Use of infliximab in patients with systemic juvenile idiopathic arthritis refractory to etanercept

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ABSTRACT

Objective. *To analyse the effectiveness and safety of Infliximab in a group of patients with systemic juvenile idiopathic arthritis (SJIA) who had failed treatment with etanercept in a single paediatric rheumatology clinic.*

Methods. *Patients with SJIA with active polyarthritis refractory to methotrexate (MTX) [≥ 20 mg/m²/week] for at least 3 months and to etanercept (up to 1 mg/kg twice weekly) for at least 6 months were included. All children received infliximab 3-10 mg per kg of body weight intravenously concomitantly with MTX 7.5-10 mg/week for 19 (2-113) weeks. Evaluation included ACR paediatric 30 criteria and presence of signs of systemic activity (fever, rash).*

Results. *Six patients were included. Three patients met ACR paediatric 30 criteria at 2 weeks (2 patients) and 10 weeks after initiation of infliximab. Improvement lasted for 4, 12, and 84 weeks respectively. The presence of fever/rash was not modified by the treatment. Infliximab was discontinued due to moderate side effects in 4 patients. No serious side effects were observed.*

Conclusions. *Most patients with SJIA who fail to respond to etanercept may not reach sustained improvement when switched to infliximab. The only patient in our group who improved sustainedly with infliximab did not show any systemic features at the beginning of therapy. Further controlled studies are needed in order to assess efficacy of infliximab in children with refractory SJIA.*

Introduction

Systemic juvenile idiopathic arthritis (SJIA) is an infrequent but usually severe form of juvenile idiopathic arthritis (JIA). Patients with SJIA frequently carry a worse functional prognosis, experience more frequent and severe complications, and show a poorer response to second-line agents than children with other forms of JIA(1). Several studies have shown that various cytokines, such as tumour necrosis factor (TNF), IL-1 and IL-6, play an important pathogenic role in this distinct disease (2). TNFα is probably a pivotal cytokine in the cascade leading to inflammation, since it initiates the production and secretion of inflammatory mediators such as cytokines and adhesion molecules. At least 3 therapies are available to neutralize the biological action of TNFα: a chimeric monoclonal antibody (Infliximab), a human monoclonal antibody (Adalimumab) and a soluble TNF receptor (Etanercept). Investigations carried out by different groups have consistently shown that a significant proportion of patients with SJIA do not benefit from treatment with etanercept (3-5).

Infliximab, a chimeric high-affinity neutralizing monoclonal antibody directed to TNF-α, has demonstrated efficacy in the treatment of patients with rheumatoid arthritis when combined with MTX (6). Some reports have shown that infliximab is efficacious and safe in patients with JIA, although no controlled trials have been carried at the time of this report (6,7). An important question in clinical practice is the efficacy of infliximab in patients who have failed to respond to etanercept.

We investigated the effectiveness and safety of infliximab in a group of patients with SJIAwho had not reached control of their disease while treated with MTX and etanercept.

Patients and methods

This is an observational longitudinal study. Six consecutive patients with a diagnosis of SJIA(ILAR) who were refractory to MTX (persistence of active polyarthritis despite the use of higher-dose MTX [≥ 20 mg/m²/week] for at least three months) and to etanercept (persistence of active polyarthritis despite the use of 0.4–1 mg per kilogram of body weight, subcutaneously twice weekly for at least 6 months) were treated with infliximab. Patients were followed at the Rheumatology Section of a tertiary hospital in the period January 2001 – November 2003. All patients started infliximab therapy at 3–5 mg per kg of body weight, intravenously, concomitantly with MTX 7.5-10 mg/week. It was administered at 0, 2, 6 weeks followed by infusions every 4 to 8 weeks, and its dose was escalated up

