

Clinical Features of Psoriatic Arthritis

Gerald G. Krueger, MD

Abstract

The past 5 years have seen major advances in understanding the immunology and molecular biology of psoriatic arthritis (PsA), especially the impact of cytokines such as tumor necrosis factor (TNF), which has produced striking, long-term benefits in patients with rheumatoid arthritis (RA). Because PsA is not the same disease as RA, the ability to distinguish between them is important to physicians in managing patients who have clinical features consistent with an arthropathy. The development of TNF inhibitors directed specifically at the mechanisms of skin and joint inflammation offers hope to patients who suffer from the debilitating effects of PsA.

(Am J Manag Care 2002;8:S160-S170)

Psoriatic arthritis (PsA) is a debilitating inflammatory disease that affects the skin and joints. PsA may affect a significant number of patients with psoriasis. The clinical and societal impact of PsA—resulting from both skin and joint manifestations of the disease—has only recently begun to be appreciated.

Over the past 5 years, there have been significant advances in our understanding of the immunology and molecular biology of PsA, particularly the pathogenic role of cytokines such as tumor necrosis factor (TNF). Furthermore, we have observed dramatic and long-term clinical benefits in patients with rheumatoid arthritis (RA) treated with TNF inhibitors.¹⁻⁵ PsA is not the same disease as RA, and being able to

differentiate RA from PsA is an important component in the management of patients who present with clinical features consistent with an arthropathy.

The social devastation associated with PsA is enormous and has been well documented. In a sample of 180 patients with PsA, Torre Alonso et al⁶ found that 57% had erosive arthritis and 19% had marked physical limitations. Jones et al⁷ reported that 64% of their patients presenting with oligoarticular disease progressed to polyarticular disease over time. Gladman et al⁸ showed that a significant percentage of patients developed joint damage and deformities that progressed over time and contributed to functional limitation. Husted et al⁹ demonstrated that patients with PsA experience reduced health-related quality of life compared with persons from the general population. Specifically, patients reported significantly lower scores on the physical functioning, pain, role limitations, and general health perceptions scales of the Medical Outcomes Study 36-item short-form health survey.

PsA can be a debilitating disease when associated with significant skin disease and significant radiographic progression, even when patients receive ongoing therapy with conventional disease-modifying antirheumatic drugs (DMARDs).^{10,11} In one meta-analysis of published randomized trials evaluating the efficacy of DMARDs such as methotrexate and cyclosporine in the treatment of PsA,¹¹ the placebo groups in all of the trials included showed a clinically significant improvement, thereby bringing into question the efficacy of treatment with conventional DMARDs.

Patients with PsA are typically affected with psoriasis before showing signs of joint disease; approximately 15% of patients develop signs and symptoms of PsA before a diagnosis of psoriasis has been established.¹² Both rheumatologists and dermatologists manage PsA; each specialist approaches the management of PsA from his or her unique professional perspective. Dermatologists focus primarily on the skin manifestations of PsA and rheumatologists concentrate on the articular manifestations of the disease. Few controlled trials have examined the efficacy of DMARDs for both PsA and psoriasis. Hence, if PsA does not respond to the psoriasis treatment offered by the dermatologist, referral to a rheumatologist typically follows. The corollary is also true—psoriasis not responding to PsA therapy offered by the rheumatologist typically results in referral to the dermatologist. Currently available DMARDs are relatively slow acting, can inflict serious adverse reactions, and no long-term dose can universally be considered “safe and effective.”

Given these limitations, excitement has developed in response to research that has focused on novel, targeted treatments for PsA—treatments that work against both the skin and articular manifestations of the disease. Fueling the hope for better treatments are rapid advances in the understanding of the disease processes that underlie both psoriasis and PsA. Such understanding has led to the discovery of a new class of products broadly named *biologic response modifiers*. These agents are targeted to alter the cascade of cytokines, chemokines, and other cellular modulators that regulate the inflammatory state of both the skin and the joints in PsA. Some of these cytokines, particularly TNF, are currently among the most studied in a list of possible treatment targets for both psoriasis and PsA. These therapeutic approaches hold enormous promise for patients with psoriasis and PsA.

Relationship Among Rheumatoid Arthritis, Psoriatic Arthritis, and Psoriasis

PsA is classified as a seronegative spondyloarthropathy—a loosely connect-

ed group of disorders that also includes ankylosing spondylitis, Reiter’s syndrome, enteropathic arthropathy, Whipple’s disease, and Behçet’s syndrome—so called because of the absence of rheumatoid factor (RF).¹³ The cause of PsA is unknown. Clearly, genetic susceptibility and exogenous influences have roles in the etiology of the disease. The primary clinical feature that characterizes the seronegative spondyloarthropathies is enthesopathy (inflammation of sites of ligamentous insertion into bone). This destructive process affects tendons and ligaments at their insertions, resulting in tendonitis, dactylitis, and fasciitis. Full-blown PsA is characterized by a pattern of clinical features, including the combination of psoriasis with asymmetrical peripheral joint disease, variable involvement of the axial skeleton, nail disease, tenosynovitis, and enthesopathy.¹⁴ Baseline relationships in terms of disease manifestations between psoriasis and PsA have been demonstrated, particularly with regard to nail involvement and joint activity.¹⁴

