Adalimumab in Psoriatic Arthritis

CARLO SALVARANI, NICOLÒ PIPITONE, MARIAGRAZIA CATANOSO, ILARIA CHIAROLANZA, LUIGI BOIARDI, ANDREA CARUSO, GIULIA PAZZOLA, PIERLUIGI MACCHIONI, VITO DI LERNIA, and GIUSEPPE ALBERTINI

ABSTRACT. Open prospective studies and randomized controlled trials (RCT) have shown the short-term efficacy of adalimumab (ADA) in psoriatic arthritis (PsA) and psoriasis. ADA effectively treated all varied musculoskeletal manifestations characteristic of PsA, including peripheral arthritis, spinal disease, enthesitis, and dactylitis. ADA significantly inhibited structural changes on radiographs, lessened disability, and improved quality of life in patients with active PsA. One study showed the efficacy of 24-week ADA therapy on bone marrow edema and erosions, as measured by magnetic resonance imaging. The clinical and radiographic efficacy of ADA demonstrated during short-term treatment was sustained during longterm treatment. ADA was generally well tolerated and its safety profile was similar to that reported in studies of ADA in rheumatoid arthritis. Overall, ADA has a favorable risk-benefit profile in PsA. The combination of ADA and cyclosporine seems to be more effective than ADA monotherapy in patients with active PsA and inadequate response to methotrexate; however, this observation must be confirmed in RCT. (J Rheumatol 2012;39 Suppl 89:77–81; doi:10.3899/jrheum.120251)

Key Indexing Terms:
PSORIATIC ARTHRITIS PSORIASIS ADALIMUMAB

Psoriatic arthritis (PsA) is one of the most common inflammatory arthropathies in Italy. An estimated 2-3% of the Italian population is affected by psoriasis, a third of which has or will eventually develop PsA[1,2,3]. Patients with PsA are prone to developing significant disability, and have reduced quality of life and increased mortality rates compared to the general population[4]. PsA has traditionally been considered a milder and less disabling disease compared with rheumatoid arthritis (RA). However, in a population from a tertiary care center of patients with PsA, 40% had joint erosions and damage[5,6]. In addition, about 20-40% of patients with PsA have axial skeleton involvement[7,8], which may lead to functional limitation and deformity, although usually less severely than that observed in ankylosing spondylitis[9]. These and other data[10] suggest that a sizable proportion of patients with PsA have severe, potentially disabling disease requiring aggressive treatment.

The initial treatment of PsA is usually nonsteroidal antiinflammatory drugs (NSAID) and topical steroid injections, but in patients with active peripheral joint disease not responsive to NSAID, aggressive treatment with 1 or more disease-modifying antirheumatic drugs (DMARD) is indicated to suppress inflammation. In clinical practice, the most widely used DMARD are methotrexate (MTX; level of evidence B), sulfasalazine (level of evidence A), leflunomide (level of evidence A), and cyclosporine (CSA; level of evidence B)[11,12,13,14,15,16,17]. However, the efficacy of these agents in inhibiting articular erosions has not been assessed in proper controlled studies[12,13,14,15,16,17], and none have proved effective in ameliorating the symptoms of psoriatic spondylitis[11,14,18]. In addition, the effectiveness of DMARD in treating enthesitis and dactylitis is dubious.

Research studies have provided evidence that the inflammatory cytokine tumor necrosis factor-α (TNF-α) plays a key role in the pathogenesis of spondyloarthritis including PsA. In particular, *in situ* hybridization studies have revealed TNF-α in psoriatic skin[19], in the synovium[20] of clinically involved joints, and in inflamed entheses[21]. Therefore, therapies targeting TNF-α may be useful in controlling disease activity in PsA. These findings have provided the rationale for using TNF-α inhibitors in PsA, but the proof of efficacy has actually been delivered by clinical data from randomized controlled trials (RCT) of TNF-α blockers in PsA[22] as well as from observational studies[23]. An Italian study has estimated the cost-effectiveness of anti-TNF-α versus conventional therapy for PsA[4]. That study showed that anti-TNF-α therapy is cost-effective in the short-term clinical practice in the Italian health system.

Our review will focus on the published evidence on the efficacy and safety of the anti-TNF-α agent adalimumab (ADA) in PsA (Table 1).

OPEN STUDIES

The ACCLAIM trial was an open-label multicenter phase IIIb study conducted in Canada in care settings that reflected clin-

From the Rheumatology Unit and Dermatology Unit, Azienda Ospedaliera ASMN, IRCCS, Reggio Emilia, Italy.