to 10 mg/kg. Premedication with intravenous difenhydramine 1 mg/Kg and hydrocortisone 5 mg/Kg was used in all infusions. Patients concomitantly received corticosteroids (up to 0.8 mg per kilogram per day of prednisone, or up to 1.2 mg per kilogram per day of deflazacort) and NSAIDs throughout treatment. Patients were seen at the clinic every 4 to 8 weeks and data were registered in each visit. Clinical and biochemical examinations were performed at baseline and on each visit, and included: number of active joints, number of joints with limited motion, functional capacity (CHAQ), patient well-being (measured on a visual analogue scale (VAS) score ranging from 0 to 10), disease activity according to the physician (VAS), pain according to the patient or parents (VAS), ESR, presence of systemic signs (such as fever, rash, organomegaly), and haematological, serum chemical, and urine analyses.

Determination of rheumatoid factor (RF) and antinuclear antibodies (ANA) was performed every 6 months.

The outcome measures used to assess response included: (i) number of swollen joints; (ii) number of joints with limitation in motion; (iii) functional ability as measured by the Childhood Health Assessment Questionnaire (CHAQ, Argentinean validation) (8); (iv) disease activity according to the physician (VAS); (v) patient wellbeing according to the patient or parents (10); and (vi) a laboratory marker of inflammation, as measured in this study by the erythrocyte sedimentation rate (ESR). Improvement was defined according Giannini *et al*. (9), as follows: improvement of 30% or more in at least 3 of the 6 response variables with worsening of at least 30% in no more than one of these variables. Flare was defined according to the criteria used by Lovell *et al*. (10) , as follows: worsening of 30% or more in at least 3 of the 6 response variables (a minimum of 2 active joints required) with improvement of 30% or more in no more than one of these variables. Sustained response was defined as uninterrupted achievement of definition of improvement (DOI) for ≥ 6 consecutive months.

Infliximab therapy was discontinued in patients who failed to meet DOI over 6 consecutive months (lack of efficacy) or in patients with adverse events.

Written informed consent was obtained from all subjects prior to the beginning of infliximab therapy.

Table I. Baseline characteristics of patients with systemic juvenile idiopathic arthritis (SJIA) treated with infliximab.

Sex	4 F 2 M
Age at disease onset (years)*	7.5
Age at study entry (years)*	11.5
Duration of disease (years)*	3
Previous medications	
Cyclosporine	3 patients
I.V. gammaglobulin	1 patient
Etanercept	6 patients
Rash/fever at study entry	5 patients
VAS physician* (0-10)	4.56
VAS patient* (0-10)	6.06
VAS pain* (0-10)	5.38
CHAQ* (0-3)	1.69
Joints with limited motion*	18.5
Active joints*	26
ESR*	89.5
ANA-RF	0 pts

*Medians
VAS physician: disease activity according to the physician measured on a visual analogue score.
VAS patient: disease activity according to the patient measured on a visual analogue score.
VAS pain: pain according to the patient measured on a visual analogue score.
CHAQ: Childhood Health Assesment Questionare.
ANA: antinuclear antibodies; RF: rheumatoid factor.

Results

Six patients with refractory SJIA were treated with infliximab. Their demographic data is presented in Table I. Three patients had shown transient response to etanercept (they had met DOI for 1-6 months). All patients were negative for ANAand RF. Five patients presented fever and/or rash at the time of initiation of infliximab therapy. Disease activity scores are shown in Figure 1 (only patients who received at least 5 infusions are shown). Median follow-up period was 19 (2–113) weeks, for a total of 41 infusions. Only one patient is still receiving the drug at the time of this report.

Three patients met DOI, at 2 (2 patients) and 10 weeks after infliximab initiation. Improvement lasted for 4, 12, and 84 weeks respectively. The presence of fever/rash was not modified by infliximab therapy. All patients who reached improvement subsequently experienced a flare. Only one patient reached sustained response. Corticosteroids dose could be tapered or discontinued in 2 patients.

ANA and RF were not found in our patients during the period of treatment.

