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-