A relationship between psoriasis and joint manifestations was initially recognized in the early 1800s. Numerous clinicians substantiated this relationship, and in 1959 Wright introduced the term “psoriatic arthritis.”¹⁵ As our understanding of the disease increased, a variety of therapeutic approaches evolved, including the use of nonsteroidal anti-inflammatory drugs and DMARDs to treat the articular manifestations and antipsoriatic agents to treat the skin manifestations. Yet, although the condition is common, PsA has not been routinely part of trials for new drugs that have been brought to the market for arthritis; the converse is also true—drugs developed for psoriasis typically have not included joint manifestations as an outcome measure in pivotal trials. Studies that have been undertaken typically have been phase 4 trials with small sample sizes; hence, definitive conclusions are lacking. As a result, drugs developed for psoriasis do not have indications for both the skin and joint manifestations of the disease. Consequently, PsA remains a debilitating disease, with

few agents currently available to effectively treat both the articular and skin manifestations of the disease. Furthermore, therapy for PsA has largely been derived from clinical experience in RA, without corroborating evidence from studies of patients with PsA.^{11,16} The few controlled trials assessing the efficacy of various DMARDs in patients with PsA have not shown clinically significant effects.¹⁷⁻²²

Recent advances in the molecular biology and immunology of PsA have led to an increased understanding of the role of cytokines such as TNF in the pathogenesis of the events that foster inflammation in the skin and joints of patients with the disease. This understanding, in turn, has led to the development of TNF inhibitors, such as etanercept, as therapeutic agents specifically targeted to the mechanisms of cutaneous and articular inflammation in PsA.²³⁻²⁵

Prevalence

Epidemiologic studies since 1980 have demonstrated that PsA is more common

than previously believed.²⁶ The recently reported National Psoriasis Foundation Benchmark Survey for Psoriatic Arthritis²⁷ is the first research to establish the prevalence of psoriatic arthritis among US adults. In surveys conducted in December 2001 of more than 27,000 adults, 0.5% said they had been diagnosed as having PsA. That number translates to about 1 million of the total US adult population—roughly double the number that the medical community previously suspected had the disease.²⁷ The surveys showed a strong link between PsA and psoriasis. About 85% of those with PsA reported that they had psoriasis. At the same time, about one third of those with psoriasis said they had joint stiffness, but had not been diagnosed as having PsA. This finding suggests that many of these people may have had PsA and not have known it. Follow-up interviews were conducted with 448 people who had been diagnosed as having PsA. Of those, 84% said PsA had a moderate-to-large impact on their everyday lives. Seventy-five percent said they lost sleep or slept badly because of the disease, and nearly two thirds said the condition has forced them to alter their daily activities.

A recent reassessment of this question in more than 5000 patients in Northern Europe was presented at the 2001 European Academy of Dermatology and Venerology Conference,²⁸ in which it was reported that the incidence of PsA did not consistently correspond to the severity of psoriasis. The medical records of more than 700 patients in the study sample were evaluated, and 30% to 40% of patients with psoriasis had PsA.

The percentage of men and women affected with PsA is roughly equal, and the disease can appear at any age. The peak age of onset is between 45 and 54 years,²⁹ and the average time of onset is approximately 10 years after the first signs of psoriasis.

Clinical Aspects of Psoriatic Arthritis and Psoriasis

Skin Manifestations. The typical lesions of psoriasis are characterized by a sharp,

Figure 1. Typical Skin Lesion Found in Psoriasis and Psoriatic Arthritis



definable border, a bright red color, and a silvery white scale (Figure 1). The sharp border, which can usually be felt and seen, abruptly demarcates the epidermal hyperplasia and epidermal changes of psoriasis. The bright red color, which on dependent areas may have a violet hue, is indicative of the dilated superficial vasculature of psoriasis. In fact, the capillaries of psoriatic skin so closely approach the skin surface at the apex of the elongated dermal papillae that the removal of psoriatic scales frequently produces fine bleeding points (Auspitz sign).³⁰

The scaly plaques of psoriasis (Figure 2) are an almost constant feature, except possibly after effective topical or systemic therapy. Although the plaques are usually silvery white, they may assume a duller, less reflective white appearance as the scales become thicker. The scales are normally loosely adherent, and are the result of the greatly accelerated and incomplete keratinization process. They may be very thin, usually curling up slightly as they detach, or they may be piled up and thickened to produce a keratin plate or mound over the erythematous skin lesions. Much of the pain, itching, and inflammatory change is a result of the dryness and cracking of this layer. Psoriatic plaques may regress spontaneously without scarring after several weeks, months, or years. Relapses are common, and their frequency and severity in affected patients can be reduced by avoiding exacerbating factors such as stress, mechanical injury to the skin, and sunburn. The distribution is usually symmetrical, affecting the elbows, knees, buttocks, and scalp. The plaques may persist for months to years, with little change in shape or distribution of individual lesions.

