tenosynovitis (inflammation of the tendon sheath), dactylitis or "sausage digit" (inflammation of entire digit), and enthesitis (insertion of the tendon).[4]

As with other sero-negative spondylarthropathies, there can also be extra-articular manifestations of PsA. These features may include inflammation of the eye, mucous membranes, urinary system, and cardiovascular system (i.e., iritis, conjunctivitis, aortic dilation, and urethritis).[6]

There does not appear to be a difference in the prevalence of psoriasis between the sexes,[7] however, the onset of disease seems to be earlier in women.[8] The onset of psoriasis is bimodal with a median age of onset at 29.1 years.[9] Those with early disease can have a greater body surface area involved, unstable psoriasis, frequent relapses, and a higher incidence of guttate psoriasis and nail involvement.[9,10] Patients with later onset tend to have a more stable course and less severe disease, but more frequent palmoplantar pustulosis.[9,10]

The temporal sequence of disease onset can vary, making the diagnosis of PsA difficult. As high as 75%-80% of psoriasis

Form of PsA	Frequency	Joint Distribution	Other Features
Oligoarticular asymmetrical arthritis	70%	≤4 joints	dactylitis and/or monoarthritis
Symmetrical polyarthritis	15%	5 joints	erosive and metacarpophalangeal joint involvement
Predominantly DIP arthritis	5%		severe nail psoriasis
Arthritis mutilans	5%	May not have severe general disease	telescoping of fingers and toes, often associated with sacroiliitis
Spinal form	5%	Sacroiliitis	can be asymptomatic, uni/bilateral sacroiliitis, +/- peripheral joints

Table 1: PsA classification subgroups (proposed by Moll and Wright[5])
DIP = PsA in the distal interphalangeal joints of the hands

Clinical Feature	Psoriatic Arthritis	Rheumatoid Arthritis	Ankylosing Spondylitis	Reactive Arthritis	IBD
Gender	Males=Females	Males<Females	Males>Females	Males>Females	Males=Females
Most common joint pattern	Oligoarticular/ polyarticular (asymmetric)	Polyarticular (symmetric)	Oligoarticular (lower limb)	Oligoarticular (lower limb)	Oligoarticular (lower limb)
DIP joint	High	Low	Does not occur	Does not occur	Does not occur
Dactylitis	High	Does not occur	Low	Medium	Low
Enthesitis	Medium	Does not occur	Medium	High	Medium
Spondylitis	Medium	Does not occur	High	Low	Medium
Sacroiliitis	Asymmetric	Does not occur	Symmetric	Asymmetric	Symmetric
Eye symptoms	Low	Medium	Medium	High	Low
Skin/nail lesion	High	Does not occur	Does not occur	Medium	Does not occur
Rheumatoid factor positive	Does not occur	High	Does not occur	Does not occur	Does not occur

Table 2: Clinical features in psoriatic arthritis and other seronegative arthropathies (adapted from Brockbank and Gladman[17])
DIP = PsA in the distal interphalangeal joints of the hands

patients will present with cutaneous manifestation 5-10 years prior to the onset of joint complaints.[4,11] There can exist a flare in arthritis with or without a coinciding flare of psoriasis.[4]

The majority of patients with PsA have mild or moderate cutaneous manifestation,[12] and 80%-90% of this population have nail lesions.[12,13] However, 46% of patients with psoriasis (no affected joints) have nail involvement.[13] The extent and severity of both skin and joint disease correlate closely with the severity of psoriatic nail involvement, however this association is more commonly found in the DIP arthritis form of PsA.[14]

Differential Diagnosis

Distinguishing PsA from other inflammatory conditions can be challenging since the clinical features may overlap. The differential diagnosis may include: rheumatoid arthritis (RA), reactive arthritis, inflammatory bowel disease (IBD) and ankylosing spondylitis, to name a few. (See Table 2.)

To further complicate matters, other rheumatologic conditions such as osteoarthritis, soft tissue rheumatism, septic arthritis, and true RA can coexist with psoriasis. In addition, psoriasis has been found to occur with higher frequency in patients with IBD and ankylosing spondylitis.[15,16,17]

The presence of such confounding variables stresses the importance of a full history and physical examination that includes serological, radiological, and perhaps genetic investigations to aid in the diagnosis.

Making the Diagnosis

There exist several PsA classification criteria in the literature. The ClASsification criteria for Psoriatic ARthritis (CASPAR) are newly developed criteria for the diagnosis of PsA. They are simple to use, have a high specificity of 98.7%, and a sensitivity of 91.4% for the diagnosis of PsA.[18]

CASPAR Criteria

A patient must have inflammatory articular disease (joint, spine, or entheseal) with 3 or more of the following 5 criteria:

1. Current OR personal history of psoriasis, OR family history of psoriasis (1st or 2nd degree relative). Psoriasis is defined as skin or scalp disease.
2. Psoriatic nail disease including: onycholysis, pitting, hyperkeratosis on current physical exam
3. Negative for rheumatoid factor (by any method except latex)
4. History of or current dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxta-articular new bone formation, appearing as ill defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

Based on these criteria and established clinical features of PsA, a basic workup for a new patient in your office with psoriasis should include a history, physical examination, laboratory investigations, and review of treatment options as summarized below.

