Adalimumab or Cyclosporine as Monotherapy and in Combination in Severe Psoriatic Arthritis: Results from a Prospective 12-month Nonrandomized Unblinded Clinical Trial

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ABSTRACT. ***Objective.*** To assess the efficacy and safety of adalimumab or cyclosporine (CYC) as monotherapy or combination therapy for patients with active psoriatic arthritis (PsA), despite methotrexate (MTX) therapy.

Methods. A prospective 12-month, nonrandomized, unblinded clinical trial of 57, 58, and 55 patients who received CYC (2.5–3.75 mg/kg/day), adalimumab (40 mg every other week), or combination, respectively. Lowering of concomitant nonsteroidal antiinflammatory drugs (NSAID) and corticosteroids and reductions of adalimumab and/or CYC doses in responding patients were not restricted.

Results. Mean numbers of tender/swollen joints at baseline were 9.7/6.7 in CYC-treated, 13.0/7.8 in adalimumab-treated, and 14.5/9.4 in combination-treated patients, indicating lesser disease severity of patients assigned to the first group. The Psoriatic Arthritis Response Criteria at 12 months were met by 65% of CYC-treated ($p = 0.0003$ in favor of combination treatment), 85% of adalimumab-treated ($p = 0.15$ vs combination treatment), and 95% of combination-treated patients, while the American College of Rheumatology-50 response rates were 36%, 69%, and 87%, respectively ($p < 0.0001$ and $p = 0.03$ in favor of combination treatment). A significantly greater mean improvement in Health Assessment Questionnaire Disability Index was achieved by combination treatment (–1.11) vs CYC (–0.41) or adalimumab alone (–0.85). Combination therapy significantly improved Psoriasis Area and Severity Index-50 response rates beyond adalimumab, but not beyond the effect of CYC monotherapy. Doses of NSAID and corticosteroids were reduced in combination-treated patients; CYC doses and frequency of adalimumab injections were also reduced in 51% and 10% of them, respectively. No new safety signals were observed.

Conclusion. The combination of adalimumab and CYC is safe and seemed to produce major improvement in both clinical and serological variables in patients with severely active PsA and inadequate response to MTX. (First Release Sept 1 2011; J Rheumatol 2011;38:2466–74; doi:10.3899/jrheum.110242)

Key Indexing Terms:
ADALIMUMAB CYCLOSPORINE PSORIATIC ARTHRITIS
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Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory arthritis that affects 0.3%–1% of the general population and 10%–30% of patients with psoriasis[1]. Patients with PsA may experience persistent inflammation, progressive joint damage, and substantial morbidity and disability, and may have a reduced life expectancy[2,3]. Therapeutic interventions in moderate to severe PsA are similar to those utilized in rheumatoid arthritis (RA) and include nonbiologic disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX), cyclosporine (CYC), sulfasalazine, and leflunomide, all of which have a degree of efficacy in PsA patients with peripheral arthritis[4].

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Moreover, biologic agents that target the proinflammatory cytokine tumor necrosis factor-α (TNF-α) are well established as effective for treating PsA[5].

Adalimumab is a fully human anti-TNF monoclonal antibody shown to significantly reduce the signs and symptoms of both articular and skin manifestations, inhibit radiographic progression, and improve functional status and quality of life in patients with PsA[6,7]. CYC is a commonly used approved immunomodulatory drug for treatment of psoriasis that acts mainly at the T cell level by suspending the transcription of cytokine genes. While there are no randomized controlled trials comparing CYC to placebo in patients with PsA, its beneficial effects with regard to management of arthritis and concomitant psoriasis have been repeatedly shown in open studies[8]. In a few recent controlled trials, the efficacy of CYC in PsA was examined[9,10] compared to the other traditional DMARD.

In case of failure of monotherapy in patients with PsA, combination therapy is necessary for longterm management. Currently, some patients with moderate or severe PsA are treated with combination therapies on a daily basis, in accord with routine clinical care for patients with RA. In a recent review on combination therapies for PsA, comparative analysis of data from all 20 relevant articles published up to 2009 suggests the following. First, that the combination of CYC and MTX reduces the doses and also the side effects of each agent, allowing better disease control with less toxicity. Second, MTX, in combination with biologic agents, may have a role in decreasing side effects, but it does not appear to improve clinical symptoms beyond those attained by biologic monotherapy[11]. The hypothesis has not been addressed that the combination of CYC with an anti-TNF-α agent may be more effective than anti-TNF-α monotherapy, or that the combination may reduce the doses and the side effects of each agent. Thus, in this prospective, 12-month, nonrandomized, unblinded clinical trial, our aim was to examine the efficacy and safety of adalimumab and CYC combination therapy vs adalimumab or CYC monotherapy, for patients with active PsA despite therapy with MTX.

