Infliximab in the treatment of adult Still's disease refractory to conventional therapy

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ABSTRACT

In this study we evaluated the efficacy of Infliximab in the treatment of adult Still's disease (ASD) refractory to conventional therapy. Three patients with chronic and active ASD unresponsive to corticosteroids and methotrexate were given intravenous Infliximab infusions at a dosage of 3 mg/kg at weeks 0, 2, 6 and then once every 8 weeks. Methotrexate was maintained in all cases at a dosage of 15 mg/week, whereas the prednisone dose was modified according to disease activity. The follow-up lasted 50 weeks and disease activity improved in all cases during Infliximab therapy. Two patients presented arthralgias and sore throat at 20 and 28 weeks, that was rapidly controlled by Infliximab reinfusion every 4 weeks. One patient relapsed at 18 weeks and dropped out at 22 weeks due to an urticarioid rash after the beginning of the fifth infusion.

Infliximab may be effective in the treatment of relapse of ASD refractory to conventional therapy and requiring continuous high dose corticosteroid medication. Further studies are needed to evaluate the long-term safety, efficacy and the optimal schedule of infusion.

Introduction

Adult Still's disease (ASD) is a systemic inflammatory disorder of unknown etiology, characterized by high spiking fever, arthritis, neutrophilic leukocytosis and transient cutaneous rash. Systemic manifestations include pleuritis, pericarditis, sore throat, liver disfunctions, splenomegaly and lymphadenopathy (1, 2). Serological findings other than neutrophilic leukocytosis are hyperferritinemia, a high erythrocyte sedimentation rate (ESR) and an increase in C-reactive protein (CRP) (1, 3). The course of ASD may be acute and self-limiting, relapsing or chronic; treatment is difficult and not well codified. First-line drugs are nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (1, 2); immunosuppressive agents such as methotrexate, cyclosporin and cyclophosphamide may be useful in cases of resistance to first-line drugs or when high doses of corticosteroids are needed for disease control (4-6).

Infliximab (Remicade, Schering-Plough) is a murine-human chimeric IgGk1 monoclonal antibody that can bind to soluble tumor necrosis factor alpha (TNF-) and can also inhibit the interaction of TNF- with cellular receptors. In association with methotrexate it is effective in the treatment of active rheumatoid arthritis unresponsive to DMARDs therapy (7-9); moreover Elliot *et al.* reported that Infliximab was effective in the suppression of fever and the acute phase response in a patient with systemic juvenile chronic arthritis (10). On the basis of this finding we decided to treat three patients affected by chronic ASD, refractory to conventional therapy, with Infliximab.

Patients and methods

Diagnosis of ASD was made in all cases according to Yamaguchi's classification criteria (3). Previous treatments, and the demographic and clinical characteristics of the patients at baseline are summarized in Table I. After Ethical Committee approval, informed consent was obtained in all cases. Infliximab was infused at the dosage of 3 mg/kg at weeks 0, 2, 6 and then once every 8 weeks. From week 30, the drug was infused every 4 weeks in cases 2 and 3. Methotrexate (15 mg/week) was maintained during the study and the dosage of prednisone was changed according to disease activity. Clinical examination and laboratory evaluation, including a complete blood count, and determinations of ferritinemia, ESR, CRP, antinuclear, anti-dsDNA and anticardiolipin antibodies were performed at baseline and then before each Infliximab infusion.

Results

The variation in ESR, CRP, serum ferritin, leucocyte count, fever, prednisone dosage, and the patient's and physician's global assessment are showed in Figure 1. All patients had chronic persistent refractory disease, requiring continuous prednisone therapy ever since diagnosis. The case histories are summarized below.

Table I. Clinical, biological characteristics and treatment of the patients at baseline.