Several variants of psoriasis have been identified based on clinical features. These include plaque (discussed above), pustular, guttate, inverse (flexural), and erythrodermic (exfoliative) psoriasis.

Pustular psoriasis may appear on top of existing psoriatic plaques and may spread to uninvolved skin.³⁰ In severe cases, the pustules become confluent and form lakes of pus. Pustular psoriasis may be localized

or generalized; either form may cause severe disability. Generalized pustular psoriasis is sometimes referred to as the von Zumbusch variety, and is associated with fever, malaise, and leukocytosis. Localized pustular psoriasis is usually limited to the palms and soles. When the pustules rupture, thick scaling and fissuring occur, causing severe pain. Many patients with pustular psoriasis have psoriatic nail changes.

The clinical hallmark of guttate psoriasis is a generalized, rapidly developing, small, tear-shaped psoriatic plaque. Guttate psoriasis is commonly seen in children and young adults, and may be triggered by streptococcal infections of the respiratory tract as well as, many dermatologists believe, other upper respiratory tract infections.^{30,31} Flare-ups of guttate psoriasis may also be precipitated by withdrawal of systemic corticosteroid therapy, drug sensitivity, and miliaria.³¹

Inverse psoriasis affects the axillary and gluteal folds, the submammary area, and the navel. In these intertriginous sites, the lesions are erythematous and moist, with-

Figure 2. Psoriatic Plaque



out the scaling that is characteristic of plaque psoriasis. Because of constant friction and maceration, the lesions of inverse psoriasis may become extensive and spread to previously normal skin. Pruritus and discomfort are more common in inverse psoriasis than in plaque, pustular, or guttate psoriasis because the lesions are more likely to become inflamed and fissured.

Erythrodermic psoriasis is characterized by diffuse erythema and scaling, and is often associated with fever, chills, and malaise.³⁰ In severe cases, there may be hypothermia and hypoalbuminemia secondary to skin exfoliation. Erythrodermic psoriasis may involve the entire skin, including the trunk, extremities, nails, hands, feet, face, and scalp. It is sometimes seen as a rebound phenomenon following withdrawal of systemic corticosteroids or secondary to irritation from topical anti-psoriatic preparations.

Pustules are not a regular feature of most clinical types of psoriasis, although on close inspection they may be seen, especially during acute episodes.

Nail involvement—usually nail pitting—helps confirm the diagnosis of PsA because it occurs in most cases. Other nail abnormalities seen in PsA are onycholysis, subungual hyperkeratosis, furrows or transverse depressions (Beau's lines), leukonychia (white spots or patches under the nails), oil spotting (reddish-brown spots under the nail), and crumbling nail plates.³² Nail lesions occur more commonly among patients with PsA than those with psoriasis uncomplicated by arthritis; therefore, these lesions may help to identify patients with psoriasis who are destined to develop PsA.³³

Although it is accepted that all types of psoriasis may occur in patients with PsA,⁷ the relationships between skin and joint lesions are not clear.

Joint Manifestations. A classification scheme for PsA based on joint manifestations proposed by Moll and Wright³² (Table 1) describes 5 patterns of disease:

Predominantly Distal Interphalangeal Arthritis. Distal interphalangeal arthritis is considered the classic form of PsA, although this pattern accounts for only about 5% of cases.³² This condition can occur as the sole presentation or in combination with other patterns. It may be symmetric or asymmetric and can involve many joints or only a few. In many cases, adjacent nail(s) may have psoriatic changes. Progressive bony erosions are common.

Arthritis Mutilans. Although this pattern occurs in only 1% to 5% of PsA cases, it is important because it is characterized by severe disease with osteolysis of the phalanges, metatarsals, and metacarpals.^{30,32}

Symmetric Polyarthritis. The clinical picture of symmetric polyarthritis resembles that of RA, in that inflammation of the metacarpals and the proximal interphalangeal joints is prominent. However, several features help distinguish it from RA. It usually runs a milder course; subcutaneous nodules and other extra-articular manifestations of RA are not usually seen; and, as with all forms of PsA, patients are usually RF negative.

Oligoarthritis. This is the most common pattern of PsA, accounting for more than half of cases.³² It is characterized by asymmetric involvement of fewer than 4 joints. Any joint can be involved. Arthritis in a single knee may be the first sign of oligoarthritis.

Spondylitis and/or Sacroiliitis. This pattern resembles ankylosing spondylitis but is considered a separate entity. Human leukocyte antigen (HLA)-B27 is

Table 1. Psoriatic Arthritis: Moll and Wright Classification of Joint Involvement

■	Predominantly distal interphalangeal arthritis
■	Arthritis mutilans
■	Symmetric polyarthritis
■	Oligoarthritis
■	Spondylitis and/or sacroiliitis

Source: Reference 32.

less likely to be present and disease is generally less disabling than in patients with ankylosing spondylitis. The axial skeleton tends to be involved in an atypical fashion; the lumbar spine is the most common site of involvement. Sacroiliitis is present in about one third of cases, often with bilateral changes. Spondylitis may occur alone or in association with peripheral arthritis.

