Sustained Clinical Response and High Infliximab Survival in Psoriatic Arthritis Patients: A 3-year Long-Term Study

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Objective: To investigate the efficacy, toxicity, and survival of infliximab in patients with psoriatic arthritis (PsA).

Methods: Thirty-two patients with PsA, refractory to at least 2 disease-modifying antirheumatic drugs, were included in this prospective, open-label, uncontrolled study. All had active disease, defined as having a tender or swollen joint count ≥6, Psoriasis Area and Severity Index (PASI) scores ≥10, and erythrocyte sedimentation rate ≥28 mm Hg/h, or C-reactive protein ≥10 mg/L. The primary endpoints were the percentage of patients who achieved the Psoriatic Arthritis Response criteria (PsARC) and the improvement of PASI. Patients were treated with infliximab (5 mg/kg) at weeks 0, 2, 6, and every 8 weeks thereafter for a period of 3 years. Data concerning infliximab efficacy, tolerability, concomitant therapy, adverse events, and drug discontinuation were recorded. The clinical response according to the American College of Rheumatology (ACR) criteria as well as the disease activity for 28 joint indices score (DAS-28) were also recorded.

Results: After the third year of treatment, PsARC was achieved by 23/32 of patients, PASI 70 by 24/32, and PASI 90 by 23/32. A significant improvement of ACR and DAS-28 was noted. Clinical improvement was associated with a reduction of acute phase reactants. Eight patients withdrew from the study primarily for acute allergic reactions. After the first year, infliximab survival was 84%, while after the second year, it was 75%, which was maintained throughout the third year of treatment.

Conclusion: Infliximab was effective, safe, and well tolerated in patients with PsA. The clinical response was maintained for a period of 3 years with high infliximab survival.

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Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy with a prevalence between 0.05 and 1% and an equal sex distribution. Psoriasis affects 1 to 3% of the population, with approximately 30% of patients developing PsA (1-3). It is a heterogeneous group of joint diseases ranging from mild synovitis to severe erosive arthritis. Erosive and deforming arthritis occurs in 40 to 60% of PsA patients and is progressive from the first year of diagnosis (4,5). On the other hand, psoriasis is a common, persistent, relapsing inflammatory skin disease that can be associated with significant morbidity. Quality-of-life studies in psoriasis reveal a negative impact on patients comparable with that seen in cancer, rheumatoid arthritis, and heart disease (6-8). All standard systematic therapies for severe psoriasis and PsA are associated with the potential for major long-term toxicity and a proportion of patients have treatment-resistant disease (5,9).

Biological therapies have emerged over the last 6 years as potentially valuable alternative options for both diseases (10,11). Currently, agents targeting tumor necrosis factor-α (TNF-α), etanercept, infliximab, and adalimumab are licensed for the treatment of PsA and psoria-

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sis. Several randomized controlled trials and open-label studies suggest that these TNF-α blockers lead to an improvement in skin and joint manifestations in PsA patients (12-16).

Infliximab, a chimeric monoclonal anti-TNF-α antibody, was effective and safe in a number of short controlled trials in PsA (14,15,17,18). However, a large number of patients stopped therapy because of lack of efficacy or because of adverse drug reactions (18). Thus, it is important to know how long infliximab is effective and which are the most frequent and serious adverse events. In an attempt to answer these questions, we investigated the efficacy, toxicity of infliximab therapy, and drug survival in patients with refractory PsA and recalcitrant psoriasis.

MATERIALS AND METHODS

In a recent epidemiological study by our group, 221 patients with PsA were identified, giving a prevalence of 56.6 cases per 100,000 inhabitants and an incidence of 3.02 cases per 100,000 inhabitants (2). From these, 41 patients with severe PsA and recalcitrant severe psoriasis were recruited into this prospective, uncontrolled, open-label study between January 2003 and December 2003 from the rheumatology clinic of the University Hospital of Ioannina, Greece. All patients fulfilled the European Spondylarthropathy Study Group criteria (19) and were refractory to at least 2 disease-modifying antirheumatic drugs (DMARDs). Despite the fact that the above European Spondylarthropathy Study Group criteria were the most acceptable for the classification of PsA, these criteria have a low sensitivity and specificity (20).