MATERIALS AND METHODS

Patients. All patients were adults with an established diagnosis of PsA[12] and active joint disease. Arthritis persisted under MTX therapy (25 mg weekly or less, for a minimum of 6 months) in all 176 patients; 120 and 86 patients had previously failed leflunomide and sulfasalazine therapy, respectively. MTX was discontinued for at least 1 month before enrollment. The main exclusion criteria were history of cancer or lymphoproliferative disease; positive serology for hepatitis B or C or human immunodeficiency virus; active inflammatory bowel disease; uncontrolled diabetes mellitus and/or hypertension; unstable ischemic heart disease; recent stroke; kidney function impairment; neurological symptoms suggestive of central nervous system demyelinating disease; and history of active infectious and/or granulomatous disease. In addition, patients who had received treatment with TNF-α antagonists, CYC, tacrolimus (oral or topical), or alefacept, and patients receiving intravenous infusions or intraarticular injections of steroids within 4 weeks of baseline were excluded. Concomitant therapy with oral corticosteroids (10 mg prednisolone equivalent/day or less) and nonsteroidal antiinflammatory drugs (NSAID) was not restricted, providing that doses were stable during the 4 weeks prior to baseline. No patient who participated in this study received psoralen plus ultraviolet A (UVA) phototherapy or oral retinoids.

Study protocol, evaluation of treatment outcome, and safety. A prospective, 12-month, nonrandomized, unblinded clinical trial in which CYC (2.5–3.75 mg/kg/day), adalimumab (40 mg subcutaneously every other week), or combination therapy of both at the same initial dose was given. Between September 2007 and February 2009, 176 consecutive patients attending the outpatient rheumatology clinic of the First Department of Propedeutic and Internal Medicine, Laikon Hospital, or patients referred to the clinic by collaborating practicing rheumatologists were screened. Of the 176 patients, 170 were found eligible to participate in the trial and subsequently received either CYC (n = 57) or adalimumab (n = 58) or their combination (n = 55). There was no clinical bias in the allocation of patients in any of the 3 groups; 76 patients were assigned randomly; however, further randomization was not possible due to logistic reasons related to inability of covering the cost of adalimumab in 32 patients who participated in the study; these patients instead received CYC. The remaining 62 patients were randomly assigned to the adalimumab group (n = 32) and the combination therapy group (n = 30). Reduction or discontinuation of adalimumab and/or CYC in responding patients, as well as concomitant NSAID and corticosteroid doses in every responding patient, was not restricted. Clinical variables were assessed and laboratory evaluations were obtained at baseline, at Day 15, and at Months 1, 2, 3, 4, 5, 6, 8, 10, and 12. All assessments were performed by rheumatologists in an open-label fashion.

The study was conducted according to the Declaration of Helsinki and approved by ethical committees in regard to existing regulations.

The primary efficacy endpoint was the Psoriatic Arthritis Response Criteria (PsARC) at 12 months, which was modified by using a 0–100 mm visual analog scale (VAS) for the patient or physician global assessment of disease activity, instead of the Likert scale used in the original PsARC[13]. We considered as treatment failures those patients in whom the arthritic condition and/or psoriasis remained unchanged or deteriorated at 12 weeks, as well as those patients who did not fulfill PsARC response criteria at the end of the trial. Other efficacy variables included the 20%, 50%, and 70% improvements in the American College of Rheumatology response criteria (ACR20, ACR50, and ACR70) for determining improvement in RA[14], as well as the 20-question Disability Index of the Health Assessment Questionnaire (HAQ-DI; score 0–3)[15]. Additional response evaluations included the following: erythrocyte sedimentation rate (ESR; Westergren), C-reactive protein (CRP) by laser nephelometry, total number of tender and swollen joints (those routinely evaluated in RA plus the first carpal metacarpal phalangeal joints and the distal interphalangeal joints of the toes), patient's VAS assessment of pain, patient's global VAS assessment of disease activity, doctor's global VAS assessment of disease activity, evaluation of dactylitis (uniform swelling of an entire digit) of the hands and feet (using the total score of 0–60, with each digit rated 0 = absent to 3 = severe), and evaluation of enthesitis, by clinical examination of the proximal insertion of the Achilles tendon and plantar fascia (using the total score of 0–4, with each insertion rated 0 = enthesitis absent or 1 = present). For patients with prominent axial involvement, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was applied[16]. For patients with psoriasis involving at least 2.5% of body surface area at baseline the Psoriasis Area and Severity Index (PASI)[17] was used at baseline and 6 and 12 months; PASI was also used to assess the response of psoriasis rated as 50% improvement (PASI50), 75% improvement (PASI75), and 90% improvement (PASI90). For the PASI score, skin lesions were rated on the basis of erythema, induration, desquamation, and anatomic location (head, trunk, upper extremities, and lower extremities), with the involved area of each anatomical part factored into the overall value. The Nail Psoriasis Severity Index (NAPSI), evaluating nail matrices and nail beds of both hands, was used for the evaluation of possible psoriatic nail disorder (score 0–80)[18].

Safety was assessed in terms of possible adverse events by means of full clinical evaluation at every visit, while at the same time patient opinion was taken under consideration. Laboratory evaluations including routine hematology, clinical blood chemistry tests, and urinalysis were considered in the safety assessments. Serious adverse events were defined as any adverse reaction resulting in death or life-threatening condition, a significant or permanent disability/incapacity, a malignancy, or hospitalization.

