Sustained Clinical Response in Psoriatic Arthritis Patients Treated with Anti-TNF Agents: A 5-year Open-Label Observational Cohort Study

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Objective: To investigate the efficacy, toxicity, and drug discontinuation in patients with psoriatic arthritis treated with anti-tumor necrosis factor agents.

Methods: Sixty-five patients with active disease were included in this open-label study. They had tender or swollen joint count ≥5, Psoriatic Arthritis Severity Index (PASI) score ≥10, and erythrocyte sedimentation rate ≥28 mm Hg/1st hour and/or C-reactive protein ≥10 mg/L. All were refractory to at least 2 disease-modifying antirheumatic drugs. Thirty were treated with infliximab, 25 with etanercept, and 10 with adalimumab. Infliximab (5 mg/kg body weight) was given intravenously at weeks 0, 2, 6, and every 8 weeks thereafter; etanercept was given subcutaneously (25 mg twice a week), while adalimumab was given subcutaneously (40 mg every other week) for a period of 5 years. Data concerning anti-tumor necrosis factor efficacy tolerability, adverse events, and drug discontinuation were recorded. The percentage of patients who achieved the Psoriatic Arthritis Response Criteria (PSARC), the improvement of PASI, the improvement according to the American College of Rheumatology (ACR) criteria, and the disease activity for 28 joint indices score (DAS-28) were recorded.

Results: After 5 years, PSARC was 60%, PASI 70 was 66.7%, PASI 90 was 63.3%, while ACR 50 was 56.7% for the patients treated with infliximab. Moreover, PsARC was 64%, PASI 70 and PASI 90 were 68%, while ACR 50 was 56% for those treated with etanercept. Furthermore, in the adalimumab group PsARC was 56%, PASI 70 and PASI 90 were 58% and 50%, respectively, while ACR 50 was 50%. Additionally, DAS-28 scores were significantly improved. Thirteen patients treated with infliximab, 6 with etanercept, and 5 patients with adalimumab were withdrawn. At the end of treatment, the survival of infliximab was 56.7%, for etanercept 76%, and for adalimumab 50%.

Conclusion: All drugs were effective, safe, and well-tolerated. The clinical improvement was maintained through the 5 years with satisfying infliximab and adalimumab survival and high etanercept survival.

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Psoriatic arthritis (PsA) has been defined as a unique inflammatory arthritis associated with psoriasis (1). The exact prevalence of PsA is unknown. Estimates of PsA in the general population vary from 0.04% in the Faroe Islands to 1.2% in Sweden (2-5). The course of PsA is variable, ranging from a mild nondestructive disease to a severe debilitating erosive arthropathy, while about 20% of the patients develop a very destructive disabling form of arthritis (6,7). Moreover, the burden of disease is demonstrated both in terms of progression of clinical and radiological damage and in terms of quality of life of these patients. Patients with PsA have reduced quality of life

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and functional capacity compared with patients with psoriasis or healthy controls (8-10), not to mention that they are at an increased risk for death with a standardized mortality ratio of 1.62 (11). Nonsteroidal anti-inflammatory drugs do not modify the course of the disease, nor do they prevent development or progression of erosions. Thus, if there is erosive disease, patients should be treated aggressively with disease-modifying antirheumatic drugs (DMARDs) (12). Except for methotrexate (MTX), which was initially used for psoriasis and then for PsA, and rheumatoid arthritis (RA), most other DMARDs were extrapolated from the treatment of RA. In a meta-analysis of drugs used in PsA performed in 2000, only parenteral MTX and sulfasalazine were considered effective in PsA (13,14). In a more systematic review, those medications did not prove very effective in PsA (15). Over the last decade there has been interest in the pivotal role that tumor necrosis factor (TNF) α, a proinflammatory cytokine, plays in inflammation of skin and synovium. TNF acts in the early stages of the inflammatory process during which it can stimulate T-cell activation and induce the expression of interleukin (IL)-2, pro-inflammatory cytokines (such as IL-1 and IL-12), and pro-inflammatory chemokines (such as IL-8) (16). Thus, several randomized controlled trials have shown good efficacy and safety of anti-TNFα therapy in PsA patients (17-21); however, only few long-term studies have been published (22-24). Recently we reported on the impressive clinical and laboratory improvement in PsA patients treated with infliximab in a 3-year study (23). Here, we report the results of the 5-year extension of this study in which we investigate the long-term efficacy, safety, and reasons for anti-TNFα discontinuation.