C. Salvarani, MD; N. Pipitone, MD, PhD; M. Catanoso, MD; I. Chiarolanza, MD; L. Boiardi, MD; A. Caruso, MD; G. Pazzola, MD; P. Macchioni, MD, Rheumatology Unit, Hospital of Reggio Emilia; V. Di Lernia, MD; G. Albertini, MD, Dermatology Unit, Azienda Ospedaliera ASMN, IRCCS.

Address correspondence to Dr. C. Salvarani, Unità di Reumatologia, Azienda Ospedaliera ASMN, IRCCS, V. le Risorgimento n 80, 42100 Reggio Emilia, Italy. E-mail: salvarani.carlo@asmn.re.it

Table 1. Open studies and randomized controlled trials (RCT; with their extensions) evaluating the efficacy and safety of adalimumab (ADA) in psoriatic arthritis (PsA).

Studies	Objectives
Open studies	
Gladman[24]	To evaluate the effectiveness and safety of ADA in patients with active PsA and an inadequate response to prior therapy
Van den Bosch[25]	To evaluate the effectiveness of ADA in patients with PsA and identify predictors of good clinical response for joint and skin lesions
Anandarajah[26]	To assess the effect of ADA on bone marrow edema, synovitis, effusion, and erosions in PsA, as measured by MRI
Karanikolas[27]	To assess the efficacy and safety of ADA or CYC as monotherapy or combination therapy for patients with active PsA, despite MTX therapy
RCT and their extensions	
Mease[28]	To evaluate the efficacy and safety of ADA compared with placebo in the treatment of active PsA (ADEPT trial)
Gladman[29]	To evaluate the efficacy and safety of ADA over 48 weeks in patients with active PsA (ADEPT trial extension)
Mease[30]	To evaluate the longterm effectiveness and tolerability of ADA in the treatment of PsA (ADEPT trial extension)
Gladman[31]	To identify independent predictors of radiographic progression in PsA for patients treated with ADA or placebo in the RCT ADEPT
Genovese[32]	To test the efficacy and safety of ADA in patients with PsA who have failed previous DMARD therapy

MRI: magnetic resonance imaging; CYC: cyclosporine; MTX: methotrexate; DMARD: disease-modifying antirheumatic agents.

ical practice[24]. Study enrollment criteria were consistent with the eligibility requirements for Canadian patients with PsA to receive biologic therapies.

Patients were treated with ADA 40 mg every other week in addition to their standard antirheumatic therapies in a 12-week, open-label study. The primary efficacy measure was at least 20% improvement in the American College of Rheumatology response criteria (ACR20) at Week 12. Secondary efficacy measures included ACR50 and ACR70 responses, Psoriatic Arthritis Response Criteria (PsARC), change in the percentages of patients with dactylitis and enthesitis, and Psoriasis Area and Severity Index (PASI) 50 and 75 responses. Physical function was evaluated using the Health Assessment Questionnaire Disability Index (HAQ-DI).

A total of 127 patients were enrolled. At Week 12, patients achieved ACR20, ACR50, ACR70, and PsARC response rates of 78%, 55.9%, 21.3%, and 70.1%, respectively. PASI50 and PASI75 response rates were 64.7% and 47.1%, respectively. A statistically significant improvement occurred in the percentages of patients with active dactylitis and enthesitis. A mean improvement in HAQ-DI was also observed. No serious adverse events related to ADA therapy were reported. These results, obtained from a clinical study conducted in a care setting that reflected routine practice, confirmed the efficacy and safety of ADA observed in the previous RCT.

The STEREO trial (SafeTy and Efficacy of adalimumab in patients with active psoriatic arthritis – an open-label, multinational study to evaluate the Response to Every-Other week adalimumab when added to insufficient standard therapy including patients who failed prior treatment with other TNF inhibitors) was a prospective, 12-week, uncontrolled study that evaluated the treatment effect of ADA in > 400 patients with PsA who were eligible for treatment with TNF-α inhibitors in daily rheumatology practice[25]. This study also evaluated predictive factors of a good clinical response for joint and skin lesions.