Statistics. All available data of the intent-to-treat (ITT) population were used in this analysis and the last observation carried forward technique was used. Analysis of data was based on descriptive and inferential statistical methods. Measures of central tendency and dispersion were calculated for all variables at study entry. Chi-square test (or Fisher's exact test in case of low cell count) was used to assess the differences of ACR, PsARC, and PASI outcomes between treatments, and OR were calculated respectively. Mixed-model analysis was employed to evaluate the alteration of all clinical variables from baseline to 6 months and 12 months. Time, treatment, and time × treatment were treated as fixed factors, while patients were fitted as a random effect. Least-square means and differences with the associated 95% CI are presented as generated by the mixed models. Exploratory plots were produced in order to illustrate the relationship between treatments. All tests were 2-sided and statistical significance was set at 5%.

RESULTS

Baseline characteristics and disposition of patients. As shown in Table 1, baseline demographic and disease characteristics were comparable between the CYC group (n = 57), the adalimumab group (n = 58), and the combination therapy group (n = 55), with the exception of 2 significant differences in disease characteristics concerning the number of tender joints and HAQ-DI; both were less pronounced in the CYC group despite a longer (not significant) disease duration. Patients' progress through the study is presented in Figure 1. A Kaplan-Meier analysis showed that overall withdrawals had no statistical difference between the 3 patient groups (data not shown). The proportion of total discontinuations was higher during the initial 6 months (25 patients) than the following 6 months (8 patients).

Clinical outcome. Percentages of patients in the 3 groups who met PsARC criteria at 6 and 12 months are shown in Figure 2. At 6 months, combination treatment appeared to be superior to CYC, but not to adalimumab (combination vs CYC: OR 5.3, 95% CI 2.1 to 13.2, p = 0.0004; and adalimumab vs combination: OR 0.4, 95% CI 0.2 to 1.1, p = 0.09); similar results were observed at 12 months (combination vs CYC: OR 9.4, 95% CI 2.6 to 33.8, p = 0.0003; and adalimumab vs combination: OR 0.3, 95% CI 0.1 to 1.2, p = 0.15). It should be noted that regarding the combination group, in addition to 3 patients who discontinued therapy because of lack of efficacy (not fulfilling PsARC response criteria; Figure 2), an additional patient with severe psoriasis was withdrawn because of persisting cutaneous lesions at the 18th week, although presenting a clear PsARC response.

As shown in Figure 3, combination-treated patients demonstrated significantly higher ACR20 (combination vs

Table 1. Baseline characteristics of patients treated with cyclosporine, adalimumab, or combination of the 2 for active psoriatic arthritis (PsA) despite methotrexate therapy.

Characteristic	Cyclosporine, n = 57, mean ± SD	Adalimumab, n = 58, mean ± SD	Combination, n = 55, mean ± SD
Age, yrs	45.9 ± 12.8	46.8 ± 14.1	45.9 ± 14.4
Female sex, %	49.1	55.2	56.4
Psoriasis duration, yrs	8.0 ± 11.3	7.8 ± 12.1	8.1 ± 11.5
PsA duration, yrs since first articular manifestation*	4.0 (1.0–10.0)	4.0 (1.0–10.0)	2.0 (1.0–5.0)
Early disease (< 2 yrs), %	40.4	43.1	54.6
Previous methotrexate dosage, mg*	15.0 (12.5–20.0)	15.0 (12.5–17.5)	15.0 (12.5–20.0)
Tender joints, n**	9.7 ± 8.0	13.0 ± 10.0	14.5 ± 11.7
Swollen joints, n	6.7 ± 6.5	7.8 ± 6.4	9.4 ± 9.6
Pain, VAS, mm	50.2 ± 23.0	58.6 ± 22.4	54.7 ± 23.2
Patient global, VAS, mm	51.6 ± 23.5	59.7 ± 21.9	57.0 ± 21.1
Physician global, VAS, mm	50.3 ± 23.4	57.3 ± 22.2	52.5 ± 18.8
HAQ***	1.01 ± 0.6	1.28 ± 0.7	1.35 ± 0.6
PASI	16.5 ± 12.0 (n = 41)	14.1 ± 13.1 (n = 43)	15.7 ± 11.1 (n = 44)
ESR, mm/h	40.3 ± 23.5	50.3 ± 22.7	47.1 ± 23.9
CRP, mg/dl	15.9 ± 18.1	24.1 ± 22.1	18.7 ± 15.9
Axial involvement, %	11	12	12
RF+, %	11	12	10
ACPA+, %	5	6	6
HLA-B27+, %	23	23	24
Systemic steroids, %	24	23	23

* Values without a normal distribution are expressed as median (25th–75th percentile). ** p = 0.0364. *** p = 0.0086. RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; VAS: visual analog scale; PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

