CHAPTER 8

Psoriatic Arthritis
A. Clinical Features

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- Psoriatic arthritis (PsA) occurs in approximately 26% of patients with psoriasis, leading to prevalence in the population of 0.3% to 1%.
- There are multiple clinical subsets of PsA reflecting variable clinical patterns including: distal joint disease, arthritis mutilans, oligoarthritis (less than or equal to four joints), rheumatoid arthritis (RA)-like polyarthritis, and spondylitis.
- Other musculoskeletal features include dactylitis (sausage digit), tenosynovitis, and enthesitis.
- Patients with PsA may also have iritis, urethritis, nonspecific colitis, and cardiovascular manifestations.
- Diagnosis is made on clinical grounds in patients with psoriasis having skin, scalp, or nail changes. Rheumatoid factor should be negative.

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis (1). Psoriasis is an inflammatory skin condition that presents with a red scaly rash often on the extensor surfaces but may also affect the scalp and flexural areas as well as palms and soles (2). It commonly affects the nails with either pits or onycholysis. Up to one third of patients with psoriasis may develop an inflammatory arthritis presenting with pain and stiffness in the affected joints. Both psoriasis and PsA affect men and women equally. PsA was distinguished from rheumatoid arthritis (RA), the prototype inflammatory arthritis, in the middle of the past century with the discovery of rheumatoid factor (RF). Whereas 85% of patients with RA are RF positive, patients with psoriatic arthritis are usually seronegative for RF. Earlier studies using the latex fixation test suggested that up to 15% of patients with PsA were seropositive (3), but more recent studies using either nephelometry or enzyme-linked immunosorbent assay (ELISA) tests reveal a prevalence of only 4% to 5% (4).

Several other features distinguish PsA from RA, including the equal gender frequency, the pattern of joint involvement, the presence of spinal involvement, and specific radiologic features. Because of the seronegative RF, the spinal involvement, and other extra-articular features seen among patients with PsA, as well as the association with human leukocyte antigen (HLA)-B27, PsA has been classified among the seronegative spondyloarthropathies.

EPIDMEMIOLOGY OF PSORIATIC ARTHRITIS

Prevalence of Psoriatic Arthritis

The exact prevalence of PsA is unknown. Estimates have varied from 0.1% to over 1% of the population (5,6). This variation may be related to the fact that there are no valid diagnostic criteria for the disease and various studies have used different case definitions. Moreover, some studies used administrative databases, some used population surveys, and others used clinical observations within hospital admissions or clinic attendees. The incidence of PsA has also varied and its true value remains unknown.

The prevalence of PsA among patients with psoriasis has varied from 6% in the Mayo Clinic (7) study to 30% in the European survey (Table 8A-1) (8). It should be noted that the Mayo Clinic study was based on an administrative database and accepted the database diagnosis of psoriasis, whereas the European survey was administered to members of a psoriasis association. A recent survey performed through the National Psoriasis Foundation in the United States identified an overall prevalence of PsA among patients with psoriasis at 11%, but this value increased to 56% when the extent of psoriasis exceeded 10 palms (9). An Italian study that was based at a clinic where dermatologists and rheuma-

TABLE 8A-1. FREQUENCY OF PSORIATIC ARTHRITIS AMONG PATIENTS WITH PSORIASIS.

AUTHOR (YEAR; REFERENCE)	CENTER	NUMBER OF PATIENTS STUDIED	PERCENTAGE PSA
Leczinsky (1948) (64)	Sweden	534	7
Vilanova (1951) (65)	Barcelona	214	25
Little (1975) (66)	Toronto	100	32
Leonard (1978) (67)	Rochester	77	39
Green (1981) (68)	Cape Town	61	42
Scarpa (1984) (10)	Naples	180	34
Stern (1985) (69)	Boston	1285	20
Zanelli (1992) (70)	Winston-Salem	459	17
Falk (1993) (71)	Kautokeino	35	17
Barisic-Drusko (1994) (72)	Osijek region	553	10
Salvarani (1995) (73)	Reggio-Emilia	205	36
Shbeeb (2000) (7)	Mayo Clinic	1056	6.25
Brockbank (2001) (74)	Toronto	126	31
Alenius (2002) (75)	Sweden	276	48
Zachariae (2003) (8)	Denmark	5795	30
Gelfand (2005) (9)	United States	601	11

tologists see patients together, identified 33% of the patients as having psoriasis (10). As can be seen in Table 8A-1, the frequency estimates for PsA among patients with psoriasis average 26%. If the prevalence of psoriasis is 1% to 3% of the population, then the true prevalence of PsA is more likely between 0.3% and 1%. A definite prevalence figure awaits valid diagnostic criteria for this disease.

Classification Criteria

Several sets of classification criteria for PsA have been proposed, although only one was derived from clinical data (11). Taylor and colleagues (12) compared several classification criteria sets for PsA. Most criteria sets were highly sensitive and specific, but the Fournie criteria (11) require HLA typing and therefore 24% of patients could not be classified. The CASPAR (Classification of Psoriatic Arthritis) group, an international group gathered to develop classification criteria for PsA, recently completed its study of the classification of PsA (4). It proposed a new set of criteria for classification of PsA which were 99% specific and 92% sensitive for PsA (Table 8A-2).

CLINICAL FEATURES OF PSORIATIC ARTHRITIS

Clinical Subsets of Psoriatic Arthritis

Psoriatic arthritis affects both peripheral joints and the axial skeleton. Wright and Moll described the clinical patterns of PsA (1). These include (1) a predominantly distal joint disease, which they identified in about 5% of their patients, and which have been variably recognized by other groups (3,10,13–21); (2) arthritis mutilans, a very destructive form of arthritis, which they identified in 5% of the patients, but which may be more frequent; (3) oligoarthritis, affecting four or fewer joints, often in an asymmetric distribution which they observed in 70% of the patients; (4) polyarthritis, indistinguishable from RA, which they detected in 15% of the patients; (5) spondyloarthritis, which occurs alone in about 5% of the patients, but may be associated with one of the other forms in about 40% of the patients. It has now been recognized that while these patterns may be helpful at disease onset, they do not stay stable over time (17,22,23). Moreover, it has been recognized that

TABLE 8A-2. CASPAR CRITERIA.

INFLAMMATORY ARTICULAR DISEASE (JOINT, SPINE, OR ENTHESEAL)		
With 3 or more points from the following:		
1. Evidence of psoriasis (one of a, b, c)	(a) Current psoriasis[a]	Psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist
	(b) Personal history of psoriasis	A history of psoriasis that may be obtained from patient, family doctor, dermatologist, rheumatologist, or other qualified health care provider
	(c) Family history of psoriasis	A history of psoriasis in a first- or second-degree relative according to patient report
2. Psoriatic nail dystrophy		Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination
3. A negative test for rheumatoid factor		By any method except latex but preferably by ELISA or nephelometry, according to the local laboratory reference range
4. Dactylitis (one of a, b)	(a) Current	Swelling of an entire digit
	(b) History	A history of dactylitis recorded by a rheumatologist
5. Radiological evidence of juxta-articular new bone formation		Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain x-rays of hand or foot

SOURCE: The CASPAR Study Group, Arthritis Rheum 2006;54:2665–2673, with permission of *Arthritis and Rheumatism*.
Specificity, 98.7%; sensitivity, 91.4%.
[a]Current psoriasis scores 2, whereas all other items score 1.

the symmetry is a function of the number of joints involved (24). Indeed, with established disease most patients with PsA present with polyarthritis (3,6).

We have recorded the patterns according to distal, oligoarthritis, polyarthritis alone or in combination with spinal disease, as well as isolated spinal disease (3,19). Because arthritis mutilans could occur within any of these groups it has not been identified as an isolated group. This classification was found to be 97% sensitive and 99% specific for PsA (12). A review of 705 patients followed prospectively at the University of Toronto PsA Clinic reveals that at presentation, 3.7% have predominantly distal joint disease but over 50% of the patients have distal joint involvement in association with another pattern. Arthritis mutilans, defined as at least one totally destroyed joint, was detected in 19.5%, whereas five or more totally destroyed joints were detected in 8.2% of the patients (Table 8A-3).

