Psoriatic Arthritis
Update on Pathophysiology, Assessment, and Management

Philip J. Mease, M.D.

Abstract
Psoriatic arthritis (PsA) is classified as a spondyloarthropathy and characterized by synovitis, enthesitis, dactylitis, and spondylitis, usually manifesting in a person with skin and nail psoriasis. Our understanding about the PsA disease state, its genetics, pathophysiology, and comorbidities, as well as our ability to assess and treat the disease, has advanced as a result of significant collaborative efforts by rheumatologists and dermatologists. This work has been primarily in the development of classification criteria, outcome measures to assess the various clinical domains, and treatment trials with agents also used for diseases such as rheumatoid arthritis (RA) and psoriasis. Biologic agents, especially the anti-TNFs, have demonstrated significant efficacy and reasonable safety in all clinical domains of the disease, resulting in amelioration of clinical symptoms, inhibition of structural damage, and improvement of function and quality of life. A number of advances in assessment and treatment have occurred in the last few years, which are highlighted in this update. This article reviews assessment and treatment of PsA, with an emphasis on recent data.

Evaluation and Management of PsA
Assessment
The key clinical features of PsA that should be assessed in order to determine disease severity and effect of treatment include peripheral arthritis, skin and nail psoriasis, axial disease, enthesitis, and dactylitis.1-3 Effective treatment leads to improvement of pain, fatigue, depression; inhibition of structural damage to joints; and significant impairment of function and quality of life, which results from combined skin and musculoskeletal disease. A potential additional benefit of adequate treatment is reduction of inflammation-induced atherogenesis and reduced early mortality from cardiovascular disease. Assessment of PsA has generally been accomplished by adapting measures used in clinical trials for RA, psoriasis, and to a lesser extent ankylosing spondylitis (AS), as well as general measures, such as the SF-36 questionnaire, which measures function and quality of life (QOL) (Table 1).4-9 Although generally not validated in PsA, these measures have proven to be reliable and to show adequate discrimination and responsiveness characteristics in therapeutic
trials. Several studies have documented the effectiveness of ultrasound and magnetic resonance imaging (MRI) in detecting inflammation in the joints and enthesal sites of PsA patients, as well as the extent of structural damage.\(^{10}\) As these measures become more widely accessible, they will enhance our ability to diagnose PsA earlier and assess the effectiveness of therapy in treating inflammation and inhibiting the progression of joint damage.

Since the majority of patients develop the skin lesions of psoriasis long before musculoskeletal clinical features, teaching both psoriasis patients and dermatologists who treat psoriasis about the potential for PsA is desirable for the sake of early detection of the disease and institution of treatment. Current estimates are that approximately 20% to 30% of patients with psoriasis will develop PsA (range of prevalence estimates is from 6% to 39%).\(^{11}\) A key element in recognition and proper management of PsA is the quality of the dermatologist-rheumatologist interaction in the co-management of the patient with PsA.\(^{11}\)

### Treatment

A comprehensive review of the evidence for effectiveness of various PsA pharmacotherapy approaches has been conducted by GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) in the process of developing international treatment recommendations (Table 2).\(^{2,3,12-18}\) It has been demonstrated that early and aggressive control of disease activity in the management of RA results in significantly better clinical and radiographic outcomes.\(^{19}\) Although a similar paradigm of “treating to

<table>
<thead>
<tr>
<th>Domains</th>
<th>Instruments</th>
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<tr>
<td>Joint assessment</td>
<td>68/66 T/S joint count, ACR, DAS, PsARC</td>
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<tr>
<td>Axial assessment</td>
<td>BASDAI, BASFI, BASMI</td>
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<td>Skin assessment</td>
<td>PASI, Target lesion, Global</td>
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<tr>
<td>Pain</td>
<td>VAS</td>
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<tr>
<td>Patient global</td>
<td>VAS (global, skin and joints)</td>
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<tr>
<td>Physician global</td>
<td>VAS (global, skin and joints)</td>
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<tr>
<td>Function/QOL</td>
<td>HAQ, SF-36, PsAQoL, DLQI</td>
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<td>Fatigue</td>
<td>FACIT, Krupp, MFI, VAS</td>
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<tr>
<td>Enthesitis assessment</td>
<td>Mander, MASES, Leeds, Berlin, SPARCC, 4-point</td>
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<tr>
<td>Dactylitis assessment</td>
<td>Leeds, present/absent, acute/chronic</td>
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<tr>
<td>Acute phase reactant</td>
<td>ESR, CRP</td>
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<tr>
<td>Imaging</td>
<td>Radiograph (modified Sharp or van der Heijde-Sharp), MRI, US</td>
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**Table 1** Measures for Assessment of Psoriatic Arthritis in Clinical Trials

