Current Perspectives in the Recognition and Management of Psoriatic Arthritis: Implications for Integrated Patient Care

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Abstract

Psoriatic arthritis (PsA), a chronic and debilitating spondyloarthropathy, is believed to affect as many as 30% of those with psoriasis. The use of tumor necrosis factor (TNF) inhibitors shows promise in the treatment of PsA and psoriasis. Etanercept, the first TNF inhibitor to be approved for use in PsA, inhibits the proinflammatory cytokine TNF in both conditions, making it possible for the clinician to prescribe a single agent to manage both the joint manifestations of PsA and the cutaneous manifestations of psoriasis. Etanercept has been shown to be well tolerated, even for long-term use, and is potentially superior to disease-modifying antirheumatic drugs.

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Psoriatic arthritis (PsA) is a chronic, potentially debilitating spondyloarthropathy that for years has gone underrecognized and undertreated. After 2 decades of renewed interest and research, it is now acknowledged that this disease can affect up to 30% of patients with psoriasis.[1,2] This translates to 450,000 patients in the United States, many of whom have not been diagnosed. A recent telephone survey conducted by the National Psoriasis Foundation suggested this number may be as high as 1 million.[3]

Although PsA may present as a symmetric, polyarticular arthritis similar to rheumatoid arthritis (RA), it is usually characterized by the presence of several unique features, including the potential for asymmetric, oligoarticular synovitis; axial and/or distal interphalangeal joint involvement; dactylitis; and entheseal inflammation.[4-6] Like RA, PsA may result in joint damage, instability, and increased mortality.[7-10] Patients with PsA may present with a confusing array of symptoms, necessitating careful differential diagnosis.

In addition to recognition and diagnosis, other unmet needs in the care of patients with psoriasis and/or PsA include appropriate specialist referral and effective pharmacotherapy (eg, medications that treat both the skin and joint manifestations of the disease). Unfortunately, the roles of the primary care physician, rheumatologist, and dermatologist are not well defined with regard to the management of patients with PsA. Patients may not be referred to the appropriate specialist at the appropriate time, and overall care may therefore be suboptimal. Thus, the cornerstones of optimal care of the patient with psoriasis and/or PsA are recognition and diagnosis, appropriate specialist referral, and effective pharmacotherapy.

Description and Etiology

Psoriatic arthritis is classified as a seronegative spondyloarthropathy, a loosely connected group of disorders, which also includes ankylosing spondylitis, Reiter's syndrome, enteropathic arthropathy, and Whipple's disease. These disorders are referred to as seronegative, because they are marked by the absence of rheumatoid factor.

Several genetic and environmental factors are believed to contribute to the

predisposition to develop PsA (**Table 1**).[11] These include the expression of certain major histocompatibility complex antigens, trauma, and joint injury as a result of repetitive motions.[11] The presence of specific genetic factors involved in the development of PsA may be encountered in the familial aggregation of this disease, although it does not follow a simple monogenic pattern of inheritance. First-degree relatives of a person with PsA are 40 times more likely to develop PsA than their unaffected spouses.[12]

Course and Prognosis

Morbidity. Until recently, PsA was commonly thought to be a relatively benign arthropathy with short-lived synovitis and little residual joint damage. It is now known that PsA may actually be a debilitating disease associated with significant radiographic progression and profound decreases in functional status, even in the setting of ongoing therapy with conventional disease-modifying antirheumatic drugs (DMARDs).[13]

In a sample of 180 patients with PsA, Torre Alonso et al[7] found that 57% had erosive arthritis and 19% had marked physical limitations. Gladman et al[8] showed that a significant percentage of patients developed joint damage and deformities that progressed over time and contributed to functional limitation. Finally, Jones et al[14] questioned the limited nature of this disease, reporting that 64% of patients presenting with oligoarticular disease progressed to polyarticular disease over time.

