

Treatment of Psoriatic Arthritis with Biological Agents

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Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in individuals with psoriasis. The primary goals in the treatment of PsA are reduction of pain; improvement in the other signs and symptoms of disease, including skin and nail involvement; optimization of functional capacity and quality of life; and inhibition of the progression of joint damage. These goals should be achieved while minimizing potential toxicities from treatment. The management of PsA should simultaneously target arthritis, skin disease, and other manifestations of PsA, including involvement of the axial skeleton, dactylitis, enthesitis, and eye inflammation. In this respect targeted biological agents, primarily tumor necrosis factor inhibitors, have emerged as generally well tolerated and highly effective alternatives to traditional disease modifying antirheumatic drugs. Herein we review the evidence regarding the treatment of PsA arthritis with biological agents.

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Definition, Epidemiology, and Relation to Skin and Nail Disease

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that occurs in persons with established psoriasis. Psoriasis precedes arthritis in more than two thirds of cases; in a minority of patients the arthritis precedes or occurs simultaneously with psoriasis. Psoriasis vulgaris and plaque psoriasis are the most common types of psoriatic skin disease observed in PsA patients. Nail changes are observed in approximately 80% of patients with PsA, compared with about 30% of patients with psoriasis. There is some evidence of a positive correlation between the severity of skin psoriasis and the occurrence of PsA.¹ However, in individual subjects, there can be a disparity between the severity and activity of disease in the skin compared with that of the joints.

PsA affects 2% to 3% of the general population. The reported prevalence of PsA among patients with psoriasis has been reported to range from 5% to 40% in various studies; a reasonable estimation in the general population would be roughly 10% to 15%. At presentation, most patients are between 35 and 50 years of age, but a juvenile form of PsA is also well recognized.² Unlike many other rheumatic diseases that have a female predominance, PsA affects men and women equally. An exception is PsA patients with spinal involvement, where the male-to-female ratio approaches 3:1.

Clinical Features and Diagnosis of PsA

Patients with PsA may demonstrate a constellation of symptoms, including peripheral arthritis, involvement of the axial skeleton (sacroilitis, spondylitis), enthesitis, dactylitis, and recurrent eye inflammation (anterior uveitis; also known as iritis).

The cardinal feature of PsA is inflammatory arthritis. Frequently there is involvement of distal interphalangeal, proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal, knee, hip, and ankle joints. Some years back, Moll and Wright³ suggested that oligoarthritis might be the most common among 5 classical patterns of joint involvement in PsA. However, observations by CASPAR (the CLASSification of Psoriatic ARthritis) study group indicate that polyarticular joint involvement in PsA is most common, with a prevalence that approaches 60% of patients.⁴

Patients with PsA commonly have enthesitis, an inflammation at the locations in which tendons, ligaments, and joint capsules attach to bone. Inflammation and swelling of the whole digit, known as dactylitis, is also observed in PsA. Notably, enthesitis and/or dactylitis can be the first manifestation of PsA. PsA patients may also have involvement of the axial skeleton, much as patients with other spondyloarthropathies, such as ankylosing spondylitis (AS).

Testing for rheumatoid factor and anticyclic citrullinated peptide antibodies is traditionally used to aid in differential diagnosis of PsA and rheumatoid arthritis (RA). The establishment of diagnosis, however, should not be made on the basis solely of the presence or absence of these serologic markers because as many as 15% of PsA patients are positive

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for rheumatoid factor, and as many as 8% of PsA patients are positive for anticyclic citrullinated peptide antibodies.⁵ Measures of acute inflammation, such as CRP and ESR, may also be normal in PsA patients, even those with active disease.