All patients had active disease, which was defined as having a tender or swollen joint count $\geq$6, Psoriasis Area and Severity Index (PASI) score $\geq$10, and erythrocyte sedimentation rate $\geq$28 mm Hg/h or C-reactive protein $\geq$10 mg/L (21,22). The primary endpoints were the percentage of patients who achieved the Psoriatic Arthritis Response criteria (PsARC) and improvement of PASI (23). Patients were treated with infliximab (5 mg/kg) at weeks 0, 2, 6, and every 8 weeks thereafter for a period of 3 years. If the clinical response was insufficient, the interval between infusions was shortened to 6 or 4 weeks. Patients were followed up at predefined times every 2 months, according to a standardized protocol. Data concerning infliximab efficacy, tolerability, concomitant therapy, adverse events, and drug discontinuation were recorded. In addition, the clinical response according to the American College of Rheumatology (ACR) 20, 50, and 70% criteria as well as the disease activity for the 28 joint indices score were also recorded at each patient's visit (24,25). Patients were excluded from the study if they had (a) a history or presence of malignant disease; (b) known liver or kidney abnormalities or history of viral hepatitis B and C; (c) major complicating illnesses such as heart or lung disease, blood dyscrasia, or amyloidosis; (d) positive tuberculin skin test using purified protein derivative (PPD)/RT23 (2 IU/0.1 mL), or an abnormal chest radiograph suggesting chronic infectious granulomatous disease, or other pathological findings. The protocol was approved by the Institutional Scientific Board of the University Hospital of Ioannina, Greece. Patients were entered into the study after reading and signing an informed consent form. All patients had a last follow-up examination in February 2007.

Definitions

Refractory PsA was defined as increasing DMARDs dosage above the standard dosage regimen, using combination therapy, and adding or increasing the dosage of corticosteroids. *Lack of efficacy* was defined as patients not fulfilling the PsARC and/or with minimal improvement of PASI score ($<$20%). *Failure of drug treatment* was defined as patients who stopped receiving the drug for more than 2 months because of lack of efficacy. *Adverse drug reactions* were defined as patients who had reactions that required the permanent discontinuation of infliximab due to life-threatening conditions or because of intolerability. *Discontinuation* was defined as patients who failed drug treatment or experienced adverse drug reactions.

Laboratory Monitoring

A complete blood count with differential and platelet count, serum liver enzymes, bilirubin, albumin, glucose, creatinine, and urine analysis were obtained before treatment and at each visit. Finally, 2 mL of serum at each visit was collected and stored at -20°C for the measurement of antibody profile.

Statistical Analysis

Standard methods of survival analysis (Kaplan–Meier) were used in which infliximab termination due to side effects, lack of efficacy, or failure of drug treatment were taken as endpoints.

RESULTS

From our cohort of 221 PsA patients, only 41 were eligible, fulfilling entry criteria. Of these, 3 refused treatment and 6 were excluded from the study (2 patients had a positive PPD skin test, 2 had type 2 diabetes mellitus, 1 was positive for hepatitis C virus infection, and another had congestive heart failure). Thus, 32 patients with negative PPD skin tests and normal chest radiographs were included in the study. The demographic, clinical, and laboratory data are shown in Table 1. There were 20 men and 12 women, with a mean age of 52.4 $\pm$ 16.0 years, psoriatic skin disease duration of 14.5 $\pm$ 11.0 years, and arthritis disease duration of 9.7 $\pm$ 6.3 years. Twenty-four patients had asymmetrical polyarthritis, 3 had classical PsA, 3 had symmetrical polyarthritis, and 2 had axial involvement. All patients had active disease with a high total joint count for tenderness and swelling, a high PASI score, and high levels of C-reactive protein and erythrocyte sed-

Table 1 Demographic and clinical features of 32 PsA patients treated with infliximab

Variables	Number
Age (yr) (mean ± SD)	52.4 (16.0)
Female/male, N (%)	12/20 (38/63)
Arthritis disease duration (yr) (mean ± SD)	9.7 (6.3)
Psoriasis disease duration (yr) (mean ± SD)	14.5 (11.0)
Swollen joints (mean ± SD)	7.5 (1.2)
Tender joints (mean ± SD)	7.8 (1.8)
DAS-28 (mean ± SD)	6.1 (1.1)
PASI (mean ± SD)	48.8 (10.5)
MTX + CsA intake, N (%)	20 (63)
MTX + LFN intake, N (%)	7 (22)
CsA + LFN intake, N (%)	5 (16)
Prednisone intake (5 mg/d), N (%)	10 (31)
ESR (mm/1st hour) (mean ± SD)	33.9 (11)
CRP (mg/L) (mean ± SD)	16.1 (5)

imentation rate. Twenty patients were on methotrexate (MTX) plus cyclosporine A (CsA), 7 patients were on MTX plus leflunomide (LFN), while 5 patients were on CsA plus LFN. Ten patients were taking small doses of prednisone (5 mg/d).