Mortality. Information regarding mortality in PsA is scarce. Current understanding of mortality in PsA stems mainly from a large-scale study performed by Gladman et al[9] and Wong et al,[10] who observed 428 patients with PsA over a period of 16 years. Results of this study indicated that patients with PsA had an increased risk of death compared with the general population. The overall survival probability over a 20-year period from the time of presentation is shown in **Figure 1**.[9] Evidence of previously active and severe disease, as manifest by the prior use of medications, radiologic changes, and elevated erythrocyte sedimentation rate (ESR) at presentation, was a prognostic indicator for death in this study.

Health-Status and Quality-of-Life Assessments. The Medical Outcomes Study 36-item short-form health survey (SF-36) is a generic measure designed to assess health status across a diverse spectrum of chronic illnesses.[15,16] The Health Assessment Questionnaire (HAQ) is a condition-specific measure of health status intended for use in rheumatic diseases only. The Arthritis Impact Measurement Scales (AIMS/AIMS2) are arthritis-specific instruments designed to assess physical functioning and pain.[17,18] The SF-36, HAQ, and AIMS2 have been shown to be reliable and valid for use in PsA as well as in RA.[19-22]

Husted et al[15] demonstrated that patients with PsA experience reduced health-related quality of life compared with general population samples. Specifically, patients reported significantly lower scores on the physical functioning, pain, role limitations, and general health perceptions scales of the SF-36. These same

Table 1. Genetic and Environmental Factors in Psoriatic Arthritis (PsA)

Genetic susceptibility predisposing to PsA trait:

- HLA-Cw6
- Other class I HLA specificities (B13, B17, B27, B38, B39)
- Non-MHC genes?

Environmental factors influencing expression of PsA trait:

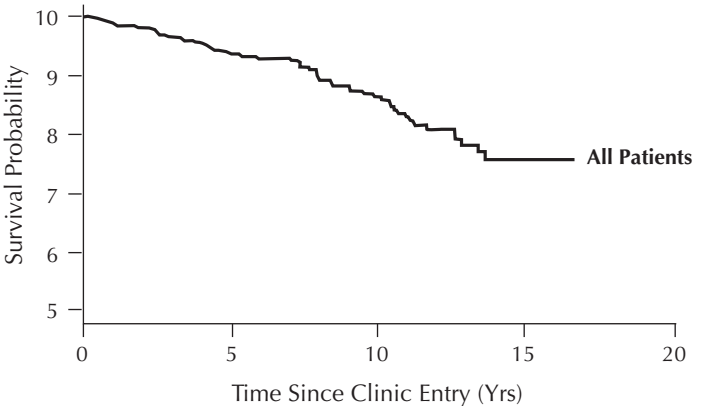
- Trauma
- Repetitive motion
- Human immunodeficiency virus infection
- Bacterial infection?

HLA = human leukocyte antigen; MHC = major histocompatibility complex.
Source: Reference 11.

authors used the SF-36 and the HAQ to compare health-related quality of life in 107 patients with PsA and 43 patients with RA.[23] Both patient populations reported reduced physical health compared with that of a general population sample. However, patients with RA demonstrated more active inflammatory disease at the time of assessment than those with PsA. Patients with PsA tended to be younger, and more were men. Although patients with PsA reported greater levels of vitality than those with RA—even after adjusting for observed differences in clinical and demographic characteristics—these patients reported more role limitations because of emotional problems and more bodily pain after adjusting for the difference in vitality and other covariates. The investigators also found that, among patients with PsA, those with severe skin disease experienced more emotional problems than those without severe skin disease. Clearly, the unique disabilities associated with PsA provide further impetus for early and aggressive therapy.

A health status instrument for patients with upper musculoskeletal conditions known as the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire was developed by Hudak et al[24] in 1996 and was validated for use in patients with PsA by Navsarikar[25] et al in 1999. The DASH Questionnaire is composed of 21 physical function items, 6 symptom items, and 3 social/role function items. The DASH scores correlate closely with clinical measures of upper extremity function in patients with PsA.[25]

Figure 1. Overall Survival in Patients With Psoriatic Arthritis



Source: Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis. Results from a single outpatient center. II. Prognostic indicators for death. *Arthritis Rheum* 1998;41:1103-1110. Reprinted with permission.