Peripheral Arthritis in Psoriatic Arthritis

The arthritis of PsA is inflammatory in nature, presenting with pain, swelling, and stiffness in the affected joints. Any joint may be affected. Early in the disease course the arthritis tends to be oligoarticular, but may become polyarticular as more joints are accrued over time. There are several clinical characteristics of the peripheral arthritis in PsA regardless of the clinical pattern. Patients with PsA are not as tender as patients with RA (25). This has practical implications both in terms of recognizing the presence of arthritis by the patients and physicians, and therefore the ability to diagnose the condition, and in terms of recognizing the need for therapy. Many patients present with deformity and joint damage, not having perceived any pain during the inflammatory phase of their disease. The presence of a bluish/purplish discoloration over the inflamed joint is typical for seronegative disease, including PsA, and may help differentiate PsA from RA even in the absence of obvious psoriasis (26). The distribution of the affected joints is another typical feature of PsA. Whereas RA tends to involve joints along the same level (all metacarpophalangeal joints, all proximal interphalangeal joints) in a symmetric distribution, PsA affects all the joints of one digit, in a ray pattern, giving the asymmetric distribution typical for the disease. Thus, the presence of distal joint inflammation as well as the ray pattern are key features in PsA (Figure 8A-1).

Psoriatic Spondyloarthritis

Spinal involvement in PsA includes inflammation in both the sacroiliac joints and the apophyseal joints of the spine. The distribution in PsA tends to be asymmetric, with only one sacroiliac joint involved and the other being spared, or with a different degree of involvement noted on sacroiliac radiographs. Likewise, the spinal involvement tends to be asymmetric, and with skip lesions (Figure 8A-2). Nonetheless, all levels of the spine may be involved (27–30). The prevalence of spinal

TABLE 8A-3. PATTERNS OF PSORIATIC ARTHRITIS.[a]

Number of patients	705
Age at onset skin (mean [SD])	28.8 (14.4)
Age at onset joints	36.1 (13.2)
Gender	57% male, 43% female
Age at presentation	43.7 (13.3)
Number of inflamed joints	10.2 (9.6)
Number of damaged joints	
Clinical	3.2 (7.5)
Radiological	4.8 (8.1)

PATTERN	AT PRESENTATION (%)	LAST VISIT (%)
Distal	3.7	1.6
Oligoarthritis	14.7	8.5
Polyarthritis	39.3	30.6
Back alone	2.4	1.4
Back plus distal	2.6	1.1
Back plus oligoarthritis	7.4	10.1
Back plus polyarthritis	29.9	45.7
Remission	0	1.1
Arthritis mutilans		
≥1 joint with stage 4 radiological damage	19.5	36.4
≥5 joints with stage 4 radiological damage	8.2	18.2

[a] Data from the University of Toronto Clinic, Toronto, Ontario, Canada.

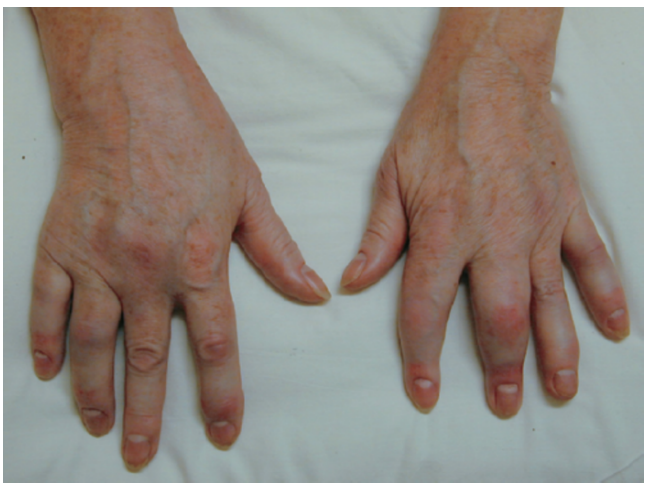

FIGURE 8A-1

Ray distribution peripheral arthritis. Note the involvement of the second, third, and fifth digits on the left hand, while the third right digit is totally spared.

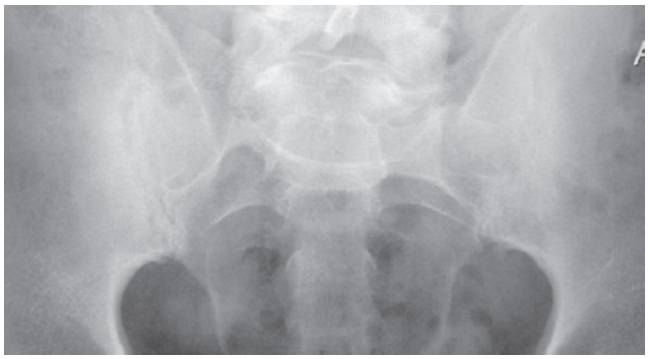

FIGURE 8A-2

Asymmetric sacroiliitis, skip syndesmophytes.

involvement in PsA has been variable, partly due to the definition used by the investigators. If radiographs are performed on each patient, then sacroiliitis may be detected quite frequently. In one study it was reported in 78% of the patients (30). After 10 years of observation, some 50% of the patients in the University of Toronto PsA Clinic have demonstrated evidence of spinal involvement defined by the presence of sacroiliitis and/or syndesmophytes. However, only a portion of these patients have clinical complaints of either pain or morning stiffness. Indeed, patients with psoriatic spondylitis do not complain of as much pain, and do not exhibit as much spinal limitation as patients with idiopathic ankylosing spondylitis (31). This may be the result of the generalized lower pain threshold noted among these patients, as well as from the fact that the disease itself may not be as severe, because fewer patients with psoriatic spondyloarthritis present with grade 4 sacroiliitis and they have fewer syndesmophytes than patients with ankylosing spondylitis (31).

OTHER ARTICULAR MANIFESTATIONS IN PSORIATIC ARTHRITIS

Dactylitis

Dactylitis, or sausage digit, is a typical feature of PsA. It refers to inflammation of the whole digit. It likely results from both synovitis in the joints of the digit, as well as tenosynovitis, particularly in the flexor tendons (32,33). Dactylitis most commonly affects the toes, but fingers are affected as well (34). Joints within digits that demonstrated acute dactylitis were more likely to develop erosions than those in digits without dactylitis, suggesting that the presence of dactylitis is prognostic for disease progression (34). It should be noted that dactylitis may become chronic, such that it is no longer

painful or red, but remains as a chronically swollen digit, which may not respond to therapeutic intervention. Helliwell and colleagues (35) proposed a method for assessing dactylitis that may be useful in clinical trials and in clinical observational cohort studies. Recently, swelling of the extremity has been recognized as a feature of PsA (36). The exact mechanism of this peripheral edema is unclear but both lymphedema and tenosynovitis may play a role (37).

Tenosynovitis

Tendonitis or tenosynovitis occurs frequently among patients with PsA. Inflammation may affect the flexor tendons of the fingers, as well as the extensor carpi ulnaris, sites that are commonly affected in RA. Achilles tendonitis is commonly seen, as is plantar fascitis. These may interfere with function and may lead to disability. In PsA, tendonitis may be associated with tendon nodules and significant functional limitation.

Enthesitis

Inflammation of the enthesis, site of insertion of tendon into bone, is another typical feature of PsA. Enthesitis may occur at any tendon insertion site, but most commonly affects the plantar fascia, Achilles tendon insertion, insertion of tendons at the knee and shoulder, as well as the pelvic bones. It has been suggested that enthesitis alone in the presence of psoriasis may be sufficient for the diagnosis of PsA (38). Indeed, the CASPAR criteria require the presence of any inflammatory musculoskeletal features, including enthesitis, together with three other features to classify a patient as having PsA (4).

EXTRA-ARTICULAR FEATURES OF PSORIATIC ARTHRITIS

Skin Disease

Skin psoriasis is a prerequisite for the diagnosis of psoriatic arthritis. There are several clinical presentations of psoriasis (2). Psoriasis vulgaris is the most common type and the most commonly associated with psoriatic arthritis. If affects the extensor surfaces, particularly elbows and knees. Psoriasis vulgaris may also affect the scalp, the gluteal folds, as well the anal cleft. Psoriasis may affect flexural areas primarily, in which case it would be hidden unless the patients are asked about it, or are totally undressed for the physical examination. Guttate psoriasis may also be associated with psoriatic arthritis, but is less common than psoriasis vulgaris (6). The most severe form of psoriasis is the erythrodermic type.

The relationship between skin and joint disease is variable (39,40). There may be a stronger association in patients whose skin and joint manifestations began simultaneously (40). It has been noted that in clinical trials for PsA the degree of skin disease is not as high as it is in clinical trials in psoriasis patients. Nail lesions have been observed in a higher frequency among patients with PsA compared to uncomplicated psoriasis (41). These may be associated with distal interphalangeal joint disease.

Other Extra-Articular Manifestations

Iritis is an extra-articular feature common to all spondyloarthropathies and is also seen among patients with PsA. Some 7% of patients with PsA present with iritis, and it can also be seen among patients with psoriasis without arthritis (3,41).