Infliximab therapy needed to be discontinued due to side effects in 4 patients, after 2, 3, 5 and 6 infusions. Perinfusional generalized urticaria led to drug withdrawal in all cases. Lip and eyelid edema also developed in 3 pts while periarticular erythema appeared in 1 patient. These events resolved after suppression of drug infusion and treatment with dyfenhydramine 1 mg/kg. No infections were observed.

Discussion

Anti-TNF therapies have shown efficacy and safety in the treatment of juvenile idiopathic arthritis that fails to respond to MTX (3,6). In children, etanercept has demonstrated to benefit over 60% of patients with refractory JIA, regardless of their disease onset (3), but there is evidence showing that patients with SJIA do not respond to etanercept as satisfactorily as patients with other subtypes of JIA (4). Although controlled studies about the efficacy of infliximab in patients with JIA are lacking, isolated reports show that this drug is a valid choice in the management of refractory JIA(6, 7).

Although infliximab and etanercept act through the same pathway, at least in theory infliximab could potentially exert a more profound immunosuppression due to a higher binding affinity and through the induction of cell lysis (11). Distinction between Infliximab and Etanercept extends beyond their structures and binding specificities. Scallon *et al.* have shown that Infliximab maintains a stable complex with soluble TNF while etanercept does not (11). This hypothesis raises the question of the usefulness of prescribing infliximab after failure to etanercept.