Pathophysiologic Hallmarks

The pathophysiologic hallmarks of PsA are psoriatic plaque, synovial inflammation, enthesopathy, and abnormal bone remodeling. The enthesis is a potentially important structure, representing the site of attachment of ligaments, tendons, capsules, and fascia to bone. Enthesopathy is a particularly troubling feature of PsA. It is characterized by an accumulation of lymphocytes and monocytes at the site of tendon or ligament insertion, resulting in inflammation and erosions (**Figure 2**), which ultimately may cause spurs and periostitis. The development of the "sausage" digit of dactylitis is based on extensive periarticular inflammation and associated edema, primarily localized to the tendons and ligaments of the digits, and principally affects their sheaths and insertion sites. Rarely, enthesopathy may result in rupture or avulsion of a tendon or ligament.

Abnormal bone remodeling is a unique feature of PsA. Unlike RA, in which bone destruction—characterized by erosions and periarticular osteopenia—is not associated with new bone formation, PsA may present with productive changes and spur formation in the same joint where bony destruction is taking place.

Clinical Manifestations

Articular Manifestations. Several articular features characterize the clinical spectrum of PsA. A classification scheme for PsA based on joint manifestations proposed by Moll and Wright[4,26] describes 5 patterns of disease: oligoarthritis, symmetric polyarthritis, predominantly distal interphalangeal joint arthritis, arthritis mutilans, and spondylitis and/or sacroili-

Figure 2. Inflammatory Enthesopathy of a Tendon Attachment

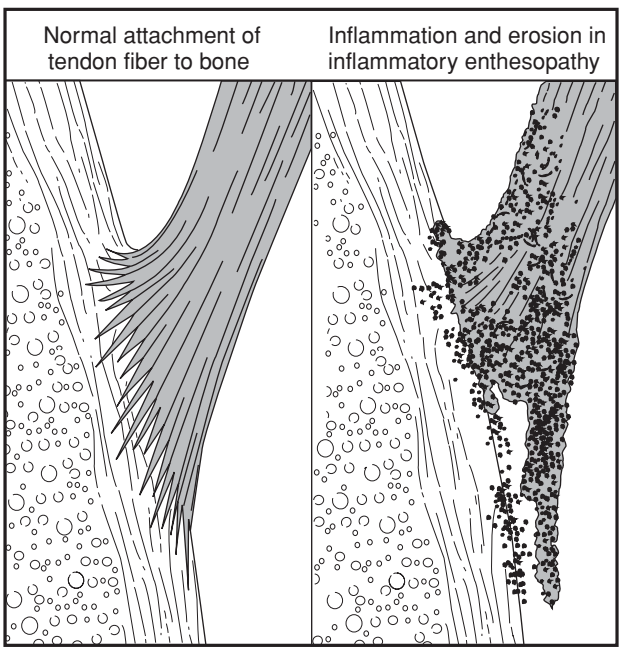


Table 2. Clinical Spectrum of Psoriatic Arthritis

Common arthropathies
- Polyarthritis
- Spinal inflammation
- Peripheral enthesitis
- Distal interphalangeal (DIP) joint arthritis
- Monarthritis/oligoarthritis
- Dactylitis ("sausage digits")

Uncommon arthropathies
- Palmar plantar pustulosis
- Synovitis, acne, pustulosis, hyperostosis, and osteolysis (SAPHO) syndrome
- Spondylodiscitis
- Arthritis mutilans
- Onycho-pachydermo-periostitis

Other features
- Arthralgia
- Chest pain

Source: McGonagle D, Conaghan PG, Emery P. Psoriatic arthritis. A unified concept twenty years on. *Arthritis Rheum* 1999;42:1080-1086. Reprinted with permission.

itis. It is important to note that there is no pathognomonic feature of PsA; the various clinical patterns of the disease may overlap considerably (**Table 2**), with evolution from 1 clinical entity to another.[27]