No specific tests are diagnostic of PsA, and the diagnosis is made on clinical grounds. The CASPAR group has published classification criteria for PsA.⁴ The criteria, which were developed to help assess whether a patient with established inflammatory arthritis has PsA or some other form of arthritis, focus on features such as the presence of skin or nail psoriasis, family history, dactylitis and other features.^{4,6}

Outcome Measures for Assessment of PsA

Most of the methodologies used to assess PsA outcomes have been adapted from those used in the evaluation of other diseases, including RA, AS, and psoriasis. The utility of these measures specifically in PsA is one of the areas of investigation by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)^{7,8} although not specifically validated in PsA, several measures performed well in clinical trials involving biologics (Table 1). This includes the American College of Rheumatology (ACR) response criteria for RA, the disease activity score (DAS), and the psoriasis area and severity index (PASI).

Treatment of PsA

Ideally, the treatment of PsA should be effective for all or most of the various manifestations of the disease that a particular patient may have, including skin, peripheral and axial joint inflammation, dactylitis, and enthesitis. Importantly, treatments should also measurably improve quality of life. The authors of several systematic reviews have addressed treatment approaches to PsA in detail and comprehensive evidence-based graded recommendations were formulated by GRAPPA.⁹⁻¹² This review will focus on the current evidence of the use of biological agents in the treatment of PsA.

Nonsteroidal Anti-Inflammatory Drugs and Traditional Disease-Modifying Anti-Rheumatic Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) can provide symptomatic relief for peripheral arthritis and spondylitis, as well as enthesitis and dactylitis in PsA patients. In general, the extent of improvement is small, although sometimes meaningful to the patient. The concern that NSAIDs might worsen skin psoriasis was not supported by a study of the relatively COX-2-specific inhibitor nimesulide.¹³ Generally, gastrointestinal side effects can be diminished by use of COX-2-selective inhibitors or by the use of a combination of NSAIDs and inhibitors of gastric acid, such as proton pump inhibitors or H₂ receptor blocking agents.

Despite a paucity of well-controlled clinical studies, methotrexate (MTX) is the most commonly used disease-modify-

Table 1 Outcome Measures in Clinical Trials of PsA

Outcome Measure	Explanation
ACR response criteria 20, 50, 70	1. 20%, 50%, and 70% improvement in tender and swollen joint counts, including CMC, and DIP joints and the feet; 2. and at least 3 of 5: • physician global assessment of disease • patient global assessment of disease • patient assessment of pain • ESR or CRP • degree of disability in HAQ score
Psoriatic arthritis response criteria	1. improvement in at least 2 of 4: • physician global assessment (0-5) • patient global assessment (0-5) • tender joint score of >30% • swollen joint score of >30% 2. one-half has to be one of the joint scores and no worsening in other criteria is allowed
DAS	Estimated using formula that includes: • number of swollen and tender joints of 28 • ESR • patients general health (GH) or global disease activity measured on a visual analog scale (VAS) 100 mm
Skin evaluation (PASI, TLS)	PASI: Psoriasis Area and Severity Index grades (0-4) average redness, thickness and scaliness of the lesions weighted by the area of involvement. PASI 75—a 75% improvement in PASI. Requires at least 3% of the body area involvement. TLS: Target lesion severity score measures erythema, induration, and scale of a single lesion at least 2 cm in diameter
Disability, function, and quality-of-life indexes	HAQ, SF36, DLQI
Radiographic indexes	Modified Sharp, modified van derHeijde/Sharp, etc.

ACR, American College of Rheumatology; DIP, distal interphalangeal joints; CMC, carpometacarpal joints; CRP, c-reactive protein; HAQ, Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; SF36, Short Form Health Survey; DLQI, dermatology Life Quality Index Assessment.

ing antirheumatic drug (DMARD) for the treatment of PsA (39% of cases), followed by sulfasalazine (SSZ; 22%). MTX is also frequently used as part of the combination regiment with SSZ, prednisone, or biological agents, such as tumor necrosis factor (TNF) inhibitors.¹² A prospective study of MTX use during a 10-year period in 59 patients indicated greater re-

sponse rates (68% vs 47%), with a >40% reduction in joint counts and a reduced rate of radiological progression among MTX users in recent years compared with historical controls. Factors associated with a greater response in that study included shorter disease duration and the use of greater dose of MTX.¹⁴ There is some evidence that patients with psoriasis may have an enhanced predisposition to hepatic damage from MTX, particularly if they have underlying type 2 diabetes mellitus or are overweight.¹⁵ Nonalcoholic fatty liver disease (NAFLD) appears to be common among psoriasis patients, particularly those that are overweight or who have other comorbidities. NAFLD may contribute to abnormalities in liver function tests during therapy with MTX or other drugs in psoriasis and PsA.