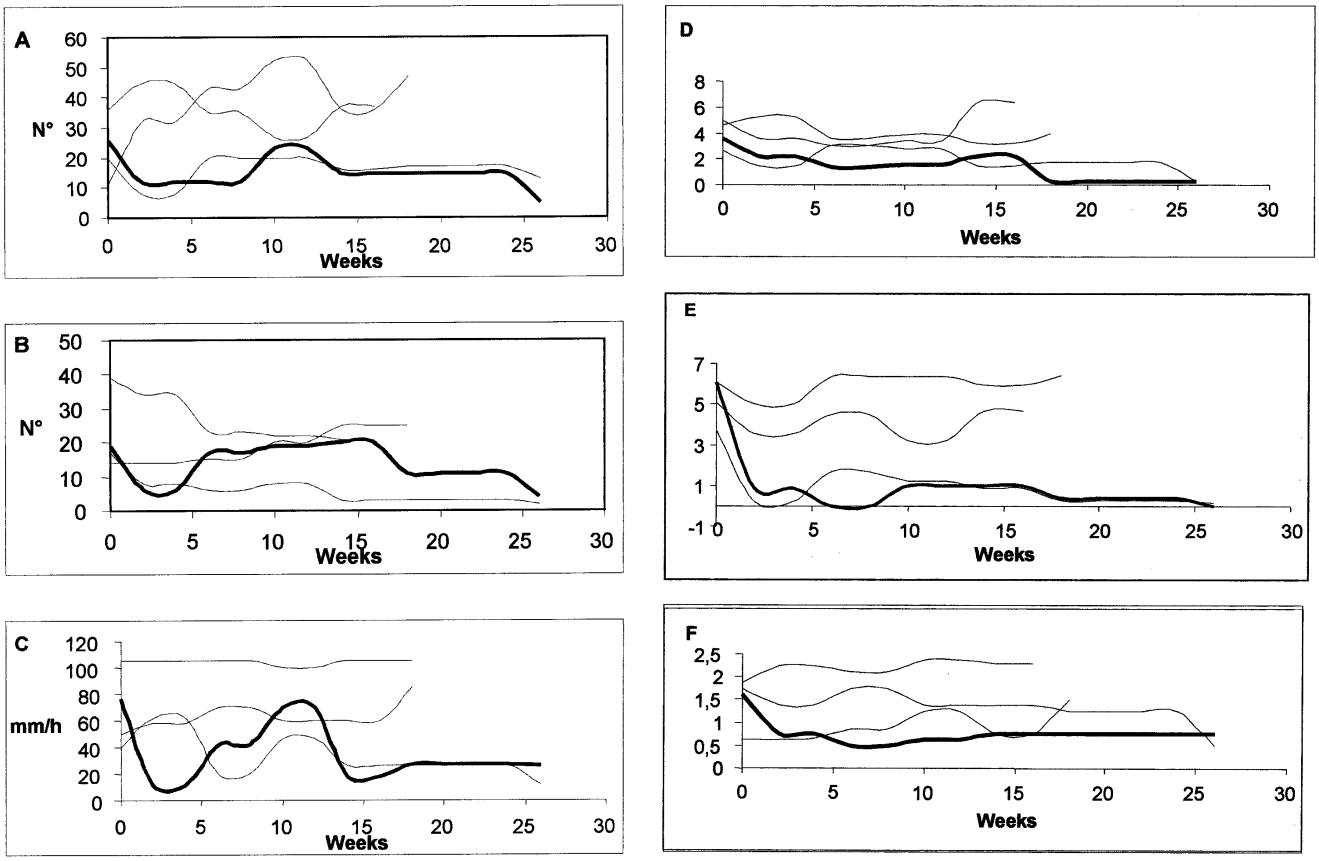

Fig. 1. Disease activity in 4 patients with systemic juvenile idiopathic arthritis (SJIA) treated with infliximab. (**A**) active joints; (**B**) joints with limited motion; (**C**) ESR; (**D**) VAS physician; (**E**) VAS patient; (**F**) CHAQ. Lines represent different patients. Patient — showed a sustained response and he is still receiving infliximab (113 weeks).

Some investigators have found that patients with rheumatoid arthritis who fail to respond to etanercept may show good responses to infliximab (6), while others have not (12). Our study shows that most patients with SJIAwho fail to respond to etanercept may not reach sustained improvement when switched to infliximab, while adverse reactions seem to be frequent. Interestingly, the only patient who reached sustained improvement on infliximab had not showed systemic features at the beginning of therapy.

Several pilot studies have showed that infliximab is safe and efficacious in children with JIA, but since children with SJIA represented a minor proportion of patients in those studies, conclusions about the efficacy of the drug in this subgroup cannot be drawn. Elliot *et al*. described the control of systemic features but persistence of arthritis after two doses of infliximab (cA2) on a patient with SJIA (7). Accordingly, Kraetsch *et al*., found that fever, hepatosplenomegaly and rash resolved after the first courses of treatment with infliximab in all 6 patients with adult onset Still's disease in their study (13). In our observation, all 5 patients who presented systemic symptoms at the time of initiation of therapy continued showing fever and rash, while articular features were modified in some of them. Our patients had a severe form of SJIA, refractory to higher dose MTX and to etanercept, and 5 of them had systemic symptoms when infliximab therapy was initiated. These features may have accounted for the observed poor response, since patients with SJIA who present systemic features seem to respond poorly to anti-TNF therapy (personal observation).

Longitudinal controlled trials are needed to define the minimal number of infliximab infusions before therapy is considered inefficacious in patients who do not meet DOI. In some case reports, improvement was achieved as early as over the first infusion while in others it only occurred after the 12th infusion (14). In our cases DOI was achieved after the 2nd infusion in 2 patients and after the 4th infusion in another one.

Four of our patients needed to discontinue treatment due to side effects, despite premedication. Although they were all reversible upon the use of higher dose of anti-histamines and suspension of the infusion, we chose not to expose susceptible patients to further possible similar or more severe infusion related side-effects. The higher frequency of adverse events in our small group may be due to our population, children with systemic-course SJIA. This subgroup of patients with SJIA has not been included in the few published pediatric series about infliximab. Tutar *et al*. reported 2 children whith SJIA who developed urticarial rash related to infliximab therapy (15).

We conclude that most patients with SJIAwho have failed to respond to etanercept do not subsequently respond to infliximab, especially if they have systemic features at the time of initiation of treatment. Moreover, they may suffer from frequent perfusion-related side effects. It is probably worthwhile treating these particularly severe patients with alternative therapies. Further controlled studies are needed to address the safety and efficacy of infliximab in children with refractory SJIA.

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