Because the various clinical patterns of PsA may overlap and because most patients with PsA have peripheral joint involvement, there is a trend toward simplifying the classification scheme by grouping the first 4 Moll and Wright patterns into a single category: peripheral. The ankylosing spondylitis–like pattern remains a separate category. An additional category—extra-articular osseous manifestations—has also been proposed.[28]

Nail involvement in PsA, usually in the form of nail pitting, helps to confirm the diagnosis of PsA, because it occurs in the majority of cases. Other nail abnormalities observed in PsA include onycholysis, subungual hyperkeratosis, furrows or transverse depressions (Beau's lines), leukonychia (white spots or patches under the nails), and crumbling nail plates.

Cutaneous Manifestations. Psoriasis and the skin manifestations of PsA are characterized by the development of well-marginated, erythematous papules and plaques that are covered with layers of flaking or adherent thick, silvery white to gray scales. If the scales are removed, minute bleeding points may be exposed (Auspitz sign).[1] As shown in **Figure 3**, individual papules may be small and erythematous with very little scale, described as guttate (droplike), or may coalesce to form small plaques, which may be covered with a rupial or ostraceous (dirty or shell-like) scale. As papules and plaques enlarge, they may acquire odd shapes as central areas involute (**Figure 4**). The sharp border, which can usually be felt as well as seen, abruptly demarcates the epidermal hyperplasia and epidermal changes of psoriasis. Any clinical type of psoriasis may occur in patients with PsA.[14]

Predicting Disease Progression. Because of the poor prognosis for people with active disease, it is necessary to treat early, prevent erosions, and maintain

function. The clinical course of PsA, however, characteristically varies from patient to patient. Therefore, it would be beneficial to be able to recognize patients at risk for developing more severe disease. In the past, the lack of a systematic approach to disease assessment limited the usefulness of clinical follow-up studies. This changed in the mid 1990s with the identification of several factors to predict disease progression.

Gladman and Farewell[29] demonstrated that accurate follow-up of actively inflamed joint count may provide additional information about the course of the disease. These investigators determined that, for each actively inflamed joint, there was a 4% chance of increased progression of damage at a subsequent visit. Joint counts over time were therefore predictive of the progression of articular damage.

Factors that may contribute to disease progression include a high number of swollen joints, the presence of actively inflamed joints, and an elevated ESR.[30] The human leukocyte antigens (HLA) associated with PsA—B27 and B39—are also risk factors for disease progression, as is the HLA class II antigen DQw3.[31]

Figure 3. Typical Skin Lesion Found in Psoriasis and Psoriatic Arthritis

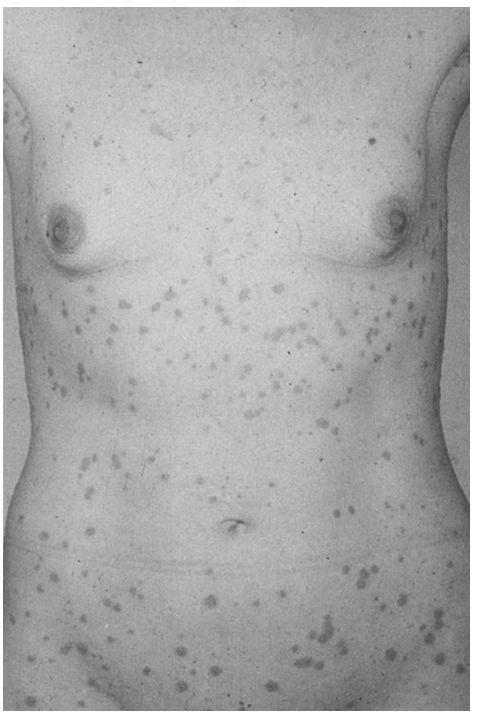
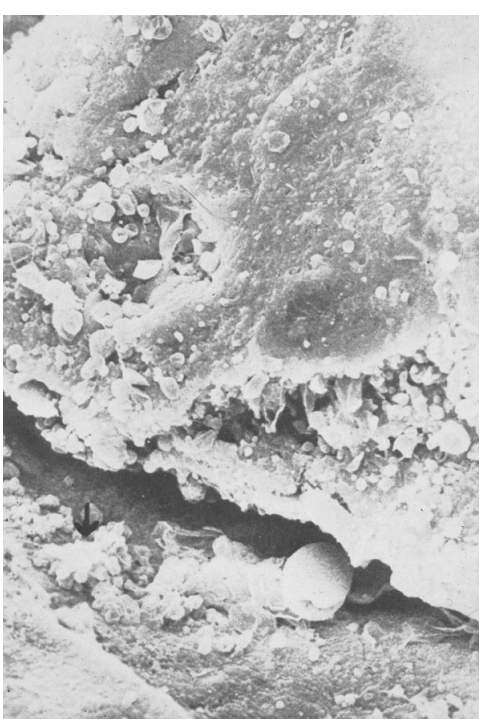