Urethritis is also a feature of seronegative disease. It is less common in PsA than in the other members of the spondyloarthritis group.

Bowel involvement may occur in patients with PsA and is usually nonspecific colitis (42,43).

Cardiac abnormalities have been reported among patients with PsA, including dilatation of the base of the aortic arch which occurs in ankylosing spondylitis. More recently it has been recognized that patients with PsA are at risk for cardiovascular disease (44). This may be related to the metabolic abnormalities associated with PsA, including hyperlipidemia, hyperuricemia, as well as lifestyle factors such as obesity and smoking (44,45).

DIAGNOSING PSORIATIC ARTHRITIS

The diagnosis of PsA should be considered in any patient who presents with an inflammatory arthritis in the presence of psoriasis. However, not all patients with psoriasis presenting with arthritis have PsA. PsA must be distinguished from RA. Because psoriasis occurs in 1% to 3% of the population and RA occurs in about 1%, the chance of a patient having both RA and psoriasis is 1:10,000. If a patient with psoriasis and inflammatory arthritis has rheumatoid nodules, they are more likely to have coexistence of RA with psoriasis. On the other hand, if they are RF negative, have distal interphalangeal joint disease, and have nail lesions, they are much more likely to have PsA even if they present with a symmetric polyarthritis. The presence of spinal disease also tips the balance towards PsA. Because of the involvement of distal joint disease, PsA must be distinguished from osteoarthritis. Osteoarthritis is primarily

not an inflammatory disease. Therefore, if the distal interphalangeal joints are inflamed with redness and swelling, especially in the context of nail lesions, the patient is much more likely to have PsA. In patients with mono- or oligoarticular presentation, PsA must be differentiated from gout. Because patients with PsA may have an elevated serum uric acid, it is important to obtain synovial fluid for crystal analysis to determine the underlying pathophysiology.

Patients with PsA who present with inflammatory spinal disease must be differentiated from other spondyloarthropathies. Because psoriasis may be associated with Crohn's disease, with the latter being associated with spondylitis, it may be difficult to differentiate. However, as noted above, the spinal involvement in PsA tends to be asymmetric, whereas in ankylosing spondylitis and inflammatory bowel disease the spinal disease tends to be symmetric. The presence of nail lesions suggests the diagnosis of PsA (46).

COURSE AND OUTCOME IN PSORIATIC ARTHRITIS

In the past, patients with PsA were thought to have a milder disease than patients with rheumatoid arthritis (47). However, over the past 20 years it has become clear that the disease is more severe than previously thought. A study of 220 patients with PsA demonstrated that 67% of the patients had erosive disease at presentation to clinic, and 20% of the patients had a very severe form of arthritis, similar to what had been reported for RA (3). More recently, 47% of the patients with PsA seen in clinic within 5 months of onset were found to have erosive disease by 2 years (48). Patients with PsA demonstrate disease progression over time, with more patients developing polyarthritis and an increase in joint damage both clinically and radiologically (23,49). While progression of damage may be determined first by radiographs, clinical damage may be observed at each clinic visit and should be recorded (50).

Predictors for Disease Progression

Predictors for the progression of clinical damage include polyarticular presentation and a high medication level at presentation to clinic (51,52). The number of actively inflamed joints present at each visit predict progression of clinical damage in subsequent visits (53). HLA markers may influence outcome in both positive and negative ways (see Chapter 8B). However, 17.6% of the patients with PsA sustained a remission, defined as no actively inflamed joints for at least 1 year (11,54). The remission lasted 2.6 years on average, and was associated with male gender and less active and severe disease at presentation to clinic.

Quality of Life in Psoriatic Arthritis

Patients with PsA demonstrate reduced quality of life and function compared to the general population (55,56). Indeed, quality of life among patients with PsA was similar to that of patients with RA (57). Patients with PsA exhibited more vitality, but also more bodily pain than patients with RA (58). While 28% of the patients did not demonstrate disability over a 10-year period, female sex and older age were associated with more disability, while longer disease duration was associated with no change in disability (59).

Mortality in Psoriatic Arthritis

Patients with PsA are at an increased risk of death compared to the general population (60). While the causes of death are similar to those seen in the general population, disease activity and severity at presentation are predictive of early mortality in patients with PsA (61). Survival in PsA seems to have improved in the past 30 years, with the most recent standardized mortality ratio reducing from 1.62 to 1.36 (62). It is possible that more aggressive therapeutic approaches have helped improve survival (63). A recent study demonstrated that there is no increased malignancy risk among patients with PsA followed over 25 years.

SUMMARY

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis, usually seronegative for RF. It presents in a number of clinical patterns. PsA may be severely disabling and is associated with an increased mortality risk. Patients with PsA should be diagnosed early and treated promptly and aggressively in order to prevent these untoward outcomes.

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CHAPTER 8

Psoriatic Arthritis
B. Pathology and Pathogenesis

CHRISTOPHER RITCHLIN, MD

- Psoriatic arthritis (PsA) histopathology differs from rheumatoid arthritis (RA), with the most striking difference in the characteristic of the synovial vasculature.
- Psoriatic arthritis is triggered by interaction between genetic and environmental factors with initiating events occurring in the skin and/or gut.
- Cellular immunity and cytokines, including tumor necrosis factor alpha (TNF-alpha), are important mediators of PsA.
- Osteoclasts are important mediators of dysregulated bone remodeling in PsA.

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis that is usually negative for rheumatoid factor (RF). Inflammation can target a range of musculoskeletal structures, including the axial skeleton, peripheral joints, attachment sites of ligaments, tendons or joint capsules onto bone (entheses), and tendon sheaths. Joint manifestations may be highly localized and mild in some patients, while others may experience widespread inflammation and damage that results in significant functional decline. Moreover, as discussed in the previous chapter, several clinical subsets of PsA have been described (symmetric polyarthritis, asymmetric oligoarticular arthritis, spondylitis, arthritis mutilans, and predominant distal interphalangeal disease) and it is not known whether these distinct clinical entities are orchestrated by the same disease mechanisms. Joint dysfunction can arise not only as a result of bone resorption and cartilage degradation, but also from diffuse soft tissue inflammation (dactylitis) and new bone formation in the form of ankylosis or periostitis.

PATHOLOGY

The histologic changes in the peripheral joints are similar to those observed in rheumatoid arthritis (RA) but important distinctions have been noted. One of the most prominent features is a striking increase in synovial vascularity, characterized at the macroscopic level by dilated and tortuous blood vessels that contrast sharply with the linear pattern observed in RA (1). At the histologic and ultrastructural level, psoriatic synovial vasculature displayed endothelial cell swelling, inflammatory cell infiltration, and marked thickening of the vessel wall (2). Monocytoid cells infiltrate the subsynovium but in PsA the numbers are less than in RA. Immunopathologic features observed more commonly in PsA compared to RA were increased vascularity, prominent neutrophil infiltration, and increased expression of the mature monocyte marker CD163 by subsynovial monocytes (3). Infiltrating CD4+ lymphocytes predominate in the synovial tissue, whereas CD8+ T cells are present in the synovial fluid (4,5). Ectopic lymphoid aggregates have been noted in psoriatic synovium. No significant pathologic differences were found between oligo- or polyarticular PsA and the psoriatic synovial histology was more similar to other forms of spondyloarthropathies (SpA) than to RA (6).

The inflamed synovial membrane or pannus, comprised of fibroblastoid cells and activated macrophages, is invasively destructive. Fibroblastoid cells release metalloproteinases (MMP)-1, 2, and 3, which degrade cartilage, while MMP-9 is localized to vessel walls (7). Osteoclasts are present in deep resorption pits at the bone–pannus junction. Biopsies of entheseal inflammation sites revealed CD8+ T cells in the underlying subchondral bone and macrophages infiltrating the tendon (8,9). Studies of bone and synovium from patients with axial PsA have not been performed, but imaging studies suggest an entheseal-based pathology with prominent osteitis in the underlying bone (Figure 8B-1) (10). Dactylitis is most likely a form of flexor tenosynovitis, although pathologic studies of involved digits have not been published.

