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CLINICAL RESEARCH STUDY

Infliximab therapy in established rheumatoid arthritis: An observational study

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KEYWORDS:
Established rheumatoid arthritis; Infliximab; Discontinuation; Adverse events; Infections.

ABSTRACT

PURPOSE: To investigate the efficacy, toxicity and drug discontinuation rate in an observational study of patients with established rheumatoid arthritis treated with infliximab.

SUBJECTS AND METHODS: Between September 1999 and June 2003, we enrolled 84 patients with rheumatoid arthritis who were being treated with infliximab. All patients met the American College of Rheumatology criteria for rheumatoid arthritis and had been refractory to (or did not tolerate) at least two disease-modifying antirheumatic drugs. Patients entering the study had a negative purified protein derivative skin test, were fully informed about the treatment regimen, and were followed up at predefined times according to a standardized protocol. Data concerning infliximab dosage, tolerability, adverse events, concomitant therapy, dosage interval, and drug discontinuation were all recorded. In addition, the clinical and laboratory variables according to the American College of Rheumatology 20% and 50% response criteria and the disease activity score for the 28 joint indices were also recorded.

RESULTS: There were 61 women and 23 men with a mean age of 59 ± 8 years and mean disease duration of 11 ± 6 years. Seventy–five percent (63/84) were seropositive for IgM rheumatoid factor. After the first year of treatment, 84.5% of patients continued to be treated with infliximab, whereas this percentage was 73% after the second year and 59% after the third year of treatment. The American College of Rheumatology 20% response criteria was met by 59/84 (70%) of patients, and 38/84 (45%) of the patients achieved the 50% response criteria in the first year of treatment. At the second year of therapy, the American College of Rheumatology 20% response criteria were reached by 35/84 (42%) of the patients and the 50% response criteria by 27/84 (32%). At the third year of treatment with infliximab, the American College of Rheumatology 20% and 50% response criteria were achieved by 13/84 (15.5%) and 10/84 (12%) of the patients, respectively. Twenty-eight of eighty-four (33%) patients discontinued infliximab therapy. The risk of drug discontinuation decreased with the concomitant use of methotrexate. The main reasons for drug discontinuation were adverse drug reactions (16/84, 19%), followed by lack of efficacy (9/84, 11%). The main reasons for drug discontinuation due to side effects were immediate hypersensitivity reactions (9/84, 11%) and infections (6/84, 7%).

CONCLUSION: Infliximab was found to be an alternative treatment with a relatively acceptable toxicity profile, despite the fact that two patients developed pulmonary tuberculosis. After the third year of therapy, 59% of patients continued to be treated with infliximab. The concomitant use of methotrexate was associated with the continuation of infliximab therapy.

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Rheumatoid arthritis is a chronic inflammatory disease that affects the synovium, and causes joint damage and bone destruction.[1] Persisting inflammation of the synovium leads to pannus formation and prolonged inflammation causes destruction of the cartilage and bone, resulting in erosions.[1,2] Thus, therapy of rheumatoid arthritis requires continuous treatment and a delicate balance between benefits and risks. A number of new agents have emerged over the last decade that have broadened treatment options for rheumatoid arthritis.[3] One of them is the biological agent infliximab, a chimeric monoclonal antibody that binds with high affinity and specificity to tumor necrosis factor alpha.[2] The efficacy and safety of infliximab have been established in a number of short controlled trials in rheumatoid arthritis patients.[4-6] However, a large number of rheumatoid arthritis patients had to stop infliximab therapy because of lack of efficacy or because of adverse drug reactions. Thus, rheumatologists and physicians should know for how long infliximab is effective and safe, and which are the most frequent and hazardous adverse events.

In an attempt to answer the above questions, we investigated infliximab efficacy, drug survival, and reasons for drug discontinuation during the disease course in an observational study of patients with established rheumatoid arthritis.

Methods

Eighty-four rheumatoid arthritis patients with established disease, refractory or intolerant to at least two disease-modifying antirheumatic drugs were recruited between September 1999 and June 2003 from the Rheumatology Clinic of the University Hospital of Ioannina. All patients fulfilled the American College of Rheumatology criteria for rheumatoid arthritis.[7] Patients were fully informed about the treatment regimen and entered the study after having read and signed an informed consent form. They were followed up at predefined times according to a standardized protocol. The protocol has been approved by the Institutional Scientific Board of the University Hospital of Ioannina, Greece. Infliximab was given intravenously (infusion time >2 hours) in a loading dose of 3 mg/kg/body weight at weeks 0, 2, 6 and every 8 weeks thereafter. If the therapeutic response was insufficient, then the dose of infliximab could be increased to 5 mg/kg/body weight, keeping the same dosage interval. If this failed to give an acceptable treatment response, the interval was shortened to 6 or 4 weeks. Data concerning infliximab efficacy, tolerability, concomitant therapy, adverse events, and drug discontinuation were all recorded. In addition, the clinical and laboratory variables according to the American College of Rheumatology criteria[8] and disease activity score for the 28 joint indices[9] were also recorded. All patients had a last follow-up examination in May 2004.

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Definitions

Refractory rheumatoid arthritis was defined as increasing disease-modifying antirheumatic drugs dosage above standard dosage regimen, using combination therapy, and adding or increasing the dosage of corticosteroids.[10,11] *Lack of efficacy* was defined as patients not fulfilling the American College of Rheumatology 20% criteria[8] or the disease activity score for 28 joint indices improvement >1.2 score.[9] The American College of Rheumatology response criteria required 20% improvement of tender and swollen joint count, plus 20% improvement in 3 of the following: patient's pain assessment, patient's global assessment, physician's global assessment, patient's self–assessed disability, and acute phase reactants (erythrocyte sedimentation rate, C–reactive protein).[8] *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 decided when patients presented failure of drug treatment or experienced adverse drug reactions.[12]

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. Finally, 2 mL of blood serum of patients (at each visit) were taken and stored at −20°C for the measurement of an 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 the endpoint. A Cox regression model was used for drug discontinuation, which included age, sex, presence of rheumatoid factor, time interval between infusions (>2 months vs. <2 months), infliximab dosage (3 mg vs. >3 mg), concomitant use of methotrexate versus non usage, and concomitant use of cyclosporine A versus non usage, as well as the presence or absence of antinuclear antibodies as covariates.

Results

During the recruitment period (September 1999 to June 2003), 95 rheumatoid arthritis patients were investigated. Of