<table>
<thead>
<tr>
<th>Table 2</th>
<th>PsA Treatments(^{3})</th>
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<tr>
<td></td>
<td>Peripherally Arthritis</td>
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<tr>
<td>NSAIDs</td>
<td>X</td>
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<tr>
<td>Intra-articular steroids</td>
<td>X</td>
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<tr>
<td>Topicals</td>
<td>X</td>
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<td>Physiotherapy</td>
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<tr>
<td>Psoralein UVA/UVB</td>
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<tr>
<td>DMARDs (MTX, CsA, SSA, Lef)</td>
<td>X</td>
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<tr>
<td>Biologics (anti-TNF antagonists)</td>
<td>X</td>
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PsA Treatments. Anti-TNF, tumor necrosis factor inhibitor; CsA, cyclosporin A; DMARD, disease-modifying antirheumatic drug; LEF, leflunomide; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; SSZ, sulfasalazine.
target” of remission or low disease activity state (LDAS) has not been carefully studied in PsA, it is anticipated that similar benefits would result from early and “tight control” intervention in the patient with risk factors for a moderate to severe disease course. Part of the ability to achieve tight control has to do with the ability to quantify disease severity in RA, using measures such as the DAS scoring system. This RA scoring system may not be appropriate in terms of quantitative threshold to define “remission” in PsA and does not capture the additional clinical features of PsA, enthesitis, dactylitis, spine, and skin disease. GRAPPA and other groups are actively trying to ascertain if a composite disease activity score, addressing all clinical domains of PsA, can be developed that will be easy to perform and meaningfully capture the impact of each domain on outcomes. Coates and colleagues led an exercise among GRAPPA members, based on reviewing hypothetical cases, which led to the definition of “minimal disease activity” (MDA) criteria for PsA (Table 3). These criteria were validated by assessing patients using Gladman’s patient cohort in Toronto and in interventional trial datasets. The development of this instrument is a step toward “treatment to target” in PsA.

Clinical predictive factors for progressive disease in PsA include polyarticular involvement, elevated acute phase reactants, evidence of physical disability, and erosive joint disease, as well as demonstration of lack of response to initial therapeutic agents. Work is also underway to characterize soluble biomarkers that can identify patients at risk for a more severe disease course, as well as serve as markers of treatment response.

### Pharmacotherapy

Patients with mild forms of musculoskeletal inflammation may use nonsteroidal antiinflammatory drugs (NSAIDs), analgesics, or low dose corticosteroids, as well as receive intra-articular or enthesal injections of steroids. There is little trial evidence for the efficacy of these agents in PsA, since this evidence has been primarily developed in RA, AS, and osteoarthritis (OA).

### Oral Disease Modifying Antirheumatic Drugs (DMARDs)

Traditional disease modifying antirheumatic drugs (DMARDs) have shown very limited efficacy in PsA. That said, methotrexate (MTX) is one of the most commonly used systemic medications in PsA, despite minimal evidence of efficacy in a small controlled trial. Whereas MTX may benefit symptoms of arthritis and psoriasis, its ability to treat enthesitis and dactylitis, and to inhibit structural damage has not been prospectively assessed. 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. Using evidence from AS, since not assessed in PsA, MTX is not considered to be effective in treating spine disease. The potential for MTX-induced hepatotoxicity has been a special concern for dermatologists, based on the finding of greater hepatotoxicity in psoriasis than RA in older serial liver biopsy studies. A current hypothesis is that this is at least partly related to the tendency of psoriasis patients, and to a lesser extent PsA patients, to be obese and have non-alcoholic hepatic steatosis (fatty liver) as a concomitant liver problem, as well as other factors, such as excess alcohol use. Dermatologists, but not rheumatologists, have historically recommended periodic liver biopsy for safety monitoring. New guidelines for MTX monitoring in dermatology do not require biopsy. Although the combination of MTX and tumor necrosis factor (TNF) inhibitors in RA has been shown to be superior in all clinical parameters of efficacy, including inhibition of structural damage, this has not been systematically assessed in PsA. A recent trial conducted in PsA patients naïve to MTX, comparing infliximab plus MTX versus MTX monotherapy, demonstrated greater efficacy in clinical measures in the combination group. In clinical practice, MTX may sometimes be discontinued after initiation of biologic therapy if there is concern about hepatotoxicity, only to be re-initiated if the patient experiences inadequate control of disease with biologic monotherapy.