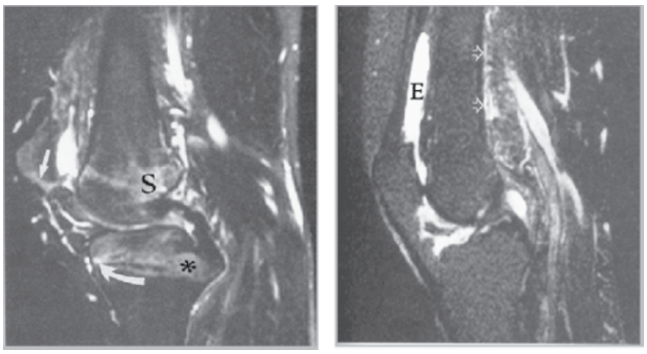


FIGURE 8B-1

Fat-suppressed T2 weighted magnetic resonance imaging (MRI) scans in PsA and RA. In the left panel, a psoriatic knee demonstrates extensive bone marrow edema in three areas: the anterior patella (*straight arrow*), superior insertion of the posterior cruciate ligament (S), and marked subchondral bone marrow edema in the tibial plateau, especially at the patellar tendon insertion (*curved arrow*) and the inferior insertion of posterior cruciate ligament (*). In the right panel, a rheumatoid knee shows a joint effusion (E) and focal increased signal limited to vessels behind the femur. (Modified from McGonagle D et al., Arthritis Rheum 1998;41:694–700, with permission of *Arthritis and Rheumatism* and Wiley Periodicals, Inc.)

PATHOGENESIS

In the current paradigm, PsA is triggered by a complex interaction between genetic and environmental factors. Given the temporal relationship with psoriasis, it is likely that the initiating events involve both innate and acquired immune responses that arise in the skin and spread to the joint in susceptible individuals. Recent studies have underscored the central role of inflammatory cytokines in joint inflammation and destruction. Treatment interventions directed at these molecules have provided effective treatment options and uncovered novel disease mechanisms.

Genetic Basis of Psoriatic Arthritis

Moll and Wright found that 5.5% of first-degree relatives of PsA probands developed inflammatory arthritis—an inheritability risk that is greater than observed in psoriasis (11). Several genetic loci have been implicated in the predisposition to psoriasis and PsA, but the strongest effect has been linked to alleles in the major histocompatibility complex (MHC). Earlier association studies in PsA focused attention on HLA-Cw6, in addition to HLA-B13 and -B17 (B57). These associations reflect the strong linkage disequilibrium between HLA-Cw6 and HLA-B57, and HLA-Cw6 and HLA-B13, which extends into the MHC class II region. In individuals with PsA, the association with HLA-Cw6 is slightly weaker than in psoriasis. A smaller proportion of cases have an association with HLA-B27, chiefly in patients with predominant spinal disease. HLA-B27 in the presence of HLA-DR7 and HLA-DQw3 in the absence of HLA-DR7 predict progression, while HLA-B22 is protective. Other reports noted an association with HLA-B38 and -B39, as well as with other alleles in linkage disequilibrium. The presence of HLA-DR*04 shared epitope is associated with worse radiological damage (12,13).

Major histocompatibility complex class I molecules could promote PsA by presenting arthritogenic peptides to CD8+ lymphocytes or by selection of a T-cell repertoire that is autoreactive in skin and joints. Another mechanism recently described indicates that natural killer (NK) cell activity is controlled through interactions between killer immmunoglobulinlike receptors (KIR) and MHC class I genes, particularly Cw6. PsA patients have a genetic profile of KIR alleles that lower the threshold for NK activations (14). Two recent reports have also found associations of PsA with interleukin 1 (IL-1) and tumor necrosis factor (TNF) alleles (15,16).

It should be emphasized that the great majority of these studies have been performed in cases or families ascertained by the presence of psoriasis. Thus, to dissect disease associations specific to arthritis, two separate cohorts of psoriasis patients (with and without arthritis) must be characterized and genotyped. Furthermore, the finding that relevant HLA class I MHC alleles occur in less than 50% of PsA patients may reflect involvement of non-HLA genes in the causal pathway.

Environmental Factors

Compelling evidence suggests that trauma and infection play a role in the etiologic pathway of PsA. Koebner phenomenon, described as psoriatic lesions arising at sites of trauma, occurs in 24% to 52% of psoriasis patients (17). The development of PsA following trauma to a joint, with the suggested name of the *deep Koebner phenomenon*, has also been reported in the Toronto longitudinal observational cohort, where 50 of 203 (24.6%) patients reported a traumatic event prior to the diagnosis of PsA (18). Subclinical trauma may also contribute to the distal interphalangeal (DIP) joint arthritis, dactylitis, and enthesitis, although this relationship has not been formally studied. It is also important to note that a history of trauma has been reported in only a minority of PsA patients.

Some studies suggest involvement of bacterial agents in psoriasis and possibly PsA. A strikingly high association between guttate psoriasis and preceding streptococcal pharyngitis and tonsillitis exists in children (19). The link between Gram-positive infection and PsA was suggested by high levels of circulating antibodies to

microbial peptidoglycans and elevated levels of group A streptococcus 16S RNA in the peripheral blood of PsA patients (20). Both streptococcal and staphylococcal superantigens promote inflammation and upregulation of keratinocyte TNF in noninvolved psoriatic skin, but not other inflammatory dermatoses, elucidating the potential importance of this novel immune pathway in psoriasis (21).

Cellular Activation and Cytokine Pathways in Psoriatic Arthritis

Recent evidence indicates that cells of the innate immune system may direct the early events in psoriatic joint inflammation. The effector cells of the innate response are keratinocytes, dendritic cells, neutrophils, monocytes/macrophages, and NK cells. In a mouse model of PsA, targeted keratinocyte deletion of JunB and c-Jun, components of the AP-1 transcription factor that is involved in cellular differentiation and proliferation, resulted in psoriasiform skin lesions and subsequent arthritis with features of joint destruction and new bone formation (22). This model demonstrated that disruption of keratinocye function could promote an inflammatory response in the skin that spreads to the joint via mechanisms that involve T cells and TNF signaling pathways. Activated plasmacytoid and monocytoid dendritic cells (DC) have been detected in the dermis of psoriasis plaques and both of these DC subsets were isolated from PsA joint fluid (23). As previously mentioned, prominent neutrophil and monocyte infiltrates are present in psoriatic skin and synovium. The role of NK cells in PsA has not been elucidated, but the finding that specific alleles associated with NK cell receptor are associated with susceptibility to psoriasis and PsA suggests that they may contribute to the pathogenesis (14). Moreover, cytokines involved in the innate immune response have been detected in psoriatic synovium, including IL-1, IL-8, IL-15, and TNF-alpha (24).

Several lines of evidence demonstrate that TNF-alpha is a pivotal cytokine in psoriatic joint inflammation. First, elevated levels of TNF-alpha have been detected in joint fluid and in psoriatic synovial supernatants (24). Second, immunohistochemical studies demonstrated upregulation of TNF-alpha in the psoriatic synovial membrane and skin (25,26). Third, histopathologic analysis of synovial specimens from PsA patients treated with anti-TNF agents revealed decreased vascularity, synovial lining thickness, and mononuclear cell infiltration following treatment (Figure 8B-2) (27,28). Fourth, clinical trials revealed that anti-TNF agents significantly lessen inflammation in the psoriatic plaque, entheses, flexor tendons, and the axial skeleton (see Chapter 8C) (29).

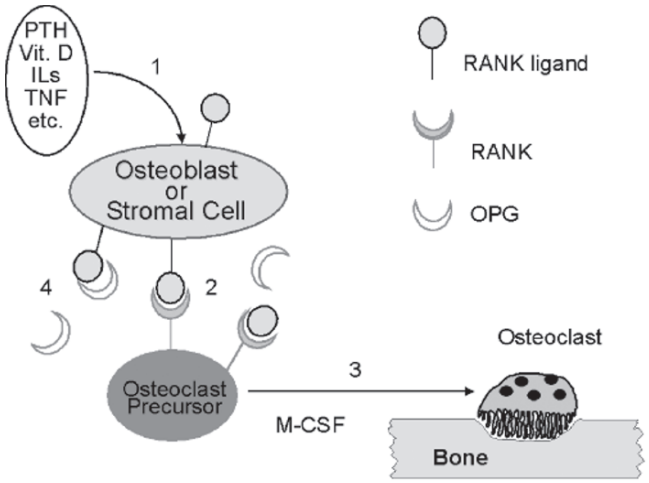


FIGURE 8B-2

Representative images of CD3+ and CD68+ immunohistochemical staining and TUNEL assay in psoriatic synovial tissues at baseline and 48 hours after initiation of infliximab therapy. A significant decline in infiltrating CD3+ T cells and CD68+ macrophages was noted. Therapy was not associated with increased apoptosis as measured by the TUNEL assay. (From Goedkoop AY et al., Ann Rheum Dis 2004;63:769–773, with permission of *Annals of the Rheumatic Diseases*.)