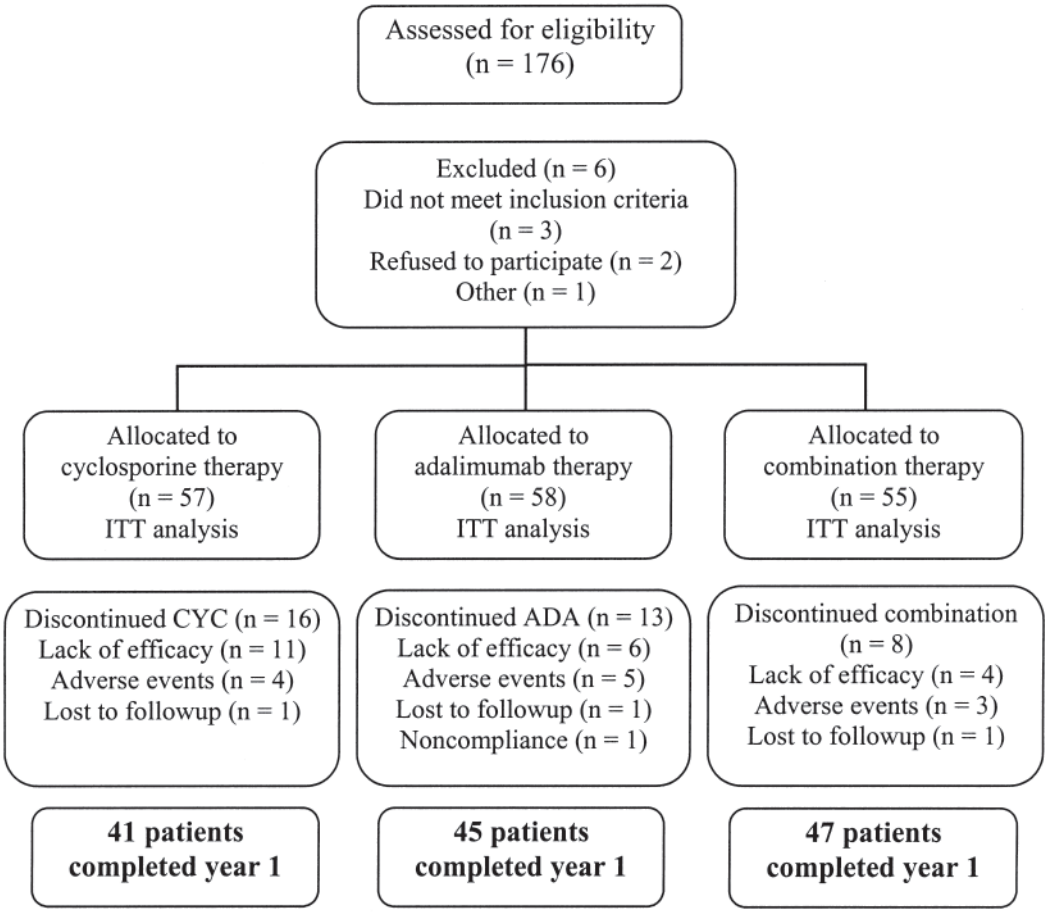

Figure 1. Patient progression through the study. CYC: cyclosporine; ADA: adalimumab; ITT: intent to treat.

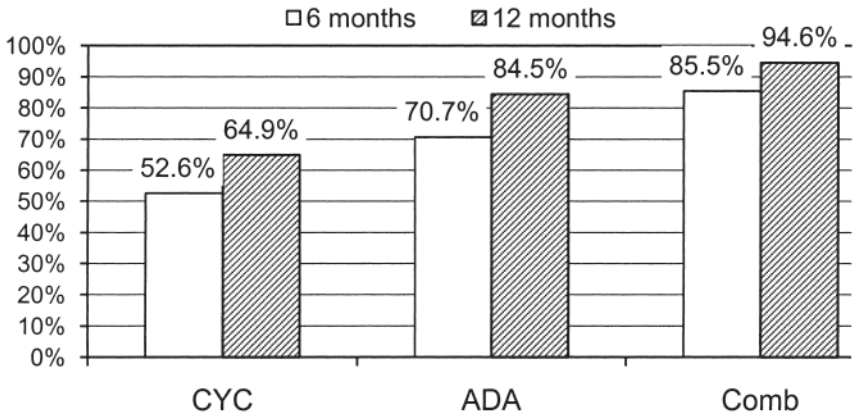

Figure 2. PsARC (Psoriatic Arthritis Response Criteria) response rates at 6 and 12 months in patients treated with cyclosporine (CYC), adalimumab (ADA), or their combination for active PsA.