Other DMARDs have demonstrated limited effectiveness or are not yet available in the United States. Although, the largest number of controlled trials of traditional DMARD therapy in PsA has been conducted with sulfasalazine, its utility remains limited because of the absence of effect in the skin and occasional gastrointestinal intolerability. Leflunomide, a pyrimidine antagonist, has shown effectiveness in PsA and is formally approved for PsA treatment in Europe at a dose of 20 mg per day. Cyclosporine can achieve rapid improvement of the skin lesions of psoriasis, but evidence for its effectiveness in musculoskeletal disease is scant, and its utility is limited by concerns regarding the adverse effects of hypertension and renal insufficiency. It has been used in combination with adalimumab.

### Biologic Response Modifiers

Biologic agents currently approved for treatment of PsA are the anti-TNF compounds etanercept, infliximab, adalim--

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### Table 3 Minimal Disease Activity (MDA) Criteria in PsA

<table>
<thead>
<tr>
<th>Patients are Classified as “in MDA” When They Meet Five of Seven Criteria</th>
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<tbody>
<tr>
<td>1. Tender joint count ≤ 1</td>
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<tr>
<td>2. Swollen joint count ≤ 1</td>
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<tr>
<td>3. PASI ≤ 1 or BSA ≤ 3</td>
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<tr>
<td>4. Patient pain VAS ≤ 15</td>
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<tr>
<td>5. Patient global activity VAS ≤ 20</td>
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<tr>
<td>6. HAQ ≤ 0.5</td>
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<tr>
<td>7. Tender enthesal points ≤ 1</td>
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BSA, body surface area; HAQ, Health Assessment Questionnaire; PASI, Psoriasis Area Severity Index; VAS, visual analog scale.

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umab, and golimumab. Controlled phase II trials have been completed with the T-cell modulating agents alefacept and abatacept and the IL12/23 inhibitor, ustekinumab. Some agents, such as the IL1 inhibitor, anakinra, have not shown efficacy compared to placebo in PsA.36 Several other agents either approved or in development for RA and psoriasis will be assessed in PsA in the future.

**TNF-α Inhibitors**

The efficacy and safety of etanercept in PsA was pivotal in a phase III trial in 205 patients.37 Approximately half of the patients were on background MTX and stratified, based on MTX use, to etanercept (50 mg per week) or placebo. Significant improvement was demonstrated in joints, inhibition of structural damage (demonstrated radiographically), skin, function, and QOL. Two-year extension data demonstrated sustained efficacy in all domains.38 Background MTX made no difference on outcomes. The drug was tolerated well and no safety issues emerged apart from those seen in clinical trial and general clinical experience with etanercept in RA.

More recently, the PRESTA (Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis) trial assessed 752 patients with high active PsA and psoriasis [average body surface area (BSA) involvement with psoriasis, 31%] randomized to a standard dose of etanercept approved for PsA, 50 mg/wk (group 1), versus a dose approved for psoriasis, 50 mg twice a week for 12 weeks, followed by 50 mg/wk thereafter (group 2).39 American College of Rheumatology (ACR) and enthesitis scores improved similarly in both dose arms at 12 and 24 weeks. Of those patients with enthesitis, assessed by Achilles tendon and plantar fascia insertion tenderness, 65% and 66% in groups 1 and 2, respectively, had no enthesitis at week 12 and 76%, and 75% had none at week 24. Similarly improved dactylitis scores were noted, demonstrating the ability of etanercept to effectively treat these aspects of PsA, but no additional advantage was achieved in musculoskeletal domains by using the higher dose initially. On the other hand, substantial improvement of skin lesions occurred to a greater extent in the higher dose group, with a Psoriasis Area Severity Index (PASI) 75 response at week 12, seen in 55% versus 36% (p < 0.001) in groups 2 and 1, respectively, and 70% and 62% at week 24 (p < 0.05).

In a recent serial skin biopsy study in psoriasis patients using etanercept, transcripts of cytokines in the TH17 cell pathway were diminished, presumably based on decreased stimulation of IL23 by TNF.40 Traditionally, anti-TNFs are considered to affect TH1 pathway cells and cytokines, so these results demonstrate the immunologic cross talk that occurs amongst various inflammatory cell pathways.

The effectiveness of infliximab, a chimeric monoclonal antibody administered 5 mg/kg intravenously, was demonstrated in PsA in a pivotal trial of 200 patients.41 As with etanercept, efficacy in all clinical domains of PsA, including inhibition of joint damage was established.