SSZ has demonstrated efficacy in PsA, although the response is often modest. The largest randomized controlled trial compared 2 g of daily SSZ vs placebo in 221 PsA patients.¹⁶ Responses that used a composite index assessing peripheral arthritis were significantly greater in the treatment compared with placebo group but was small in extent (ie, response of 58% vs 45%, respectively).

Leflunomide (LEF) is another DMARD that is used in PsA. A large international randomized controlled study compared LEF 20 mg/d versus placebo in 190 PsA patients.¹⁷ Fifty-nine percent of patients receiving LEF compared with 30% of placebo-treated patients improved at week 24 when a composite index of peripheral joint inflammation was used (the ACR20, see Table 1). LEF was also effective in controlling skin disease as measured by PASI scores: 22% of patients in LEF group achieved PASI75 response compared with only 2.2% in placebo group. The study did not address radiographic progression of the joint damage.

Cyclosporine is another DMARD that can be effective for some patients with PsA. It has established efficacy for skin disease and can also improve arthritis and peri-articular symptoms. However, its use is somewhat limited by nephrotoxicity and other concerns.¹⁸ Azathioprine had been used in PsA patients, although there are limited data suggest that it may improve arthritic and skin features of PsA patients.¹⁹ Generally, traditional DMARDs appear to have modest effects on arthritis and skin disease and only minimal or no effect on progression of radiological joint damage. Of note, they seem to have no effect on axial (spinal) disease in PsA; this has been similarly observed in patients with other spondyloarthropathies, such as AS.

Biological Agents in the Treatment of PsA

The introduction of biological agents, particularly inhibitors of the proinflammatory cytokine TNF, has resulted in dramatic improvements in the ability to treat patients with PsA.

TNF Inhibitors

Etanercept

Etanercept is a soluble recombinant P75 TNF-receptor-Fc fusion protein, which binds to and antagonizes TNF. It is

approved for the treatment of RA, juvenile idiopathic arthritis, PsA, AS, and psoriasis. Etanercept is administered subcutaneously at a dose of 25 mg twice a week or 50 mg once a week. In psoriasis, an initial 12-week dose of 50 mg twice a week is used.

An initial double blind placebo controlled study enrolled 60 PsA patients with a mean disease duration of 9 years. Roughly 40% of patients were on MTX <20 mg/wk.²⁰ Patients received either placebo or subcutaneous etanercept at a dose of 25 mg twice weekly for 12 weeks. At 12 weeks, significantly more patients achieved the ACR20, ACR50, and ACR70 (73%, 50%, 13%, respectively) in the etanercept arm compared with placebo (13%, 3%, 0, respectively). The median improvement in PASI score was 46.2% patients who received etanercept compared with 8.7% in the placebo group ($P = 0.0032$). Thirty-four percent of patients in the treatment arm had 100% improvement in health assessment questionnaire (HAQ) score vs 1% in placebo.

The larger, pivotal double-blind placebo-controlled study enrolled 205 patients with PsA (mean disease duration 9 years) to evaluate twice-weekly subcutaneous administration of 25 mg of etanercept in PsA.²¹ In this study 42% of patients remained on MTX (mean dose of 15 mg wk⁻¹). At 12 weeks ACR20 criteria were achieved in 59% of patient on etanercept compared with 25% on placebo ($P < 0.0001$). These results were sustained at 24 and 48 weeks. At 24 weeks there was 54% improvement in HAQ disability index in etanercept-treated patients compared with 6% in placebo ($P < 0.0001$). Etanercept was well-tolerated. An open-label 1-year extension of the aforementioned study enrolled 71 patients who received placebo/etanercept and 70 patients who received etanercept/etanercept 25 mg twice a week.²² Of note radiographic progression was less prominent in the etanercept group compared with the placebo group as assessed by changes in a composite radiographic score that assesses peri-articular erosions and joint space narrowing in peripheral joints (ie, the Sharp score).