Figure 4. Psoriatic Plaque



Optimizing Treatment of Psoriasis and Psoriatic Arthritis

Conventional DMARDs used in the treatment of PsA include methotrexate (MTX), cyclosporine, sulfasalazine, gold salts, D-penicillamine, antimalarial preparations, and azathioprine. Unfortunately, definitive data regarding the efficacy of these agents in PsA are lacking. Three large studies of sulfasalazine in PsA demonstrated modest improvement in joint symptoms, though no effect on skin disease was noted.[32-34] These trials did not address the issue of progression of joint damage in PsA. Only 1 controlled trial of MTX in PsA has been published.[35] This small trial, which included 21 patients, demonstrated the efficacy of MTX in treating both skin and joint manifestations of the disease, although the authors felt that toxicity was a limiting issue. Two controlled trials of cyclosporine

in PsA have been published; 1 evaluated the effectiveness of cyclosporine versus MTX, and the other assessed the effectiveness of combination therapy with cyclosporine and MTX.[36,37] Both provided evidence for efficacy; again, toxicity was a limiting factor. In the comparative study, drug discontinuation because of adverse effects was noted in 41% of cyclosporine-treated patients and in 28% of MTX-treated patients.[36]

In general, early discontinuation of DMARD therapy because of poor efficacy or intolerable side effects remains a problem. Data from studies in RA show that, with the exception of MTX, therapy with DMARDs must be discontinued within a few months to a few years.[38,39] Conversely, as many as 60% of patients treated with MTX are still taking the drug after 5 years.[40]

The selection of a specific DMARD is driven primarily by balancing efficacy and relative safety against individual patient factors. Specific factors that influence DMARD selection include the dose, schedule, and route of administration; long-term monitoring requirements; and safety profile. All currently available DMARDs are relatively slow acting and may cause serious adverse reactions. Finally, there is an obvious advantage to selecting DMARD therapy that works against both the articular and cutaneous manifestations of PsA.

Recently, an increased understanding of the role of cytokines—particularly tumor necrosis factor (TNF)—in the pathogenesis of PsA has led to the development of TNF inhibitors for therapeutic use in PsA. Etanercept (ETA), the first TNF inhibitor approved for use in PsA, inhibits the proinflammatory cytokine TNF in both PsA and psoriasis. Concentrations of TNF have been shown to be increased in the synovial fluid and synovium of patients with PsA and in the skin of those with psoriasis.[41-44] Previously, TNF inhibition with ETA has been shown to diminish the activity of RA.[45-50]

ETA is indicated for reducing signs and symptoms of active arthritis in patients with PsA, and it can be used in combination with MTX in patients who do not respond adequately to MTX alone.[51] Mease et al[52] recently reported the results of a 3-month, randomized, double-blind, placebo-controlled study of 60 patients with PsA and psoriasis. Study patients had psoriasis for a mean of approximately 20 years and PsA for a mean of 11.5 years. Those achieving partial benefit with MTX were allowed to continue treatment with it during the study. This subgroup, which contained 28 (47%) patients, was evenly distributed between the ETA and placebo groups. All other DMARDs and topical medicines for psoriasis were discontinued. Background use of nonsteroidal anti-inflammatory drugs or prednisone (10 mg/day) was allowed.