Some clinical overlap has been noted within the various patterns of PsA (Table 2),^{6,34} with evolution from one clinical entity to another. As the disease progresses and more joints become involved, patients may move from an oligoarticular presentation to a polyarticular pattern; if radiographs are performed, the presence of a spondyloarthropathy may be recognized in a patient who previously had not complained of any back pain. Conversely, as patients who present with polyarthritis improve, the number of joints involved may be reduced and the pattern of joint involvement may become oligoarticular. These patterns of joint involvement are not different arthropathies, but different presentations of the same arthropathy—namely, PsA.

A characteristic finding in several types of PsA is dactylitis (“sausage digit”), in which the entire digit appears swollen because of inflammation involving the tendons and periosteum as well as the joints. Factors that may contribute to disease progression include a high number of swollen joints, the presence of actively inflamed joints, and an elevated erythrocyte sedimentation rate.³⁵ Because of the poor prognosis for people with active disease, it is necessary to treat early, prevent erosions, and maintain function.

Radiographic Features. Radiographic features seen in patients with PsA are those of inflammatory arthritis. They may include the distinctive asymmetric pattern of joint involvement; sacroiliitis and spondylitis; bone erosions with new bone formation; bony ankylosis; and distal interphalangeal joint involvement.³⁶ “Pencil-cup” deformities may occur as a result of “whittling” of the proximal phalanges and expansion of the base of the distal phalanx.

langes and expansion of the base of the distal phalanx.

Bulky, asymmetric, unilateral syndesmophytes (bony outgrowths) may form in the axial skeleton. These can be present in the lumbar, thoracic, or cervical spine in a “skip” pattern, often sparing some segments. Asymmetric sacroiliac and paravertebral ossification may be present. Osteolysis may also be seen.³⁶

The presence of spurs and the periosteal reaction are characteristic of the enthesopathy of PsA.³⁶ In the spine, both typical marginal syndesmophytes and paramarginal syndesmophytes are seen.

Differentiating Psoriatic Arthritis From Rheumatoid Arthritis. Patients with PsA can be presumptively differentiated from those with RA based on several clinical features. First, in general, PsA affects fewer joints than does RA, and often has asymmetric distribution of affected joints (versus the symmetric dis-

Table 2. Clinical Features in Patients Who Present With Psoriatic Arthritis

<p>Common Features</p> <ul style="list-style-type: none"> ■ Polyarthritis ■ Spinal inflammation ■ Peripheral enthesitis ■ Distal interphalangeal joint arthritis ■ Monoarthritis/oligoarthritis ■ Dactylitis (“sausage digits”) <p>Uncommon Features</p> <ul style="list-style-type: none"> ■ Palmar plantar pustulosis ■ Synovitis, acne, pustulosis, hyperostosis, and osteolysis (SAPHO) syndrome ■ Spondylodiscitis ■ Arthritis mutilans ■ Onycho-pachydermo-periostitis

There may be some clinical overlap within the various patterns over time, with evolution from one clinical entity to another. Source: McGonagle D, Conaghan PG, Emery P. Psoriatic arthritis. A unified concept twenty years on. *Arthritis Rheum* 1999;42:1080-1086. Reprinted with permission.

tribution seen in RA). PsA, as mentioned previously, also involves the distal joints and is typically associated with nail pitting. Patients with PsA are typically RF negative, and they tend to present with milder symptoms than patients with RA. For example, patients with PsA typically experience morning stiffness for shorter periods of time than do patients with RA. Patients with PsA generally display fewer swollen and tender joints than do those with RA. Although the number of actively inflamed joints is typically lower in PsA than in RA, the number of damaged joints and the degree of joint involvement may be similar.³⁷ Finally, patients with PsA demonstrate less tenderness than do those with RA.³⁸

Socially, patients with PsA may be even more isolated than those with RA because of the open and more disfiguring appearance of skin plaques. Unlike RA, which is 3 times more prevalent in women than in men,³⁹ PsA occurs with similar frequency in men and women.⁴⁰ In addition, patients with PsA are, on average, slightly younger than those with RA.

Pathophysiology

Four key elements are part of the pathogenesis of psoriasis and PsA. They include the psoriatic plaque, psoriatic synovial inflammation, enthesopathy,

and abnormal bone remodeling. Prior to the 1990s, the role of the keratinocyte and abnormal keratocyte proliferation were emphasized in the development of psoriatic plaque. Recent experiments, however, reveal an important role for the T cell in driving this unusual skin phenotype.⁴¹⁻⁴⁵

A number of parallels can be made between what happens pathologically in the skin and what can be seen in the rheumatoid and psoriatic joint. In the skin, mononuclear cells (predominantly T cells) infiltrate the dermis. This infiltration is accompanied by increased cytokine production by these T cells, which results in the hyperproliferation of keratinocytes and the phenotypic plaque. This sequence of events is analogous to what is seen in the rheumatoid joint in the sense that in the deep layers of subsynovial tissue there is infiltration with mononuclear cells, release of cytokines, and a significant synovial proliferation of lining cells.⁴⁵