Infliximab

The IMPACT trial studied the effect of infliximab on PsA.²³ This study was a 2-phase double-blind placebo-controlled randomized study. In the first phase, intravenous infliximab 5 mg kg⁻¹ ($n = 52$) was administered at weeks 0, 2, 6, and 14. To preserve blinding and allow introduction of treatment into the placebo group, infliximab group patients received placebo infusions at weeks 16 and 18, followed by infliximab 5 mg kg⁻¹ at weeks 22, 30, 38, and 46, whereas patients in the placebo group ($n = 52$) received infliximab 5 mg kg⁻¹ at weeks 16, 18, 22, 30, 38, and 46. At 16 weeks, 65% of patients treated with infliximab have achieved ACR20 response compared with 10% in placebo. ACR50 and ACR70 response was achieved in 46% and 29% of infliximab-treated patients, respectively, compared with 0 patients in placebo group. The response was sustained at 50 weeks with a similar proportion of patients achieving ACR20, ACR50, and ACR70 response criteria. At week 16, patients in the infliximab group showed a mean improvement in the DAS28 score of 46%, compared with an improvement of 2.8% among pa-

tients in the placebo group ($P < 0.001$). The treatment groups showed similar levels of improvement at week 50. Sixty-eight percent of infliximab-treated patients achieved $>75\%$ improvement in PASI score at week 16 compared with none in placebo group. Continued therapy with infliximab resulted in sustained improvement in articular and dermatologic manifestations of PsA through week 50. The incidence of adverse events was similar between both groups.

A 2-year extension of the aforementioned study was available in 74 patients.²⁴ At week 98, 68% of infliximab-treated patients maintained an ACR20 response criteria, and 45% and 35% of patients achieved ACR50 and ACR70 response criteria, respectively. Clinically meaningful improvement from baseline to week 98 of HAQ score was also evident. Among patients with PASI score ≥ 2.5 , 64% achieved $>75\%$ improvement from baseline at week 98%. The radiographic progression was also reduced in the treatment group compared with estimated baseline radiographic progression.

The pivotal IMPACT 2 study evaluated the efficacy and safety of infliximab in a larger patient group ($n = 200$) with active PsA.²⁵ In addition to assessment of arthritis and skin disease, dactylitis, enthesopathy and quality of life were assessed. At week 14, 58% of patients receiving infliximab and 11% of those receiving placebo achieved an ACR20 response ($P < 0.001$). Also, 64% of patients receiving infliximab had at least 75% improvement in PASI compared with 2% placebo-treated patients at week 14 ($P < 0.001$). Fewer infliximab patients than placebo patients had dactylitis at week 14 (18% vs 30%; $P = 0.025$) and week 24 (12% vs 34%; $P = 0.001$). Meaningful improvements in functional status (measured as decreases in the HAQ score of at least of 0.3 of a total score of 3) were significantly more common in the infliximab group than in the placebo group (59% vs 19%; $P < 0.001$). The response was sustained at week 24 (52% vs 20%; $P < 0.001$). The effect of the treatment was maintained through 1 year as was radiographic progression of joint damage, which was also inhibited through week 50.^{26,27}

Adalimumab

Adalimumab, a human monoclonal antibody against TNF- α , was studied in several trials, including the pivotal multicenter, randomized, double blind study (ADEPT trial) involving 315 PsA patients.²⁸ At the end of 24 weeks 57% of patients receiving adalimumab achieved an ACR20 compared with only 15% of patients in placebo group. Treatment with adalimumab also was associated with better radiographic scores and quality of life, including improvement of fatigue. Another, randomized controlled trial study confirmed the efficacy of adalimumab.²⁹

In an open label extension of the ADEPT trial, adalimumab 40 mg sq. q 2 weeks showed sustained efficacy through 2 years. Significantly more patients achieved the ACR20, ACR50, and ACR70 at week 48 (58.7%, 42.7%, 27.8%, respectively) and week 104 (57.3%, 45.2%, 29.9%, respectively).³⁰ The inhibition of radiological progression of PsA was sustained for more than 2.75 years. Improvements in patient-reported outcome measures were also maintained from 48 to

104 weeks. Adalimumab maintained a good risk-benefit profile throughout this extension study.