The primary arthritis efficacy response measure in this study was the Psoriatic Arthritis Response Criteria (PsARC).[53] This composite response score requires improvement in 2 of 4 measures of disease activity (with at least 1 being a joint score), with worsening in none: patient and physician global assessments, tender joint score, and swollen joint score. A secondary endpoint for the assessment of PsA was the proportion of patients meeting the American College of Rheumatology-20 (ACR-20) response criteria (at least a 20% reduction in tender and swollen joint counts and improvement in at least 3 of the following: patient's assessment of pain, physician's global assessment, patient's assessment of disability, and C-reactive protein level).[54] The study also assessed ACR-50 and ACR-70 responses. In eligible patients, skin response was evaluated with the Psoriasis Area and Severity Index (PASI) and the target lesion score. The PASI is a composite measure based on scale, erythema, and induration and is weighted by severity and body surface area.[55] A single, preselected lesion is used to determine the target lesion score, which is based on the amount of scale, erythema, and plaque.

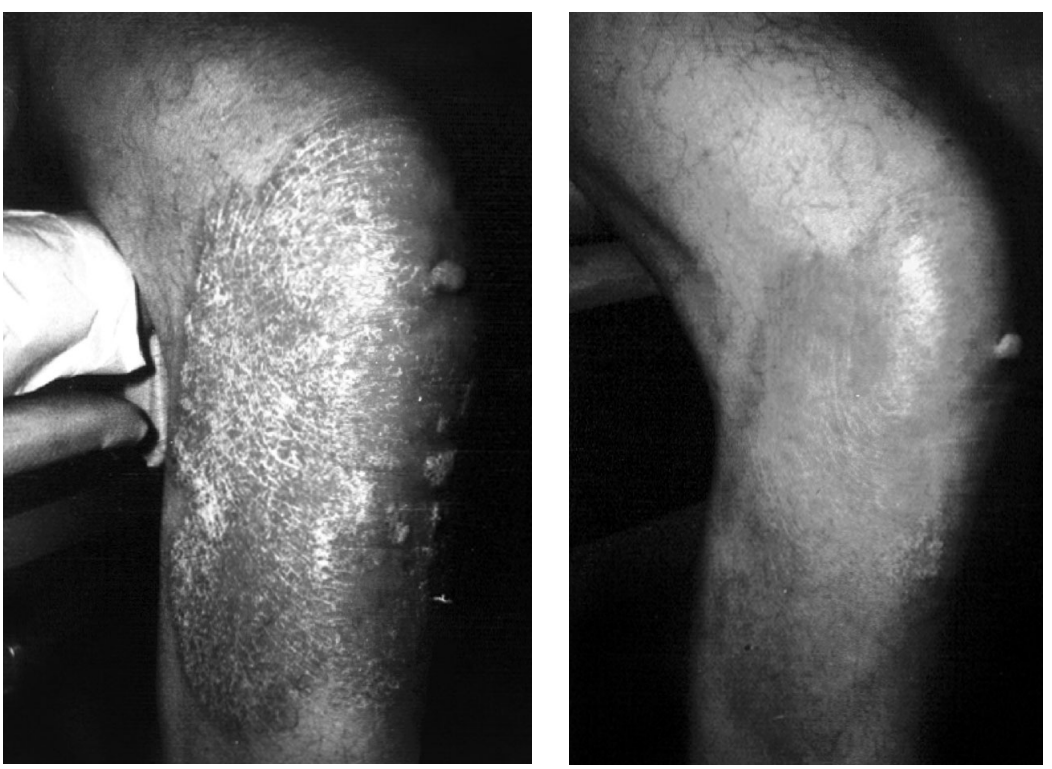
At the study endpoint (12 weeks), 26 ETA recipients (87%) responded according to PsARC criteria compared with 7 patients (23%) who received placebo. For most patients, the response was quite rapid: by 4 weeks, 23 ETA-treated patients (77%) qualified as responders. At 12