METHODS

A cohort of 221 patients with PsA was followed up in our institution, giving a prevalence of 56.6 cases per 100,000 inhabitants and of 3.02 cases per 100,000 inhabitants (4). From these, 65 patients with severe PsA and recalcitrant severe psoriasis were recruited into this open-label observational study between January 2003 and December 2003. All patients fulfilled the European Spondyloarthropathy Study Group criteria (ESSG criteria) (25) and were refractory to at least 2 DMARDs.

Study Design

At the time of enrollment, patients were required to have active PsA, defined as the presence of $\geq$5 swollen or $\geq$5 tender joints (based on joint counts of 66 and 68, respectively), a C-reactive protein (CRP) level $\geq$10 mg/L and/or morning stiffness lasting 45 minutes or longer, an active psoriatic plaque $\geq$2 cm in diameter, and negative results of serum tests for rheumatoid factor. Moreover, they were required to have negative results for active or latent tuberculosis by purified protein derivative skin and chest radiography (according to the Hellenic Association of Rheumatology guidelines for anti-TNFα therapy). Patients were treated with either etanercept (25 mg subcutaneous injections twice weekly) or infliximab (5 mg/kg) at weeks 0, 2, 6, and every 8 weeks thereafter for a period of 5 years. If the clinical response was insufficient, the interval between the infusions was shortened to 6 or 4 weeks. Moreover, patients were treated with adalimumab subcutaneously (40 mg every other week). Patients were followed up every 2 months and safety evaluations (including adverse events) and data concerning efficacy, tolerability, concomitant therapy, and drug discontinuation were recorded. The protocol was approved by the Institutional Scientific Board of the University Hospital of Ioannina, Greece. Patients were selected for treatment with individual agents after they were asked whether they wanted to receive a self-injected medication or an intravenous infusion. They were entered into the study after reading and signing an informed consent form. All patients had their last follow-up examination in December 2008.

Exclusion Criteria

Patients were excluded from this study if they had evidence of latent or active tuberculosis (that is, they had to have clear chest radiograph findings and a negative purified protein derivative skin test) or if they had chronic or clinically significant infection, malignancy, or congestive heart failure.

Monitoring

A complete blood count with differential and platelet count, as well as serum values of liver enzymes, bilirubin, albumin, glucose, creatinine, and urine analysis were obtained before treatment and at each patient's visit.

Assessments

The primary endpoint with regard to efficacy in PsA was the proportion of patients who met the Psoriatic Arthritis Response Criteria (PsARC) (26). This composite measure requires improvement in 2 factors (with at least 1 being a joint score), with worsening in none of the following factors: patient and physician global assessments, tender joint score, and swollen joint score. A secondary endpoint was the improvement of Psoriatic Arthritis Severity Index (PASI) (27), which is a composite score ranging from 0 to 72 used for assessing and grading the severity of psoriatic lesions and their response to treatment. PASI includes assessments of the extent of skin involvement, erythema, plaque thickness, and the degree of scaling. In addition, the clinical response according to the American College of Rheumatology (ACR) 20, 50 and 70% criteria (28), as well as the disease activity for the 28 joint indices score (DAS-28), was also recorded at each patient's visit.

Statistical Analysis

Standard methods of survival analysis (Kaplan-Meier) were used in which termination of anti-TNFα agents due