Golimumab

Golimumab is a newly introduced human anti-TNF monoclonal. Results of the large phase 3 multicenter, randomized, placebo-controlled study (GO-REVEAL) involving 405 patients have been published.³¹ Patients received subcutaneous injections of placebo or golimumab at doses of 50 or 100 mg every 4 weeks. Stable doses of MTX, NSAIDs, and prednisone, ≤ 10 mg d⁻¹ was allowed. At 14 weeks, compared with 9% of control patients, 51% of patients receiving 50 mg and 45% of patients receiving 100 mg of golimumab achieved ACR20 response. Further improvement of ACR 20 was observed at 24 weeks. Significantly more patients in golimumab arm achieved ACR50, ACR70 and also showed improvement in other efficacy primary end points, such as the European League Against Rheumatism response and change in DAS28-CRP and in HAQ, SF36 scores, psoriatic skin disease, enthesitis, and nail disease. In addition, inhibition of radiographic progression was demonstrated.

Certolizumab Pegol

Certolizumab pegol (Cimzia), another new TNF inhibitor that has been approved for use in RA and inflammatory bowel disease in several countries, is a Fab fragment of a humanized anti-TNF coupled to polyethylene glycol, which extends the half-life of the drug. It has been approved by Food and Drug Administration for the treatment of RA and Crohn's disease. Preliminary results indicate that certolizumab has shown efficacy in psoriasis.³² Controlled studies are planned to assess applicability of certolizumab pegol in the treatment of PsA.

Combinations of MTX and TNF Inhibitors

Most studies of TNF-inhibitors in PsA permitted concomitant use of MTX during the trials. In general, roughly 40% to 50% of the study patients were also on MTX. Subgroup analysis of patients in these studies did not show any significant difference in responses to TNF inhibitor therapy irrespective of whether the patients were on MTX. However, such a study design does not provide an answer to the key clinical question of whether the combination of TNF inhibitor plus MTX might have synergistic efficacy. Such synergy has been demonstrated in RA, but remains speculative in PsA until a *de-novo* trial comparing these therapeutic strategies (MTX or TNF-inhibitor or combination MTX plus TNF-inhibitor) is performed.

Summary of the Use of TNF Inhibitors in PsA

A summary of the pivotal randomized placebo-controlled trials of anti-TNF agents in PsA is shown in Table 2.^{21,22,25,26,28,30,31} As regards articular signs and symptoms, adalimumab, etanercept, infliximab, and most recently golimumab, appear to be similarly highly effective in the treatment of PsA.³³ Extension studies also showed similar sustained response and similar safety profile in PsA patients. It should be noted, however, at the doses studied for PsA

Table 2 Summary of the Key Randomized Placebo-Controlled Trials of Anti-TNF Agents in PsA