History

- Current OR personal history of psoriasis, OR family history of psoriasis
- Swelling of joints
- Pain or tenderness in joints
- Morning stiffness >30 minutes
- Functional capacity in activities of daily living (changes in ability to function at home and at work and impact on quality of life), etc.

Type of Psoriasis	Characteristics	Area Involved	Lesion (Size and Symmetry)	Other Findings & Complications
Plaque (80%)	Erythematous plaques with raised, sharp defined margins and thick silvery scales	Scalp, extensors, elbows, knees, and back	<1cm to >10cm (symmetrical)	Nail pitting, possible umbilicus and intergluteal cleft involvement
Pustular (<3%)	Erythema, scaling, sheets of superficial pustules with erosions; variety of subtype groups	Widespread	<1cm to >10cm (symmetrical) plaques with 1-2mm pustules	Malaise, fever, diarrhea, leukocytosis, hypocalcemia, hepatic involvement; can be severe and life threatening; associated with pregnancy, infection, and oral glucocorticoids
Scalp (79%)	Erythematous plaques with raised, sharp defined margins and thick silvery scales	Can extend to the forehead and auricular area or as a patch on occiput	Nummular, band-like or palm-sized patch	May have fissuring of superior and posterior auricular folds
Guttate	Abrupt onset, multiple small psoriatic lesions	Trunk and extremities; spares the palms and soles	<1cm "rain drop" shaped papule	Associated with *Streptococcus* infection, usually pharyngitis
Erythrodermic	Erythrodermic, diffuse exfoliation of fine scales without plaque or guttate lesions	Head to toe	Generalized	Complications due to loss of adequate barrier, such as infection, sepsis, fluid loss (electrolyte abnormalities); associated with stress, medications, burns with phototherapy and infection
Palmoplantar	Tender, erythrodermic, dry scaling patches or thickening	Palms and soles	Pustules and fissures bilateral	Less severe form of pustular psoriasis
Inverse (Flexural)	Salmon red color with defined margins, minimal scaling	Inguinal, neck, perineal, genital, intergluteal, axillary, and submammary folds	<1cm to >10cm (symmetrical)	Eczema can also be present; perspiration can irritate fissures and other lesions

Table 3: Clinical manifestations of psoriasis[8,19]

Physical Examination

- Nails: evidence of onycholysis, pitting, hyperkeratosis, oil-drop sign, and nail crumbling
- Skin: see Table 3.

Musculoskeletal

- Signs of joint inflammation such as swelling, effusion, synovial thickening, erythema, decrease in range of movement
- Other manifestations: DIP joint involvement, enthesis, dactylitis, spondylitis and sacroiliitis, eye symptoms (i.e., iritis), etc.
- See Table 1 for other characteristic findings for PsA.

Diagnostic Investigations

- Laboratory tests should include: complete blood count, erythrocyte sedimentation rate, C-reactive protein, Rh factor, and routine renal and liver function tests.
- Plain radiographs: these can be normal in the early stages of disease. However, juxta-articular new bone formation, periarticular osteopenia, and later stages may demonstrate "pencil in cup" erosive disease in the hands or feet.

Treatment

When treating the cutaneous and joint manifestations, as in PsA, each aspect of the disease must be considered. The 2 may be treated independently, although a number of systemic therapies may benefit both. Treatment options that can improve both PsA and psoriasis include:

1. Traditional systemic agents
   - Cyclosporine (3-5mg/kg PO daily)
   - Methotrexate (doses ranging from 15-25mg PO/IM weekly)
2. Biologic agents (with indication for PsA)
   - Etanercept (50mg SC bi-weekly)
   - Infliximab (5mg/kg IV at week 0, 2, 6 and then every 8 weeks)
   - Adalimumab (40mg SC every 2 weeks)

However, some may help one while adversely affecting the other. Drugs that can induce disease exacerbation include:[20]

1. Drugs that treat arthritis, but may worsen psoriasis
   - Gold
   - Systemic corticosteroids
   - Hydroxychloroquine
2. Drugs that treat psoriasis, but may worsen arthritis
   - Acitretin
   - Efalizumab

The Role of the Dermatologist

The recognition and early treatment of PsA is analogous to that of acne. We are aware of the importance of early recognition of acne and the urgency in treating it aggressively in order to induce remission and prevent further damage. The destruction of the joints in PsA follows the same principle: treat early to prevent the damage. The dermatologist who monitors a psoriatic patient can detect PsA at its earliest stage.

A study by Zanolli and Wikle concluded that a large portion of patients with psoriasis presenting to a dermatologist for treatment were recognized to have coexisting joint complaints; and the prevalence of PsA is greater than that identified by a nondermatologist.[21]

The prevalence of psoriasis is greater than PsA, and psoriasis typically precedes the joint complaints.[4,11,22] Therefore, the dermatologist is in a unique position to screen patients with psoriasis for PsA by maintaining a high index of suspicion and close follow-up. In limited cases, consultation with a rheumatologist may be necessary to make the diagnosis of PsA.