CYC: OR 10.1, 95% CI 2.8 to 36.4, p = 0.0001; and adalimumab vs combination: OR 0.2, 95% CI 0.1 to 0.7, p = 0.02) and ACR50 (combination vs CYC: OR 11.8, 95% CI 4.5 to 30.6, p < 0.0001; and adalimumab vs combination: OR 0.3, 95% CI 0.1 to 0.8, p = 0.03) response rates compared to those treated with monotherapy at 12 months. At Month 6, the rates of the more stringent ACR70 response criteria were higher only in the combination vs CYC-treated group (24% vs 5%; OR 5.6, 95% CI 1.5 to 20.8, p = 0.01), but this superior improvement was more obvious at 12

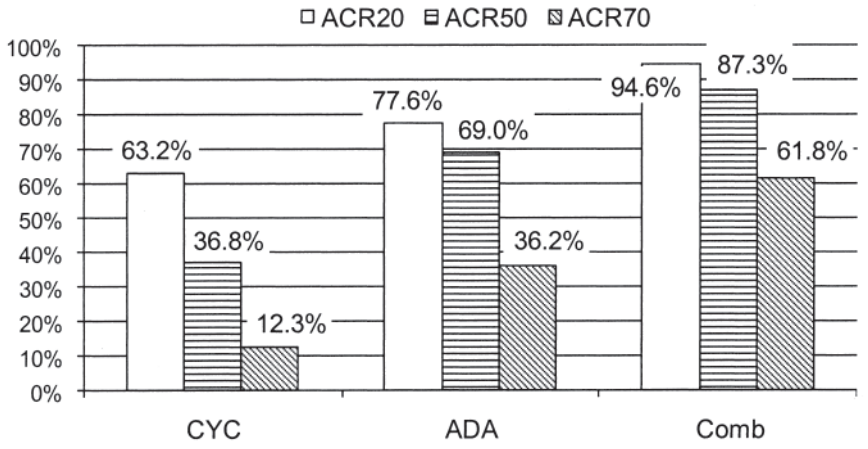

Figure 3. ACR (American College of Rheumatology) response rates at 12 months in patients treated with cyclosporine (CYC), adalimumab (ADA), or their combination for active PsA.

months vs both monotherapy groups (62% vs 12% and 36%, respectively, combination vs CYC: OR 11.6, 95% CI 4.4 to 30.2, $p < 0.0001$; and adalimumab vs combination: OR 0.3, 95% CI 0.2 to 0.7, $p = 0.01$). Moreover, inflammatory markers were gradually improved: ESR was reduced in the CYC-treated patients (–9.7 and –13.7 mm/h at 6 and 12 months, respectively), in the adalimumab-treated patients (–22.7 and –29.4 mm/h at 6 and 12 months), and in the combination-treated patients (–25.7 and –31.2 mm/h at 6 and 12 months; $p = 0.0002$ in favor of combination vs CYC; $p = 0.704$ combination vs adalimumab), while CRP was reduced in the CYC group (–7 and –8.8 mg/dl at 6 and 12 months, respectively), in the adalimumab group (–11.1 and –15 mg/dl at 6 and 12 months), and in the combination group (–12.9 and –14.9 mg/dl at 6 and 12 months; $p < 0.04$ in favor of combination vs CYC; $p = 0.982$ combination vs adalimumab).

At 12 months, 58% of CYC-treated, 74% of adalimumab-treated, and 93% of combination-treated patients had a decrease in PsA HAQ-DI score > 0.3 (difference in HAQ-DI from baseline to 12 months: –0.416 in CYC, –0.853 in adalimumab, and –1.117 in the combination group; $p < 0.0001$ and $p = 0.02$ for CYC and adalimumab vs combination group, respectively). Further, 25% of patients in the CYC group, 60% in the adalimumab group, and 68% in the combination group reached a completely normal physical function status (HAQ = 0) at 12 months ($p = 0.002$ in favor of combination vs CYC group). In patients receiving corticosteroid treatment, the mean prednisolone dosage at the end of the study was 5.3 (SD 3.2) mg/day, 4.7 (SD 3.1) mg/day, and 3.5 (SD 2.8) mg/day, in the CYC, adalimumab, and combination groups, respectively. The use of oral prednisolone did not offer an increased clinical benefit in any of the 3 groups (within-group comparison, data not shown).

In 119 patients who had skin involvement on at least 2.5% of body surface area at baseline, all 3 treatment modalities resulted in a significant reduction in the extent of psoriasis at all study visits. The percentages of patients who achieved improvement in PASI 50, 75, and 90 scores at 6 months were calculated for the CYC group: 55%, 25%, and 2.5%, respectively; for the adalimumab group: 44%, 23%, and 8%; and for the combination group: 71%, 37%, and 14%. As shown in Figure 4, at the end of the trial, 65% of CYC-treated patients had PASI50 improvement (combination vs CYC: OR 2.8, 95% CI 1.0 to 8.0, $p = 0.07$), 45% had PASI75 (combination vs CYC: OR 2.6, 95% CI 1.1 to 6.4, $p = 0.05$), and 27.5% had PASI90 (combination vs CYC: OR 1.8, 95% CI 0.7 to 4.6, $p = 0.28$). Notably, combination therapy significantly improved psoriasis beyond adalimumab's monotherapy effect (adalimumab vs combination: OR 0.2, 95% CI 0.1 to 0.6, $p = 0.005$ for PASI50; OR 0.1, 95% CI 0.0 to 0.3, $p < 0.0001$ for PASI75; and OR 0.1, 95% CI 0.0 to 0.5, $p = 0.001$ for PASI90). Also, in PASI 75 and 90, CYC-treated patients achieved a significant reduction compared to adalimumab-treated patients ($p = 0.03$ and $p = 0.04$, respectively).