weeks, 4 ETA-treated patients (13%) had no tender joints and 7 (23%) had no swollen joints. Similar dramatic responses were noted with the ACR-20, ACR-50, and ACR-70 criteria. Nineteen patients in each group had psoriasis covering >3% of their body surface area, meeting the criterion for skin response evaluation. The median improvement in PASI score among ETA-treated patients at 12 weeks was 46% compared with 9% in the placebo group. For the target lesion score, the median improvement was 50% among ETA-treated patients and 0% among those who received placebo. A 75% PASI response, which represents nearly complete resolution of skin disease, occurred in 26% of ETA-treated patients and in 0% of those who received placebo. A representative response of psoriatic lesions to ETA is shown in **Figure 5.**

During a 6-month extension phase, all patients who received ETA during the 3-month blinded phase demonstrated sustained efficacy with regard to PsARC response.[56] Furthermore, patients who received placebo during the blinded phase rapidly attained a similar degree of efficacy during the open-label extension phase. At 9 months, 28% of patients had no tender joints, 42% had no swollen joints, and 40% had a HAQ disability score of zero.

Of the 28 patients taking MTX at baseline, 12 (43%) decreased their MTX dose and 7 (25%) discontinued MTX altogether during the open-label extension. Similarly, of the 18 patients taking corticosteroids at baseline, 12 (67%) decreased their corti-

Figure 5. Area of Skin Affected by Psoriatic Lesions in a Patient With Psoriatic Arthritis. (A) Before Etanercept Therapy (B) After 12 Weeks of Etanercept Therapy



A **B**

Source: Mease PJ. Cytokine blockers in psoriatic arthritis. *Ann Rheum Dis* 2001;60:iii37-iii40. Reprinted with permission.

costeroid dose and 8 (44%) discontinued corticosteroids completely.

These data make a compelling argument for the superior efficacy and safety of ETA for the treatment of both psoriasis and PsA. Significant improvements were seen not only in the arthritis symptoms but also in the psoriatic lesions. In addition, therapy with ETA was well tolerated.

Approach to Management

Patients with PsA are typically affected with psoriasis before showing signs of joint disease; only about 15% of patients develop signs and symptoms of PsA before a diagnosis of psoriasis has been established.[11] It is likely, therefore, that the majority of patients with PsA consult a dermatologist prior to seeing a rheumatologist. However, optimal management of PsA involves a multidisciplinary approach. The dermatologist and rheumatologist each approach management of PsA from his or her unique professional perspective. If PsA does not respond to the treatment offered by the dermatologist, referral to a rheumatologist typically follows. Conversely, psoriasis that is resistant to PsA therapy offered by the rheumatologist typically results in referral to the dermatologist.

The approach to PsA management should emphasize control of both the skin and joint manifestations of the disease. In patients with severe skin disease but minimal joint disease, medications directed against skin disease (eg, MTX, other DMARDs, phototherapy, retinoid therapy) should predominate. Conversely, if joint disease is the major manifestation and skin disease is minimal, the clinician should focus on medications primarily directed at joint disease (DMARDs). If both conditions are active, ETA, with or without MTX, may be appropriate.

Conclusion

Results with TNF inhibitors in the treatment of PsA and psoriasis are encouraging. TNF inhibition as a therapeutic strategy in PsA and psoriasis represents a quantum leap over traditional disease-modifying therapies. With the addition of ETA to the disease-modifying armamentarium, a single clinician may now prescribe a sole agent to manage both the joint manifestations of PsA and the skin manifestations of psoriasis. Moreover, data from studies of RA indicate that ETA is well tolerated even when used on a long-term basis. This may represent a major advantage over traditional DMARDs, which are often discontinued after short-term use, either because of lack of efficacy or treatment-limiting toxicities.

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