The role of the acquired immune response in psoriatic joint disease is not well understood but the strong association of psoriatic arthritis with MHC class I molecules suggests that CD8+ T lymphocytes may be pivotal in pathogenesis. Immunohistologic studies on psoriatic synovial membranes, however, revealed a predominance of CD45RO+ memory T cells in the synovial lining mononuclear cell infiltrate (30). In contrast, CD8+ T cells are the principal lymphocytes in synovial fluid, some of which demonstrate oligoclonal expansion of T-cell receptor (TCR) B chains, suggesting the presence of an antigen-driven response (5). Additional support for T-lymphocyte involvement came from studies on psoriatic synovial explant tissues which produced higher levels of the helper-T-lymphocyte (Th1) cytokines IL-2 and interferon gamma (INF-gamma) protein than explants similarly cultured from osteoarthritis and rheumatoid patients (24). In contrast, IL-4 and IL-5 were not identified in psoriatic explants. This Th1 profile has been observed in both psoriasis and RA. A similar pattern of cytokine production in psoriatic synovium was shown using immunohistochemical techniques (25).

Dysregulated Bone Remodeling in Psoriatic Arthritis

In regard to bone, psoriatic joint biopsies demonstrate large multinucleated osteoclasts in deep resorption pits at the bone–pannus junction (31). Osteoclastogenesis (differentiation of osteoclasts) is a contact-dependent

process directed by osteoblasts and stromal cells in the bone marrow (Figure 8B-3) (32). These cells release two different signals necessary for differentiation of an osteoclast precursor (OCP), derived from the CD14+ monocyte population, into an osteoclast. The first, macrophage-colony stimulating factor (M-CSF) and the second, receptor activator of NF-κB ligand (RANKL), a member of the TNF superfamily, bind to RANK on the surface of OCP and osteoclasts. This ligand–receptor interaction stimulates proliferation and differentiation of OCP and activation of osteoclasts. Because permissive quantities of M-CSF are constitutively expressed in the bone microenvironment, it has been proposed that the relative expression of RANKL and its natural antagonist osteoprotegerin (OPG) ultimately control osteoclastogenesis. Interestingly, RANKL is also expressed by infiltrating T cells and synovial fibroblastoid cells in the synovial lining of inflamed joints.

In psoriatic synovial tissues, marked upregulation of RANKL protein and low expression of OPG was detected in the adjacent synovial lining. Osteoclasts were also noted in cutting cones traversing the subchondral bone supporting a bidirectional attack on the bone in psoriatic joints (31). In addition, OCP, derived from circulating CD14+ monocytes, were markedly elevated in the peripheral blood of PsA patients compared to healthy controls. Treatment of PsA patients with anti-TNF agents significantly decreased the level of circulating OCP, thus supporting a central role for TNF-alpha in the generation of this precursor population.

The mechanisms responsible for new bone formation in the psoriatic joint are poorly understood. Transforming growth factor (TGF) beta and vascular endothelial growth factor (VEGF) may be pivotal in this process given that TGF-alpha is strongly expressed in synovial tissues isolated from ankylosing spondylitis patients and synergizes with VEGF to induce bone formation in animal models (33,34). Male DBA/1 mice caged together develop an ankylosing enthesitis remarkably similar to lesions in PsA and bone morphogenetic proteins (BMP) 2 and 7 are upregulated in regions of pathologic new bone formation (35). In addition, expression of phosphorylated Smad 1 and Smad 5, important signaling molecules in the downstream BMP signaling pathway, was markedly increased in regions of new bone formation taken from the calcaneous in a patient with Achilles tendonitis and periostitis.

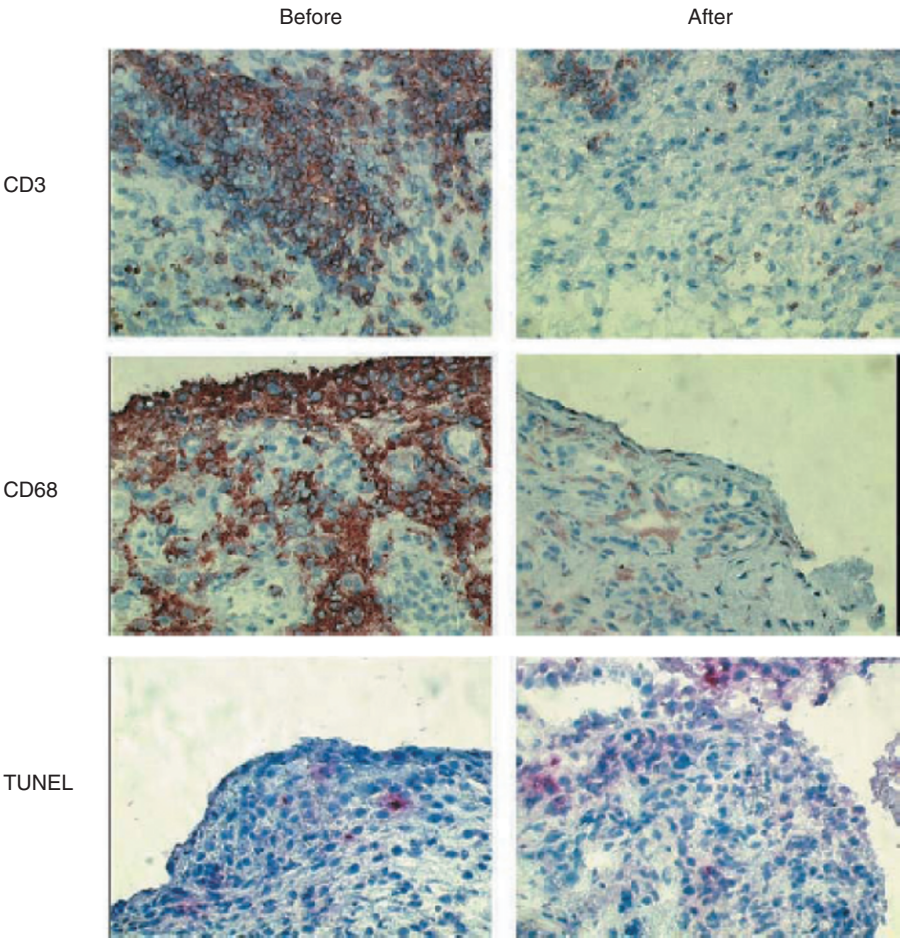


FIGURE 8B-3

Osteoclast differentiation. RANKL is expressed by osteoblasts and stromal cells in response to a variety of stimuli. In the inflamed joint, RANKL is expressed by fibroblastoid lining cells and infiltrating T lymphocytes. RANKL binds to the RANK receptor expressed on OCP and OC. In the presence of M-CSF and RANKL, OCP mature into OC capable of resorbing bone. OPG, a physiologic decoy molecule, can bind to RANKL and inhibit OC differentiation and activation. Abbreviations: RANKL, receptor activator of NF-κB ligand; OCP, osteoclast precursor; M-CSF, monocyte colony stimulating factor; OPG, osteoprotegerin.

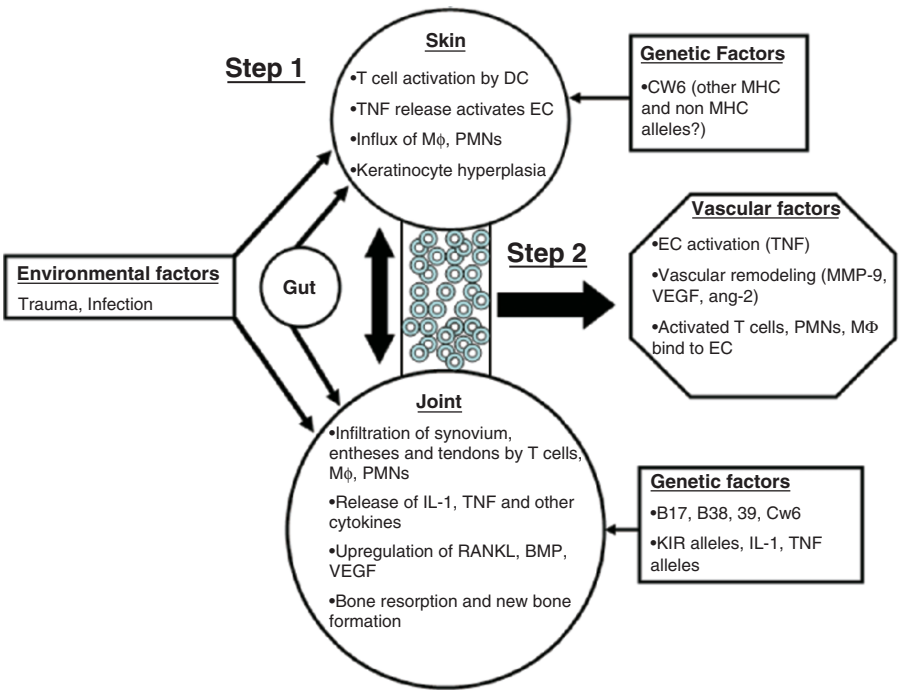
Pathogenesis of Extra-Articular Psoriatic Arthritis