In the skin, infiltration by activated T cells (CD4 and CD8) precedes the development of the psoriatic plaque.⁴⁶ The cytokine profile in psoriatic plaques is distinctive, with increased levels of interleukin-2 (IL-2) and interferon-gamma expressed.⁴⁷ An associated increase in the levels of IL-6, IL-8, and TNF has been noted.⁴⁸

In addition, the role of infection as a potential driver of the T-cell response has been touted in the psoriasis and PsA literature. For example, as already noted, guttate psoriasis may be triggered to expression by streptococcal and viral infections of the respiratory tract.³⁰ Elevated antistreptococcal antibody titers and positive streptococcal throat cultures appear to be associated with acute disease.⁴⁹ Psoriatic plaques are often colonized by bacteria. This observation has caused significant conjecture regarding an etiologic role for these bacteria in triggering either the onset or exacerbation of existing disease. However, at this time, this association remains only conjecture, as no data have been reported to support a direct link between bacteria in the plaque with disease activity.

Table 3. Genetic and Environmental Factors in Psoriatic Arthritis (PsA)

<p>Genetic susceptibility predisposing to PsA trait</p> <ul style="list-style-type: none"> ■ HLA-Cw6 ■ Other class I HLA specificities (B13, B17, B27, B38, B39) ■ Non-MHC genes? <p>Environmental factors influencing expression of PsA trait</p> <ul style="list-style-type: none"> ■ Trauma ■ Repetitive motion ■ Human immunodeficiency virus infection ■ Bacterial infection?

HLA = human leukocyte antigen; MHC = major histocompatibility complex.

Source: Reference 13.

Several genetic and environmental factors are believed to contribute to the predisposition to develop PsA (Table 3). These factors include the expression of certain major histocompatibility complex antigens (particularly HLA-B27), trauma, and joint injury as a result of repetitive motions.¹³ The presence of specific genetic factors in determining the trait of PsA is shown by the familial aggregation of PsA, although the disease does not follow a simple monogenic pattern of inheritance.¹³ The probability of a first-degree relative of a person with PsA having the disease is about 40 times greater than that in their unaffected spouses.⁵⁰ Yet PsA is pleomorphic in its expression, affecting different parts of the musculoskeletal system, skin, and other organs, and varies in its clinical manifestation from individual to individual.

Synovitis and Enthesopathy—The Pathogenic Hallmarks of Psoriatic Arthritis. Early PsA is thought to start in areas adjacent to the synovium.¹⁰ With progression, synovitis develops, which resembles the same chronic inflammatory process found in many other arthritides, including RA. PsA is further characterized by metaplastic proliferation of the synovial lining-cell layer, converting the lining from a single- into a multicelled layer; extensive infiltration of lymphocytes and monocytes; and new vessel formation simulating a granulomatous reaction.¹⁰ Early synovial damage is caused by inflammatory edema with fibrin deposition and progressive hyperplasia of the lining-cell layer, along with lymphocytic infiltration in the subsynovial layer.¹⁰ Cartilage destruction and bone erosions ensue.

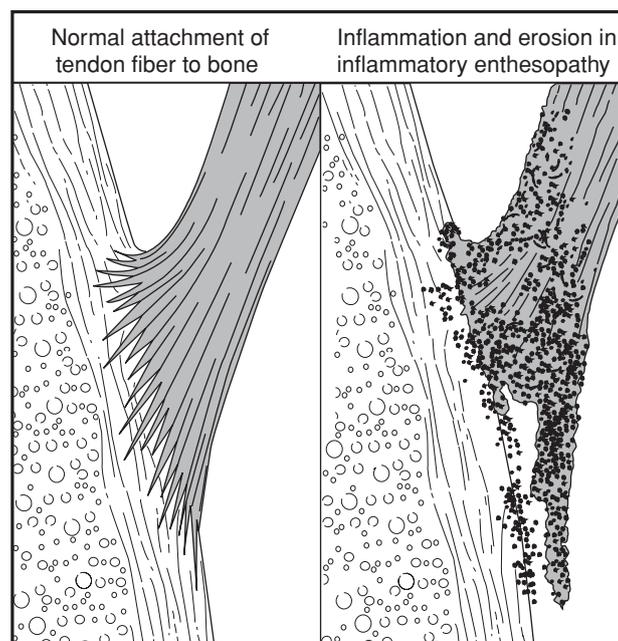
Besides synovitis, the other pathogenic hallmark of PsA is enthesopathy. Enthesopathy is characterized by an accumulation of lymphocytes and monocytes at the site of tendon or ligament insertion, resulting in inflammation and erosions (Figure 3) that eventually cause spurs and periostitis.

The enthesis is a potentially important structure, representing the site of attachment of ligaments, tendons, capsules, and fascia to bone.⁵¹ Enthesopathic fibers penetrate deep into the bony trabeculae and

form this attachment site. In enthesopathic diseases, a prominent inflammatory infiltrate can be found in this area with associated bony erosion. This abnormality can present clinically as dactylitis.