The study profile and the response to treatment are shown in Figure 1. After the first year of treatment, PsARC was achieved by 26/32 (81%) patients, while PASI 70% was reached by 27/32 (84%) and PASI 90% was reached by 26/32 (81.3%) patients. After the second year of infliximab therapy, PsARC was reached by 23/32 (72%), while PASI 70% and 90% was attained by 24/32 (75%). After the third year of therapy, PsARC was achieved by 23/32 (72%), while PASI 70% was reached by 24/32 (75%) and PASI 90% was reached by 23/32 (72%) (Fig. 1) The response to treatment was rapid and, after 6 months of infliximab therapy, the skin lesions had cleared and healed in the majority of patients (Fig. 2). This clinical improvement was sustained for 3 years, as shown in Figure 1. A similar clinical response was seen when the ACR response criteria were applied. More specifically, after the third year of treatment, ACR 20% was reached by 24/32 (75%), ACR 50% by 20/32 (63%), while ACR 70% was reached by 10/32 (31%) (Fig. 3). In addition, a significant reduction in the DAS-28 and the acute phase reactants was noted during the study (Fig. 4).

After the first year of treatment, 84% of patients continued treatment with infliximab, whereas this rate was 75% after the second year and remained the same during the third year (Fig. 5). Eight patients discontinued infliximab therapy, 5 during the first year, and 3 more during the second year (Fig. 1). More specifically, 5 patients discontinued the study due to immediate hypersensitivity reactions, 1 due to lack of efficacy, while 2 patients were lost to follow-up. In the 5 patients who did not respond to infliximab therapy, the dosage interval was shortened to every 6 weeks in 3 patients and to every 4 weeks in 2. This happened after the first year of treatment, when 10 days before the infliximab infusion these patients experienced aching and pain of their joints. After this treatment regimen, all patients responded well and continued the study. Finally, 10 patients developed antinuclear antibodies; 2 developed low titer anticardiolipin antibodies of IgM class and 1 patient developed anti-double-stranded DNA antibodies. None developed systemic lupus erythematosus.

DISCUSSION

During recent years, much has been learned about the immunopathology of psoriasis and PsA. There is evidence that proinflammatory cytokines, particularly TNF-α, may play a pivotal role in potentiating the inflammatory process (26). Increased levels of TNF-α have been observed in skin, synovial fluid, and synovial tissue from affected patients and allelic polymorphisms in the promoter region for TNF-α have correlated with certain aspects of the disease (27-30). Infliximab is effective in both psoriasis and PsA by decreasing the infiltration in skin lesions and inflamed synovial tissue soon after initiation of treatment (31). In an open-label study of infliximab in severe PsA with recalcitrant psoriasis, we reported a significant clinical benefit accompanied by clearing and healing of psoriatic skin lesions (32,33). On the basis of these results, we conducted a long-term observational study to evaluate the efficacy and safety of infliximab in patients with active severe PsA, and recalcitrant severe psoriasis in

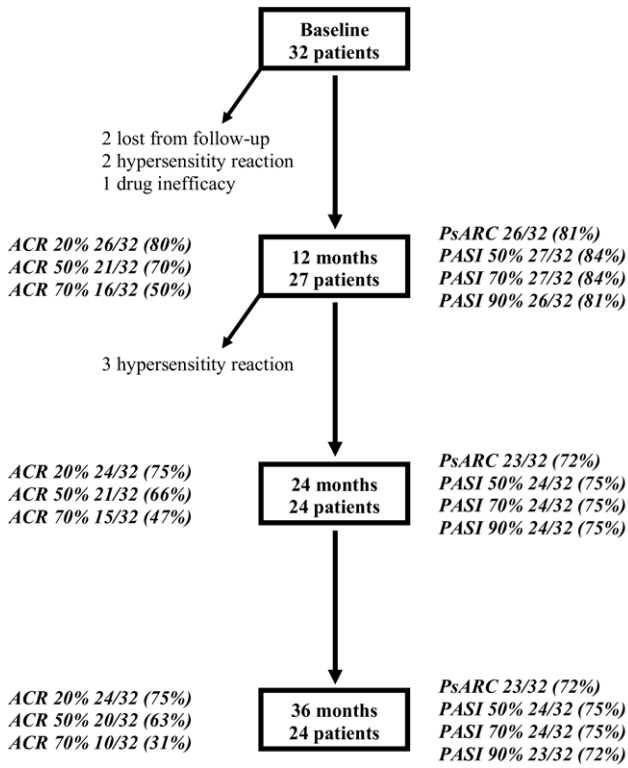

Figure 1 Trial profile and response to treatment in an intention to treat analysis.