Active axial disease, defined as BASDAI score > 4 at baseline, was present in 11, 12, and 12 patients in the CYC, adalimumab, and combination groups, respectively. At 12 months, a treatment response of spondylitis, defined as a reduction by at least 2 points of the BASDAI score, was observed in 1 (9%) patient in the CYC group, 5 (41%) in the adalimumab group, and 11 (92%) in the combination group. Dactylitis, defined as uniform swelling of a digit, was present in 7 patients at study entry (mean digit score 2.6 ± 2.1), 8 patients (mean digit score 1.9 ± 2.3), and 10 patients (mean digit score 2.5 ± 2.1) of the CYC, adalimumab, and combination groups, respectively. Improvement, defined as > 50% mean reduction of the dactylitis score, was observed in 2 (28.5%), 6 (75%), and all 10 (100%) patients in the CYC, adalimumab, and combination groups. Enthesitis was present in 13 patients of the CYC group (total sites = 1 ± 1.1), 14 of the adalimumab group (total sites = 0.9 ± 1.1),

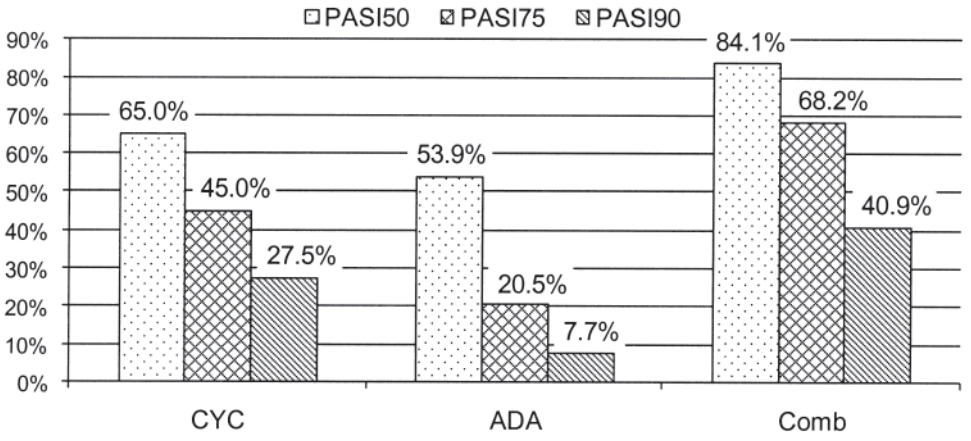

Figure 4. PASI (Psoriasis Area and Severity Index) response rates at 12 months in patients treated with cyclosporine (CYC), adalimumab (ADA), or their combination for active PsA.

and 14 of the combination group (total sites = 0.9 ± 1.2), and had resolved at 12 months in 2 (15%), 12 (86%), and 11 (78.5%) patients in the 3 groups. Finally, there were 18 CYC-treated patients, 16 adalimumab-treated patients, and 21 combination-treated patients in whom psoriatic nail dystrophy was evident at baseline, with a mean NAPSI > 10 in almost 70% of these patients. At 12 months, 8 patients (44%) in the CYC group, 9 (56%) in the adalimumab group, and all 21 (100%) patients in the combination group had improvement > 50% in NAPSI score.

Adjustment of drug doses. Administration of NSAID was discontinued in 9% of CYC-treated patients, 16% of adalimumab-treated patients, and 24% of combination-treated patients, while in 3% of the CYC group, 24% of the adalimumab group, and 35% of the combination group, administration of corticosteroids was stopped. Among CYC-treated patients, corticosteroid treatment was started in 3 corticosteroid-naive patients, while in 18 patients, an increase of the daily dose was considered necessary. In 14% of patients receiving adalimumab monotherapy, the frequency of injections was increased (every 7–12 days), while in contrast, in 10% of those receiving combination treatment, this frequency was decreased (3–4 weeks). In 37% of patients receiving CYC monotherapy the dosage was increased (25%–75%), while in 51% of those receiving combination treatment, the dosage of CYC was decreased. At 12 months the mean CYC dosage in the monotherapy group was 3.24 (SD 2.1) mg/kg/day, while in the combination group CYC dosage was 1.92 (SD 1.5) mg/kg/day.