McGonagle et al⁵² looked at the presence of high-intensity signals in the knees of patients with PsA and other spondyloarthropathies, and compared the results to those of similar studies in patients with RA. They used fat-suppressed, T2-weighted magnetic resonance imaging (MRI) to demonstrate signal intensity at the patellar attachment site, the periarticular tissues, and the bony attachments in the patella itself. Prominent enthesal abnormalities on MRI were a constant feature of new-onset synovitis in spondyloarthritis-related arthritides, but were a minor feature of RA.⁵² There were 2 significant findings on MRI in patients with spondyloarthritis-related arthritides in this study. First, focal soft-tissue edema outside the joint capsule adjacent to enthesal insertions (perienthesal edema) was common, and this edema was believed to be secondary to enthesitis. The soft-tissue

Figure 3. Inflammatory Enthesopathy of a Tendon Attachment



abnormalities outside the joint that were seen in a subset of RA patients may have been secondary to severe synovitis with nonspecific extension of the inflammatory process beyond the joint capsule. Second, bone marrow edema that was maximal adjacent to enthesal insertions was seen only in spondyloarthritis-related arthritides, and was accompanied by perienthesal edema. The pattern of bone edema seen in this study has previously been reported in relation to peripheral enthesitis and spondylitis,⁵³ which suggests a common pathogenic link between spinal disease, peripheral enthesitis, and knee synovitis in spondyloarthritis-related arthritides.

In a later article, McGonagle et al⁵⁴ suggested that enthesitis may be the link between infection and subsequent pathologic and clinical manifestations. In this model, a microorganism may emerge from the gastrointestinal or genitourinary tract, lung, or skin, and result in enthesitis with the clinical findings of tendonitis, spondylitis, synovitis, dactylitis, or localized bone damage, and the pathologic equivalents of tendon-insertion enthesitis, ligamentous-insertion enthesitis, secondary regional enthesitis, and localized synovitis (Figure 4).⁵⁴

A somewhat contrary view was published by François et al,⁵⁵ who examined the sacroiliac joints of patients with ankylosing spondylitis using standard histologic

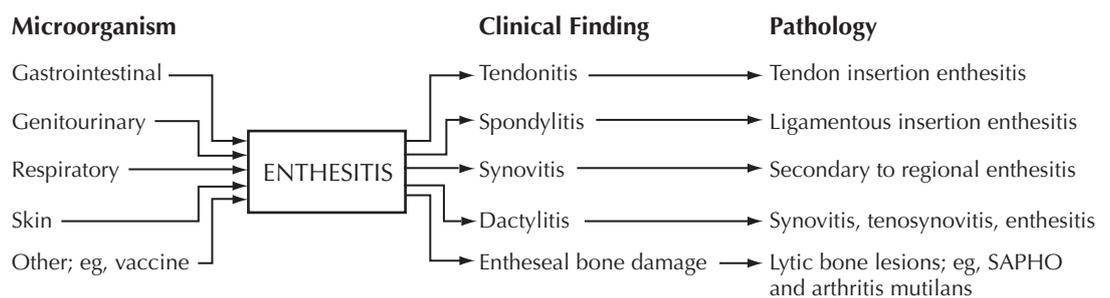
techniques. They demonstrated enthesopathic changes in 5 of 12 specimens; in 2 patients significant pannus was found to be invading the sacroiliac area with substantial subchondral bone absorption. In one biopsy with significant loss of subchondral bone, osteoclasts were present and multinuclear cells were eroding the bone. The investigators concluded that inflammation of the enthesis is part of PsA; however, controversy remains as to whether or not the enthesis is critically important to the development of ongoing inflammation and later bony damage in PsA.⁵⁵

Summary

PsA is a debilitating, chronic spondyloarthritis that for years has been underrecognized and undertreated. The social devastation associated with the skin and joint manifestations of the disease is enormous and has been well documented. Patients with PsA may have severe skin disease, debilitating and progressive joint disease, and profound decreases in functional status, even while undergoing therapy with conventional DMARDs. Many patients who have PsA or psoriasis are dissatisfied, predominantly because of the shortcomings of current therapeutic approaches.

With advances in our understanding of the pathogenesis of PsA—particularly the role of cytokines such as TNF in the gene-

Figure 4. Etiopathogenesis of Enthesitis-Related Clinical Syndromes



SAPHO = synovitis-acne-pustulosis-hyperostosis osteolysis.

Source: McGonagle D, Gibbon W, Emery P. Classification of inflammatory arthritis by enthesitis. *Lancet* 1998;352:1137-1140. Reprinted with permission.

sis of skin and joint disease—has come a potential milestone in the therapy of both PsA and psoriasis. The development of TNF inhibitors targeted specifically to the mechanisms of skin and joint inflammation in PsA and psoriasis represents a major advance in what physicians will be able to offer patients. For the first time in more than a decade, a new and innovative therapeutic modality has been developed. It is hoped that TNF inhibition will offer patients with PsA and psoriasis what traditional therapies have been largely unable to provide—sustained relief from debilitating symptoms and dramatic improvements in overall quality of life.