Gut and eye involvement are present in a subset of PsA patients. Subclinical gut inflammation was noted in 16% of 64 PsA patients on ileocolonoscopy, and this finding was limited to patients with oligoarthritis or spinal disease but not those with polyarthritis (36). Furthermore, PsA patients have an increased risk of inflammatory bowel disease compared to controls. Uveitis, both unilateral and bilateral, can occur in PsA patients, particularly in the subset with axial disease. Furthermore, both uveitis and bowel inflammation often respond to anti-TNF therapy. These clinical observations suggest a link between bowel inflammation, spondylitis, and eye disease in a subset of PsA patients that may be mediated in part by TNF. An alternative view has been proposed based on the concept of psoriatic disease in which psoriasis is viewed as a systemic disease that involves different anatomical sites in the same patient (37).

Taken together, the evidence suggests that trauma or infection in a genetically susceptible individual triggers PsA and that the initial inciting event probably occurs in the skin, resulting in activation of monocytes and T cells (Figure 8B-4). In the subset with spondylitis, the early events may arise in the gut. In some patients with psoriasis, local events in the joint promote angiogenesis followed by mononuclear cell activation accompanied by increased expression of TNF-alpha and RANKL. Circulating OCP enter the joint after binding to activated endothelial cells and undergo osteoclastogenesis and resorb bone. Elevated production of BMP and VEGF contribute to new bone formation, while MMPs released by synovial lining cells degrade cartilage and engage in blood vessel remodeling. Presumably, perpetual release of proinflammatory cytokines,

FIGURE 8B-4

PsA pathogenesis model. The major events in PsA begin in the skin (step 1) and spread to the joint (step 2). The genetic factors associated with skin or joint disease may not be identical. In step 1, DC are triggered by trauma, infection, or other signals to activate T cells. Activated T cells promote entry of monocytes into the dermis and release of TNF and other cytokines that lead to keratinocyte hyperplasia and PMNs infiltration. In step 2, activated monocytes and T cells leave the skin and enter the joint that has been subjected to trauma or infection, after binding to primed ECs. Vascular remodeling is directed by VEGF, MMP-9, and ang-2. TNF and other cytokines released by these infiltrating cells drive synovial cell hyperplasia. The lining cells promote osteoclastogenesis and subsequent bone resorption via RANKL expression and they release MMPs which mediate cartilage degradation. Inflammatory events in the subchondral bone foster enthesitis and osteitis. Activation of BMPs leads to new bone formation. Abbreviations: EC, endothelial cell; MΦ, monocyte/macrophage; MHC, major histocompatibility complex; MMP: metalloproteinase; ang-2, angiopoietin 2; VEGF, vascular endothelial growth factor; PMN, neutrophils; BMP, bone morphogenetic protein; KIR, killer immunoglobulin receptor.



particularly TNF, leads to persistent synovitis, enthesitis, and progressive matrix degradation. The events that drive the chronic influx of mononuclear cells into the joint and sustained release of proinflammatory cytokines have not been elucidated.

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CHAPTER 8

Psoriatic Arthritis
C. Treatment and Assessment

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- Multiple instruments are available for assessment of skin, joints, and quality of life in psoriasis and psoriatic arthritis (PsA).
- Management of skin and arthritis can often be accomplished with similar agents.
- Destructive arthritis should be managed by traditional disease-modifying drugs or biologic therapies.
- Tumor necrosis factor (TNF) inhibitors have shown the greatest efficacy to date in PsA.

The framework for the treatment of psoriatic arthritis (PsA) is constituted by proper diagnosis and assessment of severity of the domains of disease activity involved in PsA: peripheral arthritis, enthesitis, dactylitis, spine inflammation, and skin and nail lesions, which may be differentially active. The degree of disease activity in these domains, along with background contextual factors for the individual (age, gender, psychological and socioeconomic factors, comorbidities, etc.) determine the impact of disease on quality of life, function, and life expectancy.

Typically, a patient will be aware of having the skin condition psoriasis long before the associated arthritis occurs. In just 15% to 25% of patients will the arthritis manifest simultaneously or subsequently (1,2). Thus, many patients will be under the care of a dermatologist or primary care physician (PCP) for management of skin lesions and, as such, are in an ideal position to be queried about symptoms of musculoskeletal pain and stiffness. PsA can occur in up to 30% of patients with psoriasis, depending on method of ascertainment and severity of psoriasis (see Chapter 8A). Because other forms of arthritis may occur in a patient with psoriasis, such as osteoarthritis, rheumatoid arthritis (RA), other spondyloarthritides, and gout (see Chapter 8A), it may be prudent for the dermatologist or PCP to obtain a rheumatology consult to help clarify what type of arthritis condition is present, supplement education for the patient and family, and strategize about treatment approaches based on the diagnosis and severity (3).

Although this review will focus on pharmacotherapy of PsA, it must be recognized that optimal therapy also comprises nonpharmacotherapy approaches, including patient and family education about the disease process and therapy, exercise, nutrition, psychological counseling, physical and occupational therapy, and orthopedic surgery. There have been few studies of these modalities in PsA per se, although there has been extensive research on their value and utility in the management of arthritis in general and RA specifically, from which we can extrapolate regarding their value and utility in PsA. A key role for the rheumatologist and rheumatology office staff is to serve as a central triage point for such adjunct therapy.

ASSESSMENT OF DISEASE ACTIVITY AND THERAPY OUTCOME

Determination of disease severity and effectiveness of therapies in clinical trials and in practice requires assessment tools that have generally been adapted from similar measures used in assessment of RA and psoriasis (Table 8C-1) (4–9). These have been used in clinical trials and clinical registries of PsA patients. These measures have been shown to effectively assess peripheral joint and skin symptoms and signs, function, quality of life, and fatigue, as well as distinguish treatment from placebo. Approaches to assessment of enthesitis, dactylitis, and spine involvement are still in development. Adaptation of RA methodologies to assess change of radiographs in PsA has occurred in a number of recent clinical trials (7,8), suggesting that such approaches are appropriate in PsA despite its differences from RA. Several studies have documented the effectiveness of ultrasound and magnetic resonance imaging (MRI) in detecting

TABLE 8C-1. PSORIATIC ARTHRITIS OUTCOME MEASURES USED IN CLINICAL TRIALS.

Arthritis response
American College of Rheumatology Response Criteria (including DIP and CMC joints)
Psoriatic Arthritis Response Criteria (PsARC)
Disease Activity Score (DAS, DAS 44, DAS 28)
Radiographic assessment
Modified (for PsA) Sharp
Modified (for PsA) van der Heijde/Sharp
Skin response
Psoriasis Area and Severity Index (PASI)
Target Lesion score
Physician Global Assessment (PGA) of Psoriasis
Quality of life/function improvement
Short-Form 36 Health Survey (SF-36)
Health Assessment Questionnaire (HAQ) Disability Index
Dermatology Life Quality Index (DLQI)
Functional Assessment of Chronic Illness Therapy (FACIT)

SOURCE: Data from references 4 through 9.
ABBREVIATIONS: CMC, carpometacarpal; DIP, distal interphalangeal.

inflammation in the joints and enthesium of SpA patients, as well as the extent of structural damage (8).

PSORIASIS MANAGEMENT

The patient's individual experience with psoriasis therapies, prior to development of PsA, will have depended on the severity of skin disease. Milder disease, for example, involving less than 5% body surface area (BSA), showing less severe induration and scale, and not involving important functional or cosmetic areas such as the hands, scalp, or other visible areas, may be treated with topical corticosteroid and/or vitamin D or A analogues, as well as ultraviolet (UV) light therapy (10–12). Patients with moderate-to-severe skin disease may have been treated with systemic therapies, such as methotrexate, cyclosporine, and acitretin, as well as UV light therapy, often in a cyclic fashion to maximize therapeutic effect while minimizing treatment side effects (10–17). When psoriasis clears it does not leave residual damage, so dermatologists typically treat till clear and then withdraw therapy until lesions return. A number of strategies have been developed for intermittent as well as combination therapy, based on assessment of skin lesion severity, to achieve optimal results (17). It is important to take into account previous tolerability and effectiveness of systemic medicines used for psoriasis when considering therapeutic options for inflammatory arthritis when it develops.