Agent/Trial Name	Number of Patients, Including Placebo	Patients Meeting Response Criteria, % (at Weeks)*				
		ACR20	ACR50	ACR70	PsARC	≥75% Improvement in PASI
Etanercept						
Initial study ²¹	205	59 (12)	38 (12)	12 (12)	72 (12)	38 (12)
		55 (24)	40 (24)	10 (24)	70 (24)	40 (24)
Extension study ²²	169	64 (48)	44 (48)	13 (48)	84 (48)	40 (48)
Infliximab						
IMPACT ²⁵	200	58 (14)	36 (14)	15 (14)	77 (14)	64 (14)
		54 (24)	41 (24)	27 (24)	70 (24)	60 (24)
Extension study ²⁶	173	59 (54)	37 (54)	22 (54)	74 (54)	50 (54)
	104	62 (98)	45 (98)	35 (98)	67 (98)	64 (98)
Adalimumab						
ADEPT ²⁸	315	58 (12)	36 (12)	20 (12)	62 (12)	49 (12)
		57 (24)	39 (24)	23 (24)	60 (24)	59 (24)
Extension study ³⁰	245	59 (48)	43 (48)	28 (48)	66 (48)	59 (48)
		57 (104)	45 (104)	30 (104)	64 (104)	58 (104)
Golimumab ³¹						
Go-reveal	405					
50 mg		51 (14)	29 (14)	10 (14)	73 (14)	40 (14)
		52 (24)	33 (24)	18 (24)	70 (24)	56 (24)
100 mg		45 (14)	30 (14)	18 (14)	72 (14)	58 (14)
		61 (24)	38 (24)	22 (24)	85 (24)	66 (24)

ACR20, 50, 70, American College of Rheumatology Response criteria; PsARC, Psoriatic Arthritis Response Criteria; PASI, Psoriasis Area and Severity Index.

*Some of the percentages are estimated from published graphically represented data and may not match the exact numbers in the original data.

(25-mg biweekly) the effect of etanercept was less than that seen with the other agents. In addition, all TNF inhibitors significantly improved patients' physical function and quality of life. Further, TNF inhibitors demonstrated an ability to inhibit the progression of structural damage as assessed by radiography. TNF inhibitors were also shown to be very effective at improving enthesitis and dactylitis, the key areas of involvement in PsA.

The effect of the change from 1 anti-TNF agent to another has been studied in a small number of patients for loss of or lack of efficacy.^{34,35} The results show that in general, patients who fail 1 TNF inhibitor due to a side effect may be expected to have a better clinical response compared with patients who fail due to loss of efficacy.

T-Cell Modulators

Alefacept

Alefacept, a fusion protein of soluble lymphocyte function antigen-3 and an IgG1 Fc fragment, inhibits T-cell activation and causes depletion of T memory cells through apoptosis. A decrease in T-cell and macrophage infiltration of synovial membrane was demonstrated in a small series of patients treated with 7.5 mg intravenous alefacept weekly for 12 weeks.³⁶

A 12-week placebo-controlled, double-blind, phase 2 clinical trial of 185 patients with active PsA taking concomitant MTX, assessed responses to intramuscular injection of 15 mg of alefacept or placebo.³⁷ Compared with placebo, significantly more patients in the alefacept group achieved an

ACR20 response (54% vs 23%, respectively, $P < 0.001$). The reported side effects were generally mild. An open label extension of the study showed some increase in the percentage of patient achieving ACR50 and ACR70, although it was felt to be less potent than TNF inhibitors.³⁸

Abatacept

Abatacept, a fusion protein of soluble CTLA-4 (cytotoxic lymphocyte antigen-4) and the Fc fragment of IgG1, is an inhibitor of T-cell co-stimulation. A small open dose escalation study of abatacept demonstrated some efficacy in psoriasis. Preliminary results from a phase IIB study of abatacept in PsA were recently reported in abstract form.³⁹ The efficacy of abatacept appears to be lesser compared to that typically seen with TNF inhibitors; this was particularly notable among patients who had previously received TNF-inhibitor therapy.

Efalizumab

Efalizumab, a humanized mAb directed against LFA-1 (lymphocyte function associated antigen-1) was approved for treatment of psoriasis. However it failed in a phase II trial in PsA.⁴⁰ This agent was voluntarily withdrawn from the market due to safety concerns. B cell modulators.

Rituximab

Rituximab is a chimeric monoclonal antibody directed against the B cell antigen CD20. It selectively depletes B cells, and has been approved the treatment on non-Hodgkin's lym-

phoma and RA. There are ongoing small studies assessing rituximab in PsA.