...REFERENCES...

1. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340:253-259.
2. Moreland LW, Schiff MH, Baumgartner ER, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;130:478-486.
3. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997;337:141-149.
4. Maini R, Breedveld F, Furst D, et al. Infliximab (chimeric anti-tumor necrosis factor- α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A randomized phase III trial. *Lancet* 1999;354:1932-1939.
5. Maini RN, Ferdinand CB, Joachim RK, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor- α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1552-1563.
6. Torre Alonso JC, Rodriguez Perez A, Arribas Castrillo JM, et al. Psoriatic arthritis (PA): A clinical, immunological, and radiological study of 180 patients. *Br J Rheumatol* 1991;30:245-250.
7. Jones SM, Armas JB, Cohen MG, Lovell CR, Evison G, McHugh NJ. Psoriatic arthritis: Outcome of disease subsets and relationship of joint disease to nail and skin disease. *J Rheumatol* 1994;33:834-839.
8. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis (PsA)—An analysis of 220 patients. *Q J Med* 1987;62:127-141.
9. Husted JA, Gladman DD, Farewell VT, Long JA, Cook RJ. Validating the SF-36 health questionnaire in patients with psoriatic arthritis. *J Rheumatol* 1997;24:511-517.
10. Gladman DD, Stafford-Brady F, Chang C-H, Lewandowski K, Russell ML. Longitudinal study of clinical and radiological progression in psoriatic arthritis. *J Rheumatol* 1990;17:809-812.
11. Jones G, Crotty M, Brooks P. Psoriatic arthritis: A quantitative overview of therapeutic options. *Br J Rheumatol* 1997;36:95-99.
12. American College of Rheumatology. Psoriatic arthritis fact sheet. Available at: <http://www.rheumatology.org/patients/factsheet/psoriati.html>. Accessed November 12, 2001.
13. Winchester R. Psoriatic arthritis. In: Winchester R, Fitzpatrick TB, Eisen AZ, Wolff K, Freeberg FM, Austin KF, eds. *Dermatology in General Medicine*, 4th ed. New York, NY: McGraw-Hill; 1993:515-527.
14. Cohen MR, Reda DJ, Clegg DO. Baseline relationships between psoriasis and psoriatic arthritis: Analysis of 221 patients with active psoriatic arthritis. *J Rheumatol* 1999;26:1752-1756.
15. Wright V. Rheumatism and psoriasis: A re-evaluation. *Am J Med* 1959;27:454-462.
16. Piroo MH, Cash JM. Treatment of refractory psoriatic arthritis. *Rheum Dis Clin North Am* 1995;21:129-149.
17. Cuellar ML, Espinoza LR. Methotrexate use in psoriasis and psoriatic arthritis. *Rheum Dis Clin North Am* 1997;23:797-809.
18. Clegg DO, Reda DJ, Manias E, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. *Arthritis Rheum* 1996;39:2013-2020.
19. Palit J, Hill J, Capell HA, et al. A multicentre double-blind comparison of auranofin, intramuscular gold thiomalate, and placebo in patients with psoriatic arthritis. *Br J Rheumatol* 1990;29:280-283.
20. Farr M, Kitas GD, Waterhouse L, Jubb R, Felix-Davies D, Beacon PA. Sulfasalazine in psoriatic arthritis: A double-blind placebo-controlled study. *Br J Rheumatol* 1990;29:46-49.
21. Willkens RF, Williams HJ, Ward JR, et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum* 1984;27:376-381.
22. Black RL, O'Brien WM, Van Scott EJ, Auerbach R, Eisen AZ, Bunim JJ. Methotrexate therapy in psoriatic arthritis. *JAMA* 1964;189:743-747.
23. Yazici Y, Erkan D, Lockshin MD. A preliminary study of etanercept in the treatment of severe, resistant psoriatic arthritis. *Clin Exp Rheumatol* 2000;18:732-734.
24. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: A randomized trial. *Lancet* 2000;356:385-390.
25. Mease PJ, Goffe BS, Metz J, VanderStoep A, Burge DJ. Enbrel® (etanercept) in patients with psoriatic arthritis and psoriasis [abstract]. *Arthritis Rheum* 2000;43(suppl):S403. Abstract 2019.
26. Scarpa R, Mathieu A. Psoriatic arthritis: Evolving concepts. *Curr Opin Rheumatol* 2000;12:274-280.
27. National Psoriasis Foundation. New research shows one million U.S. adults suffer from psoriatic arthritis. Others may be at risk but not know it [press release]. Portland, OR: National Psoriasis Foundation; January 16, 2002.
28. Christophers E, Griffiths CEM, Ortonne J-P, Krueger GG. Selective T cell targeting in psoriasis: A novel approach to improve clinical outcomes. Paper presented at: 10th Congress of the European Academy of Dermatology & Venerology: Skin and