A screening questionnaire could be designed for patients presenting to the dermatologist for the first time with psoriasis. The Psoriasis and Arthritis Screening Questionnaire (PASQ)[23] that was developed by our group was created using the CASPAR criteria as its framework. This questionnaire does not replace a proper history, but reminds us to consider the diagnosis of PsA in any patient with symptoms of psoriasis, regardless of the severity of the cutaneous manifestations.

Conclusion

The dermatologist is in a strategic position for early diagnosis, intervention, and appropriate management of the patient with PsA at its onset. The skin and joint involvement in PsA can significantly affect a patient's function and quality of life, and may increase cardiovascular morbidity and mortality.[24] These effects, in turn, may have significant impact on the family and society in general. Early diagnosis and effective therapy for PsA can prevent the progression of joint damage, and possibly induce a remission of the disease.

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Update on Drugs

Class	Name/Company	Approval Dates/ Comments
Melanoma	**Triphendiol** (formerly NV-196) Marshall Edwards, Inc.	The US FDA granted orphan drug status to this multiple signal transduction regulator (MSTR) in February 2008 for the treatment of Stage IIB to Stage IV malignant melanoma. This novel agent targets a certain tumor-specific protein, which triggers a cascade of events that induces cancer cell death.
Melanoma	**Cyclic pentapeptide vascular-targeting agent** *ADH-1* Adherex Technologies	The US FDA granted orphan drug designation in February 2008 to this molecularly-targeted therapy. The designation was granted for concomitant use with melphalan (alkylating agent) for the treatment of Stage IIB/C to Stage IV melanoma. ADH-1 selectively targets N-cadherin, which is frequently overexpressed in malignant neoplasms; it also promotes apoptosis and inhibits tumor angiogenesis.
Crohn's Disease	**Certolizumab pegol** *Cimzia*® UCB S.A.	The US FDA approved this PEGylated anti-TNFαbiologic therapy in April 2008 for the treatment of Crohn's disease. This antibody is indicated for adults with moderate-to-severe disease who are inadequate responders to conventional therapies. The development of other indications for this drug include rheumatoid arthritis and psoriasis.

Drug News

Psoriasis	A recently published study conducted by Smith, et al.*, looked at combination therapy with acitretin and biologic agents for the treatment of moderate-to-severe psoriasis. Successful management of recalcitrant disease often necessitates the amalgam of several therapeutic approaches. A vast body of clinical evidence exists for the use of acitretin in the treatment of psoriasis, and the same can be said for the mounting data on biologic therapies, however, limited data is available on their combined use. The investigators performed chart reviews on 15 psoriasis patients who received concomitant treatment with a biologic agent and acitretin. Management, side-effects, and abnormal laboratory results during combination treatment were assessed. Study findings showed that clearance of psoriasis was achieved by 29% of patients, 90% improvement by 43%, 75% improvement by 14%, and no change by 7.1%. While receiving treatment with acitretin and a biologic agent, 5 patients did not require adjunct therapy. Cessation of narrow-band ultraviolet-B (UV-B) therapy was achieved by 3 patients after receiving combination therapy for an average of 2.33 months; 1 patient continued to require phototherapy (UV-B) in addition to the biologic therapy. While on combination treatment, 3 patients developed squamous cell carcinoma (SCC); however, all 3 patients had a prior history of SCC. After 3 years of etanercept and acitretin treatment, 1 patient developed non-Hodgkin's lymphoma, which prompted discontinuation of the biologic agent. Combination therapy with systemic retinoids and biologics may potentially provide an additional therapeutic option in the management of refractory psoriasis. Further investigations are warranted to establish the extended safety and efficacy of this integrated approach. *Smith EC, et al. *Int J Dermatol* 47(5):514-8 (2008 May).
FDA Warning	The US FDA issued a black box warning in March 2008 for etanercept (Enbrel®, Immunex Corp./Amgen/ Wyeth Pharmaceuticals) concerning the risk for tuberculosis (TB) and other infections. The new prescribing information replaces a bold-face warning and calls for vigilance in patient screening and monitoring for those with active disease or those who have previously tested negative for latent TB infection. Contents of the box warning includes a statement that reactivation and new cases of TB have been observed in patients being treated with tumor necrosis factor (TNF) blocking agents; however, studies have indicated a lower risk with etanercept than with other TNF receptor antagonists. Worldwide clinical trials involving 20,000 patients treated with etanercept reported the risk for TB to be 0.01%; studies in the US and Canada with over 15,000 patients reported a risk factor of 0.007%. Post-marketing surveillance continues through open-label studies. The complete box warning information may be found at: http://www.amgen.com/pdfs/misc/enbrel_healthcare_professionals_letter.pdf and http://www.fda.gov/medwatch/safety/2008/safety08.htm#Enbrel.