Therapeutic effects of the anti-tumor necrosis factor monoclonal antibody, infliximab, in four children with refractory juvenile idiopathic arthritis

X. Norambuena R.[a], J. Mallol[b], G. Ríos M.[a], F. Quevedo R.[c] and A. Quezada L.[a-d]

[a]Pediatric Unit, Hospital Dr. Exequiel Gonzalez Cortes. [b]Department of Pediatric Respiratory Medicine, School of Medicine, University of Santiago de Chile (USACH), Hospital CRS El Pino. [c]Educational Division of Health Sciences, School of Medicine, University of Chile. [d]Department of Pediatrics, School of Medicine, University of Chile.

ABSTRACT

Objective: To report the results of treatment with infliximab in patients with refractory juvenile idiopathic arthritis (JIA).

Patients and methods: A prospective study of four children with refractory JIA was carried out. Infliximab (100 mg) was administered in weeks 0, 2 and 6. Subsequently, the drug was administered every 8 weeks. The following parameters were assessed at the beginning and at the end of the follow-up period: number of joints with active arthritis, number of joints with a limited range of motion, physician overall assessment of disease activity, parent assessment of the child's overall well-being, pain assessment scores, and erythrocyte sedimentation rate. Improvement was rated according to the definition of the American College of Rheumatology (ACR 30). Paired sample tests were used for statistical analysis.

Results: Three girls and one boy aged between 10 and 16 years old with a history of JIA ranging from 1 to 9 years were included. The patients received infliximab for a period of 11 to 33 months (average 22 months). There was a significant decrease in the number of swollen joints ($p < 0.05$), joints with a limited range of movement ($p < 0.04$), pain score assessment ($p < 0.005$), physician overall assessment ($p = 0.002$), maternal evaluation ($p < 0.001$), the patient's own evaluation ($p < 0.001$), and duration of morning stiffness ($p < 0.001$). Both steroids and methotrexate dosages were reduced and no adverse effects or infections were registered.

Conclusions: Infliximab improved joint inflammatory indexes and clinical assessments. This improvement increased the quality of life of the patients and their families, suggesting that the use of biological therapy is a good option in refractory JIA.

Key words: Juvenile idiopathic arthritis. Infliximab. Juvenile rheumatoid arthritis.

Correspondence:

Prof. Arnoldo Quezada L.
Enrique Matte 1525 San Miguel
Santiago de Chile
Phone-Fax: + 56-2-5557006
E-mail: aquezada@med.uchile.cl
E-mail: caromah@hemo.unc.edu.ar

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disease in the pediatric population. According to a national study, the estimated incidence in Chile is 5.6 cases per 100,000 children under fifteen years of age[1]. Presentation, clinical course, laboratory parameters, and response to therapy may vary widely. It has been necessary to classify the disease in subgroups in order to identify those patients whose prognosis and response to therapy might be different[2].

Most patients respond to conventional management with non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs), especially if administered early during the course of the illness. These agents have both, improved disease prognosis and allowed steroids doses to be reduced, consequently reducing their associated side effects.

However, a significant number of patients in the polyarticular JIA subgroups or systemic JIA with polyarticular involvement experience severe and aggressive disease resulting in erosive arthritis, joint destruction, functional disability, growth retardation and unresponsiveness to treatment, even when begun early. The persistent disease activity compounded by the cumulative side effects of long term medication has a significant impact in emotional and psychological development, quality of life and family dynamics. For these refractary groups, the use of biological therapies such as tumor necrosis factor alpha (TNFα) antagonists has been suggested[3-5]. These biological agents have shown therapeutic efficacy in Rheumatoid Arthritis (RA). They modify its course and prognosis by blocking the inflammatory activity of TNFα. This produces a down regulation of the inflammatory response resulting in decrease proliferation of synoviocytes, collagenase production, cell-adhesion molecules expression, bone resorption and cartilage destruction.

The purpose of this study is to report our clinical findings on the use of infliximab, a monoclonal antibody that neutralizes the pro-inflammatory action of tumor necrosis factor alfa (TNFα), in pediatric patients suffering from JIA refractary to conventional therapies.

PATIENTS AND METHOD

Four children with the diagnosis of JIA, followed up at the Immunology Unit of the Exequiel Gonzalez Cortes Hospital were included: two girls had systemic JIA with polyarticular involvement; one had seronegative polyarticular JIA and one boy had JIA associated to enthesitis.

Infliximab (Remicade®, Schering Plough, USA) was administered through a continuous infusion pump at dosages ranging from 2.5 to 2.9 mg/Kg/dose (median 2.75), at weeks 0, 2 and 6. Subsequently, they received the drug every 8 to 10 weeks. During the first year, patients were admitted to the hospital for treatment for a period of 24 hours. They were kept in isolation and monitored hourly. Later on, because no adverse reactions developed, hospital stay was reduced to six hours.

The following parameters were evaluated at week 0 and at the end of the follow up period: number of joints with active arthritis, number of joints with limited range of motion, physician global evaluation of disease activity and parent assessment of child's overall well-being (rating 10 for maximum disease activity and 0 for no disease activity). Likewise, pain rating by the patient was done using a visual analogue scale. Serum measurements of acute phase reactants were obtained. The definition of improvement of RA by the American College of Rheumatology (ACR 30)[6-8] was applied. This is based in the overall assessment of decreased disease activity done by a physician; overall assessment of disease activity according to the patient or his/her mother, functional ability, number of joints with active arthritis, number of joints with limited range of movement and ESR.

Improvement of at least 30 % from baseline from the beginning of the new therapy in 3 of the 6 variables included and not more than one variable worsening by more than 30 % was considered significant. In the overall assessment, a maternal evaluation was included because the patients were children. Furthermore, it was considered of clinical interest to assess morning stiffness in minutes and reduction or suspension of steroid and methotrexate.

The t-test for paired samples was employed to compare the changes in JIA parameter for each patient between entry and end of treatment with infliximab. Results are expressed as mean and standard deviation; a value of $p < 0.05$ was considered statistically significant. The protocol had the approval from the local Ethics Committee and full informed and signed consent was obtained from parents.

RESULTS

Four patients, three girls and one boy, ranging from 10 to 16 years of age, with 1 to 9 years of disease history, were included in the study. They had been taking NSAIDs, oral steroids (0.2 to 0.3 mg/kg/day prednisone equivalent), and methotrexate (10.8 to 12.7 mg/m^2/week), subcutaneously. The patient with JIA associated to enthesitis was also taking mesalazine (Salofalk®) for Ulcerative Colitis and beta-agonists plus inhaled steroids for Bronchial Asthma. The conventional therapies had proven ineffective in all four patients, whose inflammatory activity, functional limitations and poor quality of life were persistent. The duration of treatment was 22 months on average (range 11 to 33 months) at the time of this report. Table I shows the number of