In a study performed in Russia, 115 patients with relatively early PsA (mean disease duration 2.8 to 3.7 years) were randomized to receive methotrexate monotherapy (15 mg/wk) or a combination of methotrexate (15 mg/wk) and infliximab, 5 mg/kg, in the standard infusion regimen employed for this agent.42 At 16 weeks, patients in the combination arm had superior outcomes, with ACR20, 50, 70 responses of 86%, 73%, and 49%, respectively, while patients in the MTX monotherapy arm had responses of 67%, 40%, and 19%. DAS28 remission at 16 weeks in patients in the combination therapy arm reached 69%, while only 29% of patients attained DAS28 remission in the MTX monotherapy arm. Patients undergoing combination therapy had superior results as measured by PASI 75 and PASI 90 responses, as well: 97% and 71%, as opposed to only 54% and 29% in the MTX monotherapy arm. These results suggest that earlier intervention in PsA can result in very substantial improvements of disease activity, especially as seen in the combination of anti-TNF and MTX therapy, and provide a demonstration of the potential effectiveness of MTX monotherapy in such an early cohort.

Adalimumab, a fully human anti-TNF-α monoclonal antibody administered subcutaneously, 40 mg, every other week, was studied in the ADEPT (Adalimumab Effectiveness in Psoriatic Arthritis Trial (N = 313).43 As with other anti-TNFs, significant benefit in joints, skin, function, QOL, inhibition of radiographic damage, and fatigue was demonstrated. A 2-year extension study demonstrated sustained ACR and PASI responses and persistent inhibition of plain film progression.44

Golimumab is a fully human anti-TNF-α monoclonal antibody that is approved in a 50 mg monthly subcutaneous application for PsA, based on a study of 405 patients.45 At this dose, at the primary end point of 14 weeks, ACR20 was achieved by 51% versus 9% in the placebo group (p < 0.001) and ACR50, 70, achieved by 30% and 12%, respectively. A PASI 75 response was achieved by 40% at week 14 in 109 patients and by 56% at week 24 in 102 patients, with at least 3% BSA involvement evaluable for PASI. Of those patients with enthesitis, assessed by the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), significantly more showed resolution of enthesitis compared to placebo. Nail changes also significantly improved as did measures of physical function. These improvements were sustained at 104 weeks in an open extension phase of this trial.46 Inhibition of progressive joint damage at 1 year has been reported.47 Safety experience was commensurate with that of other anti-TNF agents in PsA.

A new anti-TNF-α agent, certolizumab pegol, now approved for the treatment of RA, is a subcutaneously administered pegylated Fab fragment, which is being studied in PsA (Mease, unpublished data).

Although there is scant trial evidence,47 experience in the management of PsA 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, a substantial percentage of patients will respond to another medication in this class.

Inflammatory spine disease has not been formally assessed in PsA clinical trials, due to a number of factors, including the variability of expression of this clinical domain in PsA and uncertainty about the validity, reliability, and discriminant capability of clinical and radiographic measures developed for AS when used in PsA. Anti-TNF medications have shown significant efficacy for axial manifestations of AS.48 Although NSAIDs have been shown to be beneficial for axial symptoms of AS, agents such as methotrexate, sulfasalazine, and leflunomide have not,48 suggesting that anti-TNFs are the preferred class of medicine to be used in those with inadequate responses to NSAIDs. We do not have controlled evidence to know if the same holds true in PsA, although extrapolation of the AS experience to PsA seems reasonable and has been adopted in the GRAPPA treatment recommendations.2

The anti-TNF-α medications have shown the greatest efficacy of any treatment to date in the various clinical aspects of PsA. Their efficacy in treating joint disease activity, inhibiting structural damage, and improving function and quality of life are similar, and effects on skin are similar, depending on the dose utilized. 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 population.

PsA Pharmacotherapy: Other Biologic Agents.

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. It is approved for the treatment of psoriasis in the U.S. 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 during 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, and showed sustained responses in patients undergoing a second course.49,50 PASI 75 results were 28% and 24%, respectively. Modesty of efficacy of this agent has limited its use in PsA, but it is a consideration for patients who have failed or had side effects with other medications.

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 monthly and has been approved for use in RA, based on its ability to improve composite joint scores and function and to inhibit radiographic progression. A trial in psoriasis has been conducted and shown efficacy.51 This drug has been evaluated in a phase II trial in PsA. In the standard dose arm of 10 mg/kg IV monthly (n = 40), 48% achieved an ACR20 response, compared to 19% in the placebo arm (p = 0.006), although there was greater efficacy in the subgroup not previously exposed to anti-TNF therapy.52 This agent has been tolerated well, with the main safety issue being risk of infection, comparable to the rate seen with other biologic agents.