Safety. The incidence of clinical adverse events observed during the 12 months was 77% for the CYC group, 69% for the adalimumab group, and 60% for the combination group (Table 2). Adverse events were in general predominantly mild to moderate in severity and intensity. There were 3 serious events observed in the CYC arm leading to drug discontinuation. These included a case of atrial fibrillation (14th week), a case of uncontrolled hypertension (6th week), and a case of persistent erectile dysfunction (27th week). Four serious adverse events occurred in 4 adalimumab-treated patients, 3 of whom required hospitalization: pneumonia (8th month), pericarditis (4th month), and pancreatitis at 7th month of followup. In this group, a case of severe psoriasis aggravation was also observed at 5 months. Two patients were withdrawn from the combination arm, one because of nonpalpable purpura and the other due to severe leukopenia, both of whom were reported at Week 11 after initiation of the treatment. Both adverse events were resolved after the treatment's cessation.

Throughout the 12 months of the study, 5% of CYC-treated patients, 9% of adalimumab patients, and 7% of combination patients had an alanine aminotransferase or aspartate aminotranferase value ≥ 3 times upper limit of normal. Most of adalimumab and/or combination-treated patients with elevated liver enzymes were concomitantly receiving isoniazid. Most deviations in transaminase values were transient and were resolved during uninterrupted treatment by dosage tapering of active drugs or antituberculosis prophylaxis medication. Thirteen CYC-treated (23%) and 2 combination patients (2%) presented an increased serum creatinine concentration (> 30% of the initial value).

DISCUSSION

Our study provides the first information on the efficacy and safety of the combination of a TNF-α antagonist with a calcineurin inhibitor in treatment of patients with PsA in whom active disease persisted under MTX therapy. Because the study was not randomized and the assessment was not blind, baseline numbers of tender joints and scores of HAQ-DI were significantly different among the 3 groups of patients. Thus, patients who received adalimumab, either as monotherapy or combination, had significantly more tender

Table 2. Adverse events (AE) observed during 12 months in patients treated with cyclosporine, adalimumab, or their combination for active psoriatic arthritis (PsA).

Adverse Event	Cyclosporine, n = 57, %	Adalimumab, n = 58, %	Combination, n = 55, %
Any AE	44 (77.19)	40 (68.96)	33 (60.00)
Any serious AE	3 (5.26)	4 (6.90)	2 (3.64)
Any AE leading to discontinuation of study drug	4 (7.02)	5 (8.62)	3 (5.45)
Any infectious AE	2 (3.51)	6 (10.34)	3 (5.45)
Any serious infectious AE	0 (0)	1 (1.72)	0 (0)
Common clinical AE (≥ 3% in either study branch)			
Upper respiratory tract infection	1 (1.75)	5 (8.62)	1 (1.82)
Urinary tract infection	1 (1.75)	1 (1.72)	2 (3.64)
Hypertension	9 (15.79)	1 (1.72)	1 (1.82)
Aggravated psoriasis	1 (1.75)	3 (5.17)	0 (0)
Aggravated PsA	7 (12.28)	3 (5.17)	0 (0)
Nausea/dizziness	3 (5.26)	0 (0)	1 (1.82)

joints and worse functional status than the remaining patients. Considering these limitations, there are 3 novel findings. First, the combination of adalimumab and CYC seemed to produce a major improvement in both clinical and serological variables, while many patients under the combined treatment were able to reduce the dose of each individual agent. Second, adalimumab appeared to be more effective than CYC in joint disease, but not in skin disease. Third, there were no unexpected or serious side effects in patients receiving the combination therapy during the 12-month period. Patients assigned to the combination group exhibited a smaller incidence of adverse events, a finding that may result from dosage reductions of the combined drugs. However, these results should be interpreted with caution because the study was not randomized, and the assessment was not blinded.

The PsARC was used as the primary efficacy endpoint within the study. We found that the combination therapy was superior only to CYC, at both 6 and 12 months, but not to adalimumab. In contrast, combination treatment appeared to be superior to both monotherapies in ACR50 and ACR70 response indices. This is not surprising because PsARC, although it evaluates a joint count that comprises the hand distal interphalangeal joints and foot joints, does not allow quantification of disease activity[13,19]. Moreover, in controlled studies PsARC has a low clinical sensitivity vs placebo, resembling the ACR20, while it failed to show differences between therapies in the initial trial in which it was used[13]. Of the 11 combination-treated patients, 92% showed improvement in axial involvement. Even though CYC monotherapy is not recommended for treatment of axial involvement in spondyloarthropathies, some CYC-treated patients who were unable to receive adalimumab showed a mild form of spondylitis, while at the same time they had severe active peripheral synovitis and psoriatic rash as well. Although no formal analysis was performed, many combination-treated patients also presented a dramatic response in some less frequent manifestations of PsA, such as enthesitis, dactylitis, and nail disease. Another clinical measure pointing to the efficacy of the combination regimen was the prominent decreases of dosages of CYC and adalimumab in these patients. The alleviation of NSAID in 24% and steroids in 35% of the combination-treated patients also suggests the effectiveness of the combination. The treatment recommendations for PsA from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis stressed that systemic steroid therapy for treatment of PsA is recommended only under special circumstances[4,20]. However, as in our study, almost 1 out of 4 patients with PsA is receiving prednisolone in daily clinical practice[4]. It should be noted that, in general, our patients were receiving low doses of corticosteroids, while some of them had severe articular manifestations, vigorous fatigue, and stiffness.