Of 442 patients, 94% completed 12 weeks of treatment. At Week 12, 74%, 51%, and 32% of the patients achieved ACR20, ACR50, and ACR70, respectively; 87% and 61% experienced moderate and good responses according to European League Against Rheumatism criteria, respectively. The percentage of patients with physician global assessment of psoriasis results of "clear/almost clear" increased from 34% (baseline) to 68%. The mean Nail Psoriasis Severity Index score was reduced by 44%. The safety profile of ADA in this study was consistent with results from RCT of ADA for PsA. Factors that increased the chances of achieving substantial clinical improvements were low impairment of physical function (lower HAQ-DI score), greater pain, greater C-reactive protein (CRP) concentration, polyarthritis without inflammation of large joints, prior treatment with > 2 DMARD, current treatment with sulfasalazine but not glucocorticoids, and male sex.

Anandarajah, *et al* assessed the effect of ADA on bone marrow edema (BME), synovitis, effusion, and erosions in PsA in a prospective, 24-week, open-label, pilot study[26]. Fifteen patients with active PsA received ADA every other week for 24 weeks. Magnetic resonance imaging (MRI) was performed at baseline and 24 weeks. Bone marrow edema and effusion scores improved markedly after 24 weeks of ADA, while no significant changes were noted in erosion and synovitis scores. This study confirmed the antierosive effects of ADA; however, the persistence of BME and synovitis on MRI suggested ongoing disease activity and supported the longterm use of anti-TNF therapy.

A prospective 12-month, nonrandomized, unblinded clinical trial evaluated the efficacy and safety of ADA (40 mg every other week) or CSA (2.5-3.75 mg/kg/day) as monotherapy or combination therapy for patients with active PsA, despite MTX therapy[27]. The primary efficacy endpoint was the PsARC at 12 months. That endpoint was satisfied by 65% of CSA-treated patients, 85% of ADA-treated patients, and

95% of combination-treated patients, while the ACR50 response rates were 36%, 69%, and 87%, respectively. PsARC response was significantly higher in combination-treated compared to CSA-treated patients ($p = 0.0003$), while ACR50 response was significantly higher in combination-treated compared to both CSA-treated and ADA-treated patients ($p < 0.0001$ and $p = 0.03$, respectively). A significantly greater mean improvement in HAQ-DI was achieved by combination treatment versus CSA or ADA alone. Combination therapy significantly improved PASI50 response rates beyond ADA, but not beyond the effect of CSA monotherapy. CSA doses, frequency of ADA injections, and doses of NSAID and corticosteroids were reduced in combination-treated patients.

The frequency of clinical adverse events was similar in the treatment groups. Adverse events were predominantly mild to moderate in severity and intensity. Three serious events were observed in the CSA arm, 4 in the ADA arm, and 2 in the combination arm.

The data presented in that study suggest that combination of ADA and CSA is more efficacious than ADA monotherapy in patients with active PsA and inadequate response to MTX. Further, the combination of ADA and CSA is safe.

RCT AND THEIR EXTENSIONS

An RCT [Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT)] compared the efficacy and safety of ADA versus placebo in patients with active PsA and inadequate response to NSAID[28]. Patients were randomized to receive 40 mg ADA or placebo subcutaneously every other week for 24 weeks (n = 315), and 140 patients in each study arm completed the trial. The primary efficacy endpoints were the ACR response rates, the quality of life, and the severity of skin disease in those patients with psoriasis involving at least 3% of body surface area. At Week 24, 57%, 39%, and 15% of the ADA-treated patients achieved ACR20, ACR50, and ACR70 responses, respectively, compared with 15%, 6%, and 1% of the placebo-treated patients. At the same timepoint, the mean change in the modified total Sharp score was –0.2 in patients receiving ADA versus 1.0 in those receiving placebo. Among the 69 ADA-treated patients evaluated with the PASI, 59% achieved a 75% PASI improvement response at 24 weeks, compared with 1% of the 69 placebo-treated patients evaluated. All the above differences were statistically significant. Disability and quality-of-life measures also significantly improved with ADA compared to placebo. ADA was generally safe and well tolerated, with a similar incidence of adverse reactions compared with that in the placebo group.

Patients who completed 24 weeks in ADEPT were permitted to receive open-label ADA after Week 24. The efficacy and safety of ADA during 24 weeks of blinded treatment plus 24 weeks of open-label treatment were described[29]. ADA improved joint and skin manifestations, reduced disability, and inhibited radiographic progression over 48 weeks. MTX use at baseline was not required for clinical and radiographic efficacy. ADA had a good safety profile through Week 48.