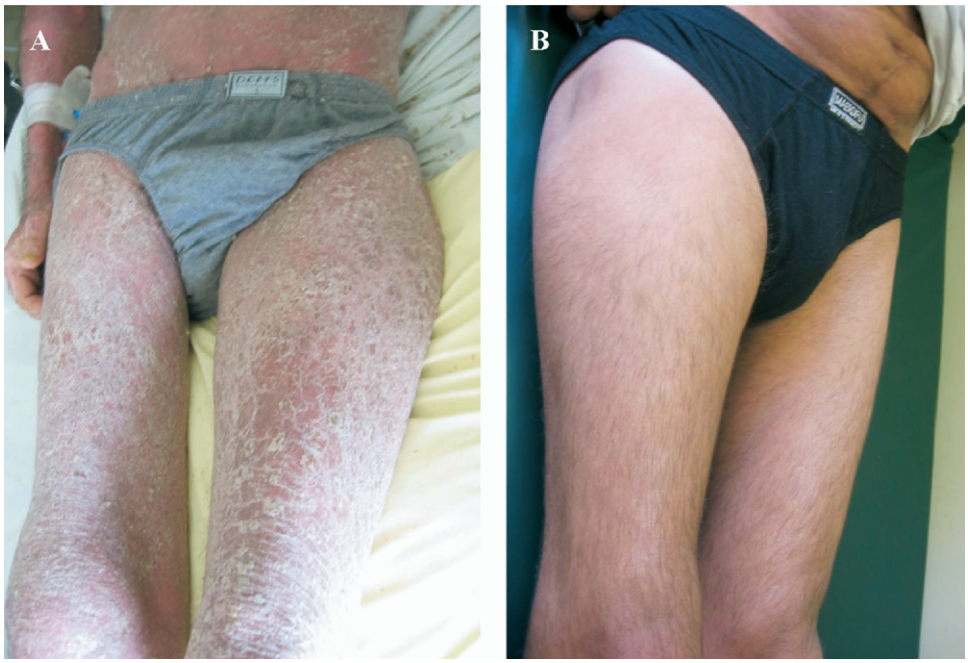

Figure 2 A 51-year-old man with extensive plaque psoriasis, which coalesced to cover most of the body. The skin lesions were thickened and hyperkeratotic (A). After 3 years of therapy with infliximab, most of the lesions had cleared (B).

whom treatment with at least 2 DMARDs had failed. Our main finding during the 3-year observational period of this study was that infliximab was effective, as measured by the PsARC and the ACR response criteria, as well as the European League Against Rheumatism response criteria and the PASI score. The second point was that 75% of our patients continued to have benefit after the third year of treatment. These results are in agreement with other clinical trials, suggesting that infliximab maintains a high degree of clinical efficacy and continues to be well tolerated in patients with PsA (14,15,17,18,34,35). However, our results differ somewhat from those of other investigators, who investigated primarily the articular component of the disease and to a lesser extent the cutaneous manifestations. In addition, no infliximab survival rates have been reported so far.

In the study by Brocq and coworkers, 46 patients with PsA were treated with etanercept (22 patients), infliximab (9 patients), and adalimumab (5 patients). Continuation rates were not significantly different across the 3 agents and overall continuation rates were 70 to 80% (36). As far as we know, our study is the first in which only patients with severe PsA and severe psoriasis were included. We showed significant improvement of PsARC and ACR clinical response with complete healing of the psoriatic lesions, which was sustained for a period of 3 years. This last finding is noteworthy because the severity of skin lesions before infliximab therapy had a negative impact on their quality of life, requiring frequent inpatient admissions to the hospital. After infliximab therapy, no further admissions were required. Another point to consider is the high rate of infliximab survival after 3 years of treatment. This is probably related to the combination treatment used in all our patients, especially the use of MTX and CsA. The above combination was demonstrated to be efficacious and safe in