The great majority of patients receiving combination treatment achieved a clinically significant reduction of HAQ-DI, as defined by > 0.3-point improvement, compared to the CYC and adalimumab-treated patients. It is well known that patient-reported outcomes, including HAQ, discriminate better than physician-reported outcomes between placebo and active drug in RA[21], and that greater disability or reduced functional status in patients with RA is associated with increased mortality[22]. Although peripheral joint damage may be less in PsA than in RA, degrees of disability and functional limitations are often similar[23]. Patients under adalimumab monotherapy reported a significant reduction in HAQ at 12 months compared to baseline (ΔHAQ-DI = –0.85). In the 24-week ADEPT study (Adalimumab Effectiveness in Psoriatic Arthritis Trial), the largest controlled study of a TNF-α antagonist in the treatment of PsA, Mease, *et al* also found a significant improvement in the HAQ-DI score (mean change = –0.40) among patients receiving adalimumab, compared to those receiving

placebo[6]. Gladman, *et al*, in the ACCLAIM open-label 12-week trial, found a reduction of HAQ-DI (–0.44) that was similar to that observed in the ADEPT trial[24]. In our study, differences in study requirements and baseline clinical components, longer duration, and the fact that all participating patients were biological agent-naive could account for the larger improvements, compared to those reported in the ACCLAIM and ADEPT studies.

In patients with PsA, cutaneous lesions negatively influence quality of life[25]. Combination therapy significantly improved PASI50 and PASI90 response rates beyond those of adalimumab, but not beyond those of the effect of CYC monotherapy. This was in contrast to the respective results on arthritis, implying different pathogenic mechanisms of skin and joint inflammation. Indeed, the CYC group showed a statistically significant result in PASI75 and PASI90, compared to the adalimumab group, while the percentage of PASI90 responders increased from 2.5% at Week 24 to 27.5% at 12 months. Accordingly, the combination-treated patients achieved a significant reduction of PASI50, PASI75, and PASI90 vs adalimumab-treated patients, while they demonstrated only a marginally better effect in the PASI75 compared to the CYC arm. To our knowledge, no published data exist on the comparison of a TNF-α antagonist and a conventional DMARD for the management of psoriasis, with the exception of a controlled trial that proved the superior efficacy of adalimumab vs MTX[26]. In a study that examined the efficacy of CYC vs MTX in moderate to severe chronic plaque psoriasis, CYC was superior in the benefit-risk ratio compared to MTX[27]. Controlled double-blind trials are needed to confirm our finding that CYC, an agent that blocks the amplification of cellular immune responses and generation of T cell effectors, appears to be more efficient in reducing skin involvement of PsA compared to a TNF-α inhibitor. Two recent 24-week open-label trials have shown the efficacy of CYC in improving cutaneous manifestations of PsA that were refractory to anti-TNF-α monotherapy. In the first study, 11 out of 103 consecutive patients with PsA receiving etanercept had insufficient response to skin disease, while being in remission of arthritis. The addition of CYC 3 mg/kg/day resulted in achievement of PASI75 in 9 of 11 patients, and no patient withdrew because of lack of efficacy[28]. In the second study, 41 patients with PsA were randomized to receive either etanercept plus MTX or etanercept plus CYC, with a good balance in regard to baseline characteristics. At the end of the study, although both therapies were equally effective in terms of DAS28 scores, the combination of etanercept with CYC was more efficacious in reducing psoriatic skin involvement[29].

Previous studies failed to show that the combination of a TNF-α inhibitor with MTX offered an additive clinical benefit in PsA, compared to anti-TNF-α monotherapy. Mease, *et al*, analyzing the results of their own 2 controlled trials in patients with PsA using etanercept and adalimumab, respectively, suggested that the ACR responses were essentially similar in subsets of patients who received or did not receive concomitant MTX[6,30]. Gladman, *et al*, after expanding the ADEPT for a 24-week open-phase period, confirmed that adalimumab treatment appeared to be efficacious for joint and skin disease of PsA, whether patients were receiving MTX at baseline or not[31]. Virkki, *et al*, using the Finnish national register of biological treatment, ascertained that use of MTX in patients with PsA under anti-TNF-α treatment (infliximab or etanercept) was not statistically associated with a higher response rate[32]. Kavanaugh, *et al*, in the GO-REVEAL study that assessed efficacy and safety of golimumab, a new anti-TNF-α agent in PsA, concluded that benefit was seen at Week 14 irrespective of use of MTX[33]. On the other hand, data presented here suggest that combination of adalimumab and CYC is more efficacious than adalimumab monotherapy, providing the potential for synergy between an anticytokine drug and a T cell immunoregulatory agent in treatment of refractory PsA.

Finally, it is encouraging that no serious, paradoxical, or unexpected short-term toxicities from combination of adalimumab and CYC were observed in patients in our study. Extensive controlled followup studies are needed to acquire more information on the efficacy of combination CYC/anti-TNF-α agent and the absence of delayed toxicity in PsA.

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