Of those who completed the ADEPT trial, 285 enrolled in an open-label extension of the study and received ADA 40 mg subcutaneously every other week for up to an additional 120 weeks[30]. Compared with 24-week and 48-week responses, inhibition of radiographic progression and improvements in joint disease were maintained in most patients during the open-label period. In particular, at Week 104, 57%, 45%, and 30% of patients achieved ACR20, ACR50, and ACR70 responses, respectively. The percentages of patients with no radiographic progression were 79% for the ADA-ADA group and 77% for the placebo-ADA group. Similarly, improvements in skin disease were maintained, with > 20% of patients achieving the strict criteria of PASI100 between weeks 48 and 104 of ADA treatment. The nature and frequency of adverse events during longterm ADA treatment were consistent with the safety profile during short-term treatment. These results thus show that ADA is effective in inducing clinical amelioration and in inhibiting radiographic progression in PsA during short-term treatment, and that these benefits are sustained during longterm treatment.

A post hoc subanalysis of the RCT ADEPT examined whether CRP or other factors were independent predictors of radiographic progression in PsA[31]. Patients were treated with either ADA (n = 144) or placebo (n = 152). Mean CRP was 64% lower by Week 2 with ADA and unchanged with placebo. Univariate and multivariate analyses indicated that elevated baseline CRP was the only strong independent risk factor for radiographic progression (for CRP > 1 mg/dl: OR 3.28, 95% CI 1.66-6.51). ADA treatment reduced risk of progression around 5-fold. The difference between mean changes in modified total Sharp score for ADA versus placebo was greatest for patients with baseline CRP > 2 mg/dl (–0.6 vs 2.6). The conclusions of the study were (1) systemic inflammation in PsA, as indicated by elevated baseline CRP, was the only strong independent predictor of radiographic progression, and (2) ADA treatment reduced the overall risk of radiographic progression and provided the greatest radiographic benefit for patients with the greatest CRP concentrations at baseline.

Another trial has been carried out to test the efficacy and safety of ADA in PsA[32]. Differently from the ADEPT study, in this trial patients were required to have failed previous DMARD therapy, the treatment groups were smaller, the double-blind period lasted only 12 weeks, and no radiographic assessment was included. Patients with active PsA were randomized to treatment for 12 weeks with subcutaneous ADA 40 mg every other week or placebo, followed by an open-label period with ADA. One hundred patients were enrolled (51 ADA, 49 placebo). At Week 12, ACR20, ACR50, and ACR70 responses were achieved by 39%, 25%, and 14% of ADA patients versus 16%, 2%, and 0% of placebo patients, respectively, while a PsARC response was achieved by 51% of ADA versus 24% of placebo patients. These differences were statis-

tically significant. At Week 12, measures of skin lesions and disability also significantly improved with ADA. After Week 12, open-label ADA provided continued improvement for ADA patients and initiated rapid improvement for placebo patients, with ACR20 response rates of 65% and 57%, respectively, observed at Week 24. Serious adverse events had similar frequencies during therapy with placebo (4.1%), blinded ADA (2.0%), and open-label ADA (3.1%). No serious infections occurred during ADA therapy.

CHOICE OF ADA IN THE TREATMENT OF PsA

All 3 TNF-α inhibitors have shown efficacy in PsA, but no head-to-head trials have been published to directly compare efficacy and safety. Therefore, the drug choice should take into account the patient's preferences as well as the available safety data and the patient's comorbidities[33]. Patients with associated inflammatory bowel disease should be treated with monoclonal antibodies including ADA, as should patients with PsA and uveitis, because uveitis has been shown to occur significantly more often during etanercept therapy than during infliximab and ADA treatment.

Open studies and RCT have clearly shown that in patients with PsA, ADA improves joint and skin manifestations, reduces disability, improves quality of life, and inhibits radiographic progression[24,25,26,27,28,29,30,31,32]. ADA is effective not only in peripheral arthritis and axial disease, but also in active dactylitis and enthesitis. The clinical and radiographic efficacy of ADA demonstrated during short-term treatment was sustained during longterm treatment[30]. ADA was well tolerated and its safety profile in patients with PsA was consistent with that reported in RA clinical trials and the postmarketing safety database[34]. Overall, ADA has a favorable risk-benefit profile in PsA. The combination of ADA and CSA seems to be more effective than ADA monotherapy in patients with active PsA and inadequate response to MTX; however, this observation must be confirmed in RCT[27].

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