In recent years, there has been extensive uptake of the biologic response modifier medications in psoriasis, all administered parenterally, based on successful clinical trials of the anti–tumor necrosis factor (anti-TNF) agents etanercept, infliximab, and adalimumab (18–20) and the T-cell modulating agents, alefacept and efalizumab (21,22). Etanercept, infliximab, and efalizumab have been approved in the United States and Europe for psoriasis and alefacept has been approved for use in the United States. Clinical studies and clinical experience, including safety and tolerability issues, with these agents in psoriasis have been extensively reviewed elsewhere (9,10,13,17,23–25). The first biologic agents approved in the United States were the T-cell modulatory agents alefacept and efalizumab, based on the key role played by T lymphocytes in psoriasis pathogenesis (26). Both block T-cell stimulation; alefacept promotes apoptosis of memory T cells and efalizumab inhibits migration of lymphocytes to the site inflammation. Both show clinically meaningful reductions in skin lesional activity and improved quality of life. A typically greater and more rapid improvement of psoriasis has been seen with the anti-TNF agents, along with correlated improvements of fatigue and quality of life and return to normal work and social life. These drugs offer an alternative to other systemic therapies or time-consuming UV light or topical therapies.

PSORIATIC ARTHRITIS MANAGEMENT

Nonsteroidal Anti-Inflammatory Drugs in Psoriatic Arthritis

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a cornerstone of therapy for most PsA patients with musculoskeletal pain symptoms, either used alone in mild disease or in combination with other therapies. Typically a patient may have already tried an over-the-counter formulation, such as ibuprofen and naprosyn, so will have a sense of their relative effectiveness and tolerability. Switching among choices of NSAIDs may be indicated to try to achieve maximum convenience, effectiveness, and tolerability. There is scant trial experience with NSAIDs in PsA documenting efficacy (27), so support for their use is primarily derived from trials in rheumatoid arthritis (RA) and osteoarthritis (OA) as well as clinical experience. There are isolated case reports of psoriasis exacerbation related to NSAID use, but this has not been felt to be of significant consequence (27).

Nonsteroidal anti-inflammatory drugs have been found to be efficacious for the treatment of spinal pain in ankylosing spondylitis, on which evidence it is reasonable to extrapolate efficacy in management of PsA spondylitis (28).

Glucocorticoids in Psoriatic Arthritis

Episodic intra-articular steroid injections can be symptomatically helpful, especially for patients with monoarticular PsA, oligoarticular disease, or a situation wherein a polyarticular patient has one or a few joints inadequately controlled by systemic therapy. Enthesitis and tendonitis may also be helped by selective steroid injection. Results tend to be short lived, thus of limited long-term use if inflammation is recurrent in that site. However, if the inflammation is transient in that site, then local injection therapy can be quite helpful. Systemic glucocorticoids should be used more judiciously than in other inflammatory arthritides because of the chance that psoriasis skin lesions will severely flare upon withdrawal of therapy (27).

Traditional Disease-Modifying Antirheumatic Drugs in Psoriatic Arthritis

Utilization of systemic disease-modifying drugs in PsA has generally been modeled after their use in psoriasis and RA. Those that are considered traditional include the oral agents methotrexate, sulfasalazine, and cyclosporine. Injectable and oral gold and azathioprine would also be considered in this group, but have been infrequently used and, in the case of injectable gold therapy, have generally fallen out of favor.

Leflunomide, a pyrimidine antagonist approved for the treatment of RA, is typically considered along with this group of agents.

Methotrexate

Methotrexate (MTX) is one of the most commonly used systemic medications in PsA, yet controlled trial evidence for its effectiveness is scant. In 1984, Willkens published a small controlled trial using dosages of the drug that were then considered potentially appropriate in the treatment of inflammatory arthritis, 7.5 mg and 15 mg per week (29). In this trial, only the physician global assessment of arthritis showed statistically significant improvement, and not the tender and swollen joint count. Skin improvements were modest. However, clinical experience with standard doses in the 15 to 20 mg per week range would suggest that the drug can be efficacious in many patients and it remains one of the most commonly used disease-modifying antirheumatic drugs (DMARDs).

Increasingly it has been recognized that MTX only partially inhibits the progression of structural damage in RA (30). This has not been prospectively assessed in PsA, but a 2-year retrospective analysis of matched PsA patients who were either on or off MTX therapy did not show any difference in radiologic progression scores in the two groups (31). Patients on chronic MTX therapy must have regular blood monitoring (blood counts, liver function tests, and creatinine). Significant elevation of liver tests or drop in blood counts should lead to adjustment of dose or cessation of therapy. A further consideration is that based on older liver biopsy studies, the suggestion has been made that there is greater proclivity to MTX hepatotoxicity in a psoriasis population than in patients with RA (32). Thus, there is often a preference by the dermatologist to limit overall use of MTX, or, if continued, to assess for liver toxicity by periodic liver biopsy (33). This is in contrast to the rheumatology experience wherein liver function tests are periodically assessed, but not liver biopsies, and MTX is used continuously and often in combination with other medications (34). Nevertheless, the practice of routine liver biopsies based on MTX dose has been questioned in the literature as more data are acquired (33–35).

Although the combination of MTX and TNF inhibitors has in RA been shown to be superior in all clinical parameters of efficacy, including inhibition of structural damage (30), this has not been assessed in PsA. Thus, in the treatment of PsA in clinical practice, MTX may sometimes be discontinued after initiation of biologic therapy and only reinitiated if the patient experiences inadequate control of disease with biologic monotherapy. Response of spinal joints has not been assessed in PsA. In ankylosing spondylitis, MTX has not been shown to benefit spinal measures of disease activity (28,36).

Sulfasalazine

The largest number of controlled trials of traditional DMARD therapy has been conducted with sulfasalazine (27). In the largest of these, 221 PsA patients were treated with sulfasalazine, 2 g/day, for 36 weeks (37). Although a composite arthritis score showed statistically significant improvement in the treatment group, the only individual measure within the responder index to do so was the patient global assessment, indicating that the effect was not strong. Further, there was no benefit to the skin and gastrointestinal intolerability was an issue. As with MTX, spine response was not assessed and controlled trials with this agent in ankylosing spondylitis have not shown efficacy in the spine domain (28).

Cyclosporine

Although cyclosporine can achieve rapid improvement of the skin lesions of psoriasis, its effectiveness in PsA has been minimally studied other than showing some effectiveness in open trials (27). Its utility is limited by concerns regarding the adverse effects of hypertension

and renal insufficiency. Regarding the combination of cyclosporine with MTX, 72 patients with incomplete response to MTX were randomized to placebo or addition of cyclosporine (38). At 48 weeks, significant improvements in tender and swollen joint count, C-reactive protein (CRP), psoriasis area and severity index (PASI), and synovial ultrasound score occurred in the combination group, but statistical differentiation between the combination and MTX-alone group occurred just in PASI and ultrasound score.

Leflunomide

Leflunomide, a pyrimidine antagonist approved in RA at a dose of 20 mg/day, was assessed in 188 PsA patients. The Psoriatic Arthritis Response Criteria (PsARC) response, the primary endpoint, was met by 59% of leflunomide-treated patients compared with 29.7% of placebo-treated patients ($p < 0.0001$). American College of Rheumatology (ACR) 20 response was achieved by 36.3% and 20%, respectively ($p = 0.0138$), and PASI 75 response by 17.4% and 7.8%, respectively ($p = 0.048$) (39). As with MTX, liver function test abnormalities may be noted and need to be monitored. Leflunomide did not benefit the spine in AS (28,36).

Tumor Necrosis Factor Alpha Inhibitors in Psoriatic Arthritis

The anti–tumor necrosis factor alpha (TNF-alpha) compounds, etanercept (Enbrel®) (40), infliximab (Remicade®) (41), and adalimumab (Humira®) (42) are approved for use in PsA as well as psoriasis skin disease.