- Environment—Perception and Protection; October 10-14, 2001; Munich, Germany.
29. **Kaipainen-Seppänen O.** Incidence of psoriatic arthritis in Finland. *Br J Rheumatol* 1996;35:1289-1291.
 30. **Anderson TF.** Psoriasis. *Med Clin North Am* 1982;66:769-794.
 31. **Whyte HJ, Baughman RD.** Acute guttate psoriasis and streptococcal infection. *Arch Dermatol* 1964;89:350-355.
 32. **Moll JM, Wright V.** Psoriatic arthritis. *Semin Arthritis Rheum* 1973;3:55-78.
 33. **Gladman DD, Anhorn KA, Schachter RK, Mervart H.** HLA antigens in psoriatic arthritis. *J Rheumatol* 1986;13:586-592.
 34. **McGonagle D, Conaghan PG, Emery P.** Psoriatic arthritis. A unified concept twenty years on. *Arthritis Rheum* 1999;42:1080-1086.
 35. **Gladman DD, Farewell VT, Nadeau C.** Clinical indicators of progression in psoriatic arthritis: Multivariate relative risk model. *J Rheumatol* 1995;22:675-679.
 36. **Gladman DD, Rahman P.** Psoriatic arthritis. In: Ruddy S, Harris ED Jr, Sledge CB, eds. *Kelley's Textbook of Rheumatology*, 6th ed. Philadelphia, PA: WB Saunders; 2001:1071-1079.
 37. **Rahman P, Nguyen E, Cheung C, Schentag CT, Gladman DD.** Comparison of radiological severity in psoriatic arthritis and rheumatoid arthritis. *J Rheumatol* 2001;28:1041-1044.
 38. **Buskila D, Langevitz P, Gladman DD, Urowitz S, Smythe HA.** Patients with rheumatoid arthritis are more tender than those with psoriatic arthritis. *J Rheumatol* 1992;19:1115-1119.
 39. **Grassi W, De Angelis R, Lamanna G, Cervini C.** The clinical features of rheumatoid arthritis. *Eur J Radiol* 1998;27(suppl):S18-S24.
 40. **Salvarani C, Olivieri I, Cantini F, Macchioni L, Boiardi L.** Psoriatic arthritis. *Curr Opin Rheumatol* 1998;10:299-305.
 41. **Ellis CN, Krueger GG.** Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 2001;345:248-255.
 42. **Granstein RD.** New treatments for psoriasis [editorial]. *N Engl J Med* 2001;345:284-287.
 43. **Nickoloff BJ.** The immunologic and genetic basis of psoriasis. *Arch Dermatol* 1999;135:1104-1110.
 44. **Robert C, Kupper TS.** Mechanisms of disease: Inflammatory skin diseases, T cells, and immune surveillance. *N Engl J Med* 1999;341:1817-1828.
 45. **Fearon U, Veale DJ.** Pathogenesis of psoriatic arthritis. *Clin Exp Dermatol* 2001;26:333-337.
 46. **Danning CL, Illei GG, Hitchon C, Greer MR, Boumpas DT, McInnes IB.** Macrophage-derived cytokine and nuclear factor κ B p65 expression in synovial membrane and skin of patients with psoriatic arthritis. *Arthritis Rheum* 2000;43:1244-1256.
 47. **Ritchlin C, Haas-Smith S, Hicks D, Cappuccio J, Osterland CK, Looney RJ.** Patterns of cytokine production in psoriatic synovium. *J Rheumatol* 1998;25:1544-1552.
 48. **Partsch G, Steiner G, Leeb BF, Dunky A, Bröll H, Smolen JS.** Highly increased levels of tumor necrosis factor- α and other proinflammatory cytokines in psoriatic arthritis synovial fluid. *J Rheumatol* 1997;24:518-523.
 49. **Quimby SR, Markowitz H, Winkelman RK.** Antideoxyribonuclease B titers in psoriasis. *Acta Dermatol Venerol* 1980;60:485-490.
 50. **Moll JHM.** Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies and Behçet's syndrome. *Medicine (Baltimore)* 1974;53:343-347.
 51. **Ritchlin C.** The pathogenesis of psoriatic arthritis. *J Musculoskel Med* May 2001;(suppl):S37-S44.
 52. **McGonagle D, Gibbon W, O'Connor P, Green M, Pease C, Emery P.** Characteristic magnetic resonance imaging enthesal changes of knee synovitis in spondyloarthropathy. *Arthritis Rheum* 1998;41:694-700.
 53. **Jevtic V, Rozman B, Kos-Golja M, Watt I.** MR imaging in seronegative spondylarthritis. *Radiologie* 1996;8:624-631.
 54. **McGonagle D, Gibbon W, Emery P.** Classification of inflammatory arthritis by enthesitis. *Lancet* 1998;352:1137-1140.
 55. **François RJ, Gardner DL, DeGrave EJ, Bywaters EGL.** Histopathologic evidence that sacroiliitis in ankylosing spondylitis is not merely enthesitis. Systematic study of specimens from patients and control subjects. *Arthritis Rheum* 2000;43:2011-2024.