Both IL-12 and IL-23 are over expressed in psoriasis plaques. IL-23 is a key cytokine that stimulates the proliferation and activation of Th17 lymphocytes, recently appreciated as important inflammatory cells in a variety of inflammatory diseases. Ustekinumab, an IL12/23 inhibitor, has shown significant efficacy, administered subcutaneously, in psoriasis.53 This agent also has shown efficacy in a preliminary PsA study.54 This was a placebo-controlled cross-over study, in which group 1 patients received 90 mg weekly for 4 weeks and subsequent placebo injections. At week 12, 42% of this group (n = 76) achieved an ACR20 response, compared to 14% in the placebo group (p = 0.0002). The drug was generally well tolerated. ABT-874 is another IL-12/23 inhibitor that shows significant and enduring skin response with monthly subcutaneous dosing and will likely be studied in PsA.55

A pilot trial of anti-IL-15 compound has shown efficacy in PsA.56 Rituximab, an anti-CD20 agent that ablates B lymphocytes and is approved for the treatment of lymphoma and RA (administered every 6 months in 2 doses separated by 2 weeks, 1000 mg each), demonstrated modest efficacy for arthritis, primarily in the subgroup of patients not previously exposed to anti-TNF therapy.57 Apremilast, an oral phosphodiesterase-4 inhibitor that suppresses multiple pro-inflammatory mediators and cytokines, was tested in a 12-week trial and showed modest efficacy (ACR20, 43.5%) in a 20 mg bid cohort.58 This agent is now being assessed in several phase III trials. Tocilizumab, a monoclonal antibody that inhibits the IL-6 receptor, is approved for the treatment of RA and will be tested in PsA. Small molecules such as the Janus kinase (JAK) inhibitors, administered orally, which have shown efficacy in RA and psoriasis, will soon be tested in PsA.

Another therapeutic approach, aimed primarily at reduction of bone erosions, is to reduce osteoclastogenesis. An inhibitor of rank ligand, denosumab has been shown not only to improve osteoporosis, but also to reduce erosion rate in RA.59 It is anticipated that this type of approach will show utility in PsA as well, especially given the known prolificity for excess osteoclast production and activation in this disease.

Treatment Recommendations

The GRAPPA group has published a set of treatment recommendations for the various clinical domains of PsA,2 based on formal literature reviews of therapies for disease of the
peripheral joints, spine, skin and nails, enthesitis, and dactyliitis and on discussions amongst GRAPPA members (rheumatologists and dermatologists). A disease severity grid was developed (Table 4) that categorized each domain as mild, moderate, or severe, based on measures of disease severity and impact on function and QOL in order to help the clinician with treatment decisions. The paper proceeds to recommend specific treatments for each clinical domain according to level of severity and impact. In parallel, a task force composed primarily of dermatologists has developed recommendations for the treatment of PsA.

Comorbidities

There is accumulating evidence that PsA patients develop cardiovascular disease (CVD) prematurely, which may contribute to the early mortality seen in this disease. Based on data from RA and psoriasis, potential contributors to CVD include inflammation-induced atherogenesis and metabolic syndrome (including obesity, hypertension, and hyperlipidemia). RA national registry data demonstrates that anti-TNF medicine usage in RA is associated with reduction in incidence of premature myocardial infarction and stroke. Similar epidemiological data is not yet available in PsA. A recent study by Tam and associates showed that use of TNF inhibitors in PsA was associated with reduction of carotid intima-media thickness and correlated with reduction in markers of inflammation, but was independent of changes in lipid profiles.

Conclusion

PsA is a multi-domain disease, characterized by inflammation of peripheral joints, skin and nails, spine, and enthesium. A number of systemic treatments for PsA (especially inhibitors of TNF-α) have demonstrated significant benefit for all disease domains, the ability to control damage as assessed by radiographic progression, and improvement of QOL and the functional status of patients. Traditional immune modulating drugs can beneficially affect many of these domains as well. A number of other agents that inhibit cytokine expression or block cellular interactions have either demonstrated benefit or are being tested in PsA. Mild disease in the joints and skin can be treated with antiinflammatories and topical treatments.

A key aspect of treatment is accurate diagnosis and assessment, which facilitates the institution of appropriate therapy in a timely fashion. Since the skin manifestations of psoriasis typically develop long before arthritis symptoms develop, the dermatologist or primary care physician is in a good position to screen for arthritis. Through appropriate treatment and coordinated care between rheumatologists and dermatologists, it appears to be possible to prevent progressive structural damage in those that are likely to progress. As well, international treatment recommendations have been developed to assist therapeutic decision-making.

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References