Other Biologics

Ustekinumab

Ustekinumab is a human immunoglobulin monoclonal antibody to the shared P-40 subunit of the cytokines interleukin (IL)-12 and -23. In binding to P-40, Ustekinumab inhibits IL-12 and IL-23 binding to IL-12R β 1 receptor found on the surface of T cells, natural killer cells, and antigen-presenting cells. The results of a phase 2 double-blind, randomized, placebo-controlled, multicenter crossover study of ustekinumab have been recently published.⁴¹ In this study patients with active PsA were randomly allocated to either ustekinumab, 90 or 63 mg, weekly for weeks 0 to 3, followed by placebo at weeks 12 and 16, or vice versa, to placebo at weeks 0 to 3 and 63 mg of ustekinumab at weeks 12 and 16. Patients were followed up to 36 weeks. A difference of 28% (95% confidence interval 14.0-41.6, $P = 0.0002$) in achieving ACR20 response was seen between the treatment and placebo group at 12 weeks. The response rate for ACR50 and ACR70 were 25% vs 7% and 11% vs 0% at week 12. One third of patients who received 4 doses of ustekinumab showed durable response even at week 36 (33 weeks after the last dose). A very similar proportion of patients who received ustekinumab after crossover at weeks 12 and 16 achieved ACR response at week 24. Notably, about 20% of the patients involved in this study failed previous anti-TNF treatment. The effect of ustekinumab on cutaneous psoriasis appears to be at least comparable and better than that of TNF inhibitors. The extent of efficacy of this compound on articular and related manifestations will be more fully delineated by ongoing studies.

Side Effects and Safety of Biological Agents Used in PsA

The safety considerations of biological agents have recently been reviewed.⁴² With more than 10 years of clinical experience, and more than 2 million patients treated worldwide across a variety of indication, the safety experience is greatest with TNF inhibitors. There is less safety experience with other biological agents in the treatment of autoimmune diseases.

As biological agents must be given parenterally, it is not surprising that the most common adverse effects are related to injection or infusion reactions. Because biological agents target molecules that have important immunosurveillance and immune-defence functions in the host, increased susceptibility to infection is a concern. All patients on biologics should be monitored for common and opportunistic infections; for TNF inhibitors, this also includes tuberculosis.

There are no controlled human studies of the biologics in pregnancy. All TNF-inhibitors agents are considered category B by the US Food and Drug Administration, whereas abatacept and rituximab are category C. Interestingly, there are numerous anecdotal reports on association between the use of TNF inhibitors and the development of psoriasis.⁴³⁻⁴⁵ A

mechanism by which biological agents could induce psoriasis is not clear. It is speculated that alteration in the cytokine pathways because of prolonged use of biological agents might be involved in the development of this paradoxical reaction.⁴⁶

Summary and Conclusions

Although they can have some beneficial effect on skin disease and peripheral arthritis, there is lack of evidence for traditional DMARDs, such as MTX, LEF, CsA, and SSZ in affecting dactylitis or enthesitis, and they are clearly ineffective in axial disease. Systemic glucocorticoids may cause a flare of psoriasis if tapered too quickly, and, therefore, should be used with caution in PsA. In contrast, biologics, particularly TNF inhibitors seem to be beneficial in skin psoriasis and across of all the manifestations of PsA, including arthritis, skin and nail disease, spinal disease, enthesitis and dactylitis. They also improve quality of life and inhibit joint damage. All the currently used TNF inhibitors appear to have comparable efficacy and safety profiles in patients with PsA. They can be used as monotherapy or in combination with MTX or other traditional DMARD. Initiation of anti-TNF agents is recommended for patients who failed one of the traditional DMARDs or as an initial therapy in patients who have poor prognosis. Other biological agents, including alefacept and abatacept, appear to be less potent than TNF-inhibitors in PsA and their use is likely to be reserved for patients who failed or cannot be treated with TNF inhibitors. These agents are usually used in combination with other DMARDs. The efficacy of ustekinumab in the treatment of PsA has been recently reported and is presently under further investigation. Additional immunomodulatory approaches are being developed; results are eagerly awaited.

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