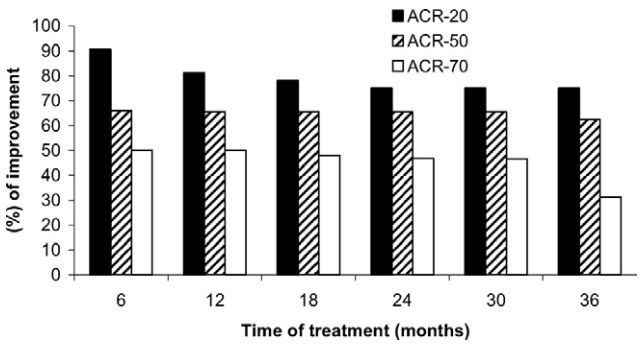

Figure 3 Improvement of ACR 20%, 50%, and 70% response criteria in an intention to treat analysis.

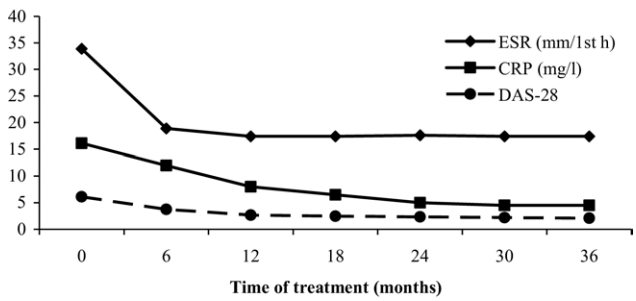

Figure 4 Reduction of erythrocyte sedimentation rate and C-reactive protein and decrease of DAS-28 throughout the study.

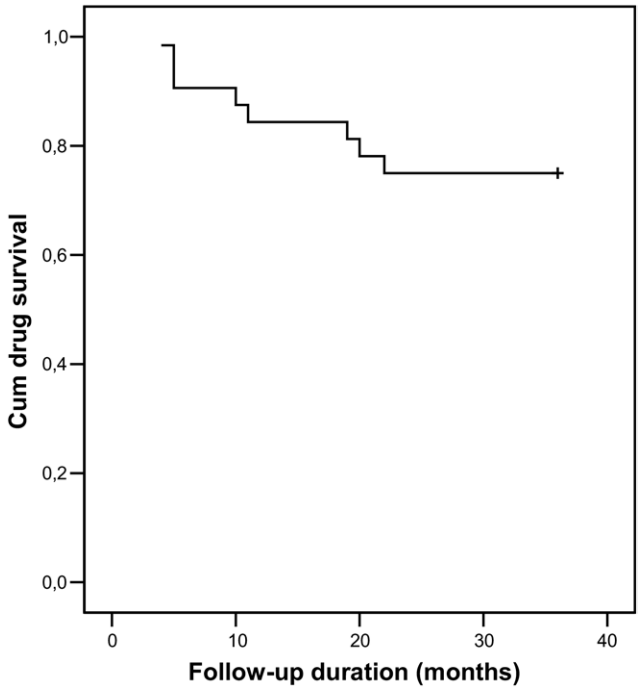

Figure 5 Infiximab survival for 32 PsA patients. After the third year of treatment, 75% of the patients continued to be treated with infliximab.

treating patients with RA and PsA and may avoid the formation of human antichimeric antibodies (HACA) responsible for infliximab inefficacy and adverse drug reactions (37-40). It should be emphasized that the formation of HACA may be inversely related to the infliximab dose; higher doses of infliximab may be less immunogenic, leading to immunological tolerance (39,40). This may also explain the high "survival rates" of infliximab in our study and its beneficial effects for a period of 3 years.

Limitations of our study are that results are based on a limited number of patients and that this is an open-label study. On the other hand, the present study is the longest with a 3-year follow-up in PsA patients.

The adverse events rates observed in this study are in line with the known safety profile of infliximab (14,15,17,18,32-36). Overall, infliximab was well tolerated. Interestingly, only patients with infusion reactions were withdrawn from the study. Furthermore, there were no serious infections, including tuberculosis, and no lupus-like syndrome, perhaps related to the strict inclusion criteria and the close follow-up.

Throughout the 3 years of infliximab treatment, a high degree of clinical response, as measured by both PsARC and PASI responses, was sustained with corresponding improvement of ACR, DAS-28, and acute phase reactants. Infliximab was well tolerated and safe. These results reinforce the notion that the positive effects of infliximab seen at 1 and 2 years remain favorable after 3 years of treatment with high "infliximab survival" in PsA patients.

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