Etanercept

Etanercept is a soluble receptor for TNF, administered subcutaneously in a dose of 25 mg twice a week or 50 mg once a week for PsA, now approved in RA, PsA, psoriasis, and ankylosing spondylitis. In the placebo-controlled portion of the phase III etanercept trial in PsA ($n = 205$), utilizing 25 mg administered subcutaneously twice a week, ACR20 response was achieved by 59% of etanercept treated patients versus 15% in the placebo group (42% and 41% on background MTX, respectively; $p < 0.0001$; 43). Skin response, as measured by the PASI score in patients with BSA involvement ≥ 3%, showed a 75% improvement in 23% and 3%, respectively, at 24 weeks ($p = 0.001$). A change of 0.51 units of the Health Assessment Questionnaire (HAQ), a measure of physical function, was noted in the etanercept group, both statistically significant and clinically meaningful (44). Improvement in quality of life, as measured by the Short Form 36 (SF-36) questionnaire, was also demonstrated in the treatment group. Inhibition of progression of joint space narrowing and erosions was shown, with 1 unit of modified total Sharp score (mTSS) progression in the placebo group and none (–0.03 units) in the etanercept group ($p = 0.001$). In the open label extension of this study, at 2 years, effectiveness was maintained in joint response, and skin response further improved to a PASI 75 response in 38%. Originally placebo patients achieved a similar degree of effectiveness in joints and skin as well as inhibition of further structural damage (45). The drug was well tolerated and no safety issues emerged apart from those seen in clinical trial and general clinical experience with etanercept in RA.

Infliximab

Infliximab is a chimeric monoclonal anti-TNF antibody now approved in RA, Crohn's, PsA, psoriasis, and ankylosing spondylitis. A phase III study of infliximab in 200 PsA patients (IMPACT II) showed significant benefit (46). Baseline demographic and disease activity characteristics were similar to those of the etanercept phase III trial. At week 14, 58% of infliximab patients and 11% of placebo patients achieved an ACR20 response ($p < 0.001$). Presence of dactylitis and enthesitis, assessed by palpation of the Achilles tendon and plantar fascia insertions, decreased significantly in the infliximab group (46). In skin evaluation, at 24 weeks, PASI 75 was achieved by 64% of the evaluable treatment group and 2% of the placebo group ($p < 0.001$). Utilizing the van der Heijde-Sharp scoring method (hands and feet), modified for PsA, infliximab-treated patients showed inhibition of radiographic disease progression at 24 weeks, although PsA-specific radiographic features, including pencil-in-cup deformities and gross osteolysis, did not differ between the treatment groups, as has been observed in other anti–TNF-alpha trials, presumably due to the more fixed nature of theses changes (47). HAQ score improved for 59% of infliximab patients, compared with 19% of placebo patients, while both the physical and mental components of SF-36 scores improved for patients receiving infliximab. Improvement was sustained at 1 year (46).

Adalimumab

Adalimumab is a fully human anti–TNF-alpha monoclonal antibody administered subcutaneously, 40 mg, every other week or weekly and is approved for RA and PsA. It was studied in a phase III study ($n = 313$), the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) (48). At 12 weeks, 58% of patients receiving adalimumab 40 mg every other week achieved ACR20 response compared with 14% of patients receiving placebo ($p < 0.001$). This response rate did not differ between patients taking adalimumab in

combination with MTX (50% of patients) and those taking adalimumab alone, similar to observations made in the etanercept and infliximab trials. Mean improvement in enthesitis and dactylitis was greater for patients receiving adalimumab, but this result did not achieve statistical significance. PASI 75 was achieved by 59% in the adalimumab-treated group and 1% in the placebo group ($p < 0.001$) in those evaluable for PASI scoring. Radiographic progression of disease was significantly inhibited by adalimumab, as evaluated by x-rays of hands and feet, using a modified Sharp score (48). Mean change in TSS was –0.2 for patients receiving adalimumab and 1.0 for patients receiving placebo ($p < 0.001$). Mean change in HAQ was –0.4 for adalimumab patients and –0.1 for placebo patients ($p < 0.001$). Mean change in the physical component of the SF-36 was 9.3 for the treatment group and 1.4 for the placebo group ($p < 0.001$).

Spine disease was not assessed in these trials, due to variability of expression of this domain in this patient group. However, significant efficacy of anti-TNF treatment of axial symptoms and signs has been demonstrated in a closely related disease, ankylosing spondylitis (28,36,49). Relative inefficacy of methotrexate, sulfasalazine, and leflunomide has been noted in ankylosing spondylitis, suggesting preference for use of the anti-TNF agents in this domain. It is unknown if the same holds true in PsA, although extrapolation of this experience to PsA seems reasonable.

In summary, the anti–TNF-alpha medications have shown the greatest efficacy of any treatment to date in the various clinical aspects of PsA. Their efficacy in joint disease activity, inhibition of structural damage, function, and quality of life are similar. There may be some differentiation in efficacy in the skin and enthesium, but all have excellent effects in these domains. These agents tend to be well tolerated and patients generally acclimate to their parenteral administration, especially when they experience significant efficacy. Safety concerns are present, such as risk for infection, but no new concerns have arisen in the PsA population compared to the more extensively studied RA patient experience (see Chapter 6C). Recent studies have also demonstrated the cost-effectiveness of anti–TNF-alpha therapy in PsA (50–52). New anti–TNF-alpha agents are being developed for use in PsA, including cimzia and golimumab, each with advantages of infrequent subcutaneous administration. Experience in management of RA with currently available anti-TNF agents suggests that when a clinician switches from one of these agents to another, if the first has not had or has lost efficacy, or caused side effects, that a substantial percentage of patients will respond to another medication in this class. Anecdotally, a similar experience has been noted in the management of PsA patients.

Other Biologic Agents

Alefacept

Alefacept is a fully human fusion protein that blocks interaction between LFA-3 on the antigen-presenting cell and CD2 on the T cell, or by attracting natural killer lymphocytes to interact with CD2 to yield apoptosis of particular T-cell clones (53). It is approved for treatment of psoriasis (21,54) and is administered weekly as a 15 mg intramuscular injection, in an alternating 12 weeks on, 12 weeks off regimen in order to allow return of depleted CD4 cells in the off period. A phase II controlled trial of alefacept in PsA ($n = 185$) showed that 54% of patients given a combination of alefacept and MTX had an ACR20 response as compared to 23% in the MTX alone group ($p < 0.001$) at week 24. PASI 75 results were 28% and 24%, respectively (55).

Efalizumab

Efalizumab is a humanized monoclonal antibody to the CD11 subunit of LFA-1 on T cells, which inteferes with its coupling with ICAM-1 on antigen-presenting and endothelial cells. It interferes with activation of T lymphocytes and migration of cells to the site of inflammation. It is administered subcutaneously, once per week and is approved for use in psoriasis (22). In a 12-week trial of efalizumab in patients with PsA, 28% of patients achieved an ACR20 response versus 19% in the placebo group ($p = 0.2717$). Because this response was not statistically significant, it is not recommended for treatment of arthritis (56).

Abatacept

Abatacept (CTLA4-Ig) is a recombinant human fusion protein that binds to the CD80/86 receptor on an antigen-presenting cell, thus blocking the second signal activation of the CD28 receptor on the T cell. It is administered intravenously once per month and has been approved for use in RA (57). A phase II trial for use in psoriasis has been conducted (58). It is anticipated that this drug will be evaluated in PsA.

Other Potential Treatments

A pilot trial of anti-interleukin (IL) 15 compound has shown efficacy in PsA (59). An IL-1 antagonist, anakinra, has not shown significant efficacy (60). A monoclonal antibody to the IL-6 receptor (MRA) is in phase III development for the treatment of RA, and will likely be tested in PsA (61). Several inhibitors of IL-12 are being evaluated in psoriasis, with good success (62), and will likely be assessed in PsA.

CONCLUSION

A number of systemic treatments for PsA, such as inhibitors of TNF-alpha, have demonstrated significant benefit for all disease domains, including inflammation in the joints, enthesium, and skin, inhibition of joint damage as assessed by radiographic progression, and improved quality of life and functional status. Traditional immune-modulating drugs can beneficially affect many of these domains as well. Agents that block the cell–cell interactions required to activate T cells are effective in the skin and may benefit the joints. Observation of the effectiveness of these agents has helped elucidate the pathogenesis of PsA and psoriasis which, in turn, may lead to more novel and effective interventions. Mild disease in the joints and skin can be treated with anti-inflammatories and topical treatments.

Development of targeted therapies has also increased interest in the accurate diagnosis and assessment of PsA, which facilitates the institution of appropriate therapy in a timely fashion. Because in the great majority of patients, the skin manifestations of psoriasis develop long before arthritis symptoms develop, the dermatologist or PCP is in an ideal position to educate about and screen for arthritis in order to make an early diagnosis and through appropriate treatment and coordinated care with rheumatologists, help prevent progressive structural damage in those that are likely to progress. Significant efforts are under way to further develop and validate outcome measures that accurately map the natural history of PsA and demonstrate the impact of increasingly effective emerging therapies on patients' function and quality of life.

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