	Patient 1	Patient 2	Patient 3
Sex	F	F	F
Age (years)	51	50	29
Disease duration (months)	57	95	65
Fever (t max °C)	39	39	38
ESR (mm/h)	54	70	38
CRP (mg/dl)	11	7.8	1.8
Serum ferritin (ng/dl)	1960	805	61
WBC (10^9/L)	15.1	30.3	11.3
Cutaneous rash	present	present	present
Swollen joints	wrists, knees, MCPs	no	wrists
Sore throat	present	present	present
NSAIDs (mg/day)	diclofenac 150	diclofenac 150	ketoprofen 300
Prednisone daily dose (mg)	30	15	20
Prednisone cumulative dose (mg)	21,750	28,580	15,400
Methotrexate (mg/week)	15 (from 1998)	15 (from 1992)	15 (from 1996)
Previous DMARDs	cyclosporin	cyclosporin	no

Patient 1

This patient was a 51-year-old woman with ASD diagnosed in 1995. After an initial remission induced by NSAIDs, prednisone (25 mg/day rapidly tapered to 7.5 mg/day), and methotrexate (15 mg/week), ASD relapsed in 1997. Cyclosporin was added and the prednisone dose was increased to 30 mg/day without any clinical improvement; cyclosporin was suspended 7 months later due to inefficacy.

In November 1999 infliximab was started in association with methotrexate 15 mg/week, prednisone 30 mg/day and diclofenac 150 mg/day. Soon after the first infusion, the patient showed regression of fever, sore throat, cutaneous rash and arthritis. Serological findings showed progressive reduction of ESR, CRP and serum ferritin, whereas the leucocyte count was stable; prednisone was tapered to 10 mg/day.

At 18 weeks ASD relapsed, with resumption of symptoms and a rise in ESR, CRP and ferritinemia. Prednisone was increased without benefit. At 22 weeks, at the beginning of the fifth infusion, the patient developed a diffuse urticarioid rash; the reaction was rapidly controlled by the suspension of infliximab and the institution of methylprednisolone treatment (20 mg I.V.). Infliximab therapy was not re-started. During the treatment antinuclear, anticardiolipin and anti-dsDNA antibodies were constantly negative. At present the patient's therapy consists of methotrexate (20 mg/week), prednisone (30 mg/day) and diclofenac (150 mg/day) and the disease is still active.

Patient 2

This patient is a 50-year-old woman with ASD diagnosed in 1992. The disease rapidly assumed a chronic course despite treatment with NSAIDs, prednisone and methotrexate. Between 1995 and 1996 cyclosporin was introduced without benefit and then suspended.

In December 1999 infliximab was added to the current therapy. The benefits were evident soon after the first infusion, with a complete control of systemic symptoms; serological findings showed normalization of ESR, CRP and serum ferritin. White blood cells did not vary during the treatment. Prednisone was tapered to 10 mg/day and the NSAID was suspended. At weeks 20 and 28 the patient reported a relapse of arthralgias and sore throat, which were rapidly controlled by the reinfusion of infliximab. After 30 weeks infliximab was given at the same dose (3 mg/kg) every 4 weeks, without any relapse. Treatment did not induce any adverse reaction and autoantibody assays were constantly negative.

Patient 3

This 29-year-old woman developed ASD in 1995. First treatments were NSAIDs and prednisone (10 mg/day). In October 1997, because of fever and leukocytosis, methotrexate (10 mg/week) was started with clinical remission. In March 1999 ASD relapsed; the methotrexate dose was increased to 15 mg/week and prednisone to 20 mg/day without clinical improvement.

In December 1999 infliximab was added. Baseline serological findings revealed high levels of ESR, CRP and leucocytosis, whereas serum ferritin was normal. The first infusion resulted in complete control of the systemic symptoms; ESR and CRP rapidly normalized, leucocyte count did not vary during treatment. Prednisone was tapered to 10 mg/day. Arthralgias and sore throat reappeared at 20 and 28 weeks, but were rapidly controlled by Infliximab reinfusion. After 30 weeks, infliximab was continued at the same dose every 4 weeks without any relapse. The patient did not show adverse reactions; antinuclear, anticardiolipin and anti-dsDNA antibodies were negative.

Discussion

The usefulness of a TNF- antagonist in the treatment of ASD was first signaled by Stambe *et al.* (11); in 1998 they reported the efficacy of thalidomide, a known inhibitor of TNF- (12), in a 44-year-old woman with a 4-year history of ASD not responsive to conventional treatment. In this case thalidomide was effective despite low plasma levels of TNF- . On the other hand, Hoshino *et al.* found high levels of TNF- , as well as interleukin-6 and interferon- , in 12 patients with ASD (13). In 1998 Elliot *et al.* showed the effectivness of Infliximab in the suppression of fever and acute-phase response in a patient with systemic juvenile chronic arthritis, without any improvement in the patient's arthritis (10).

To the best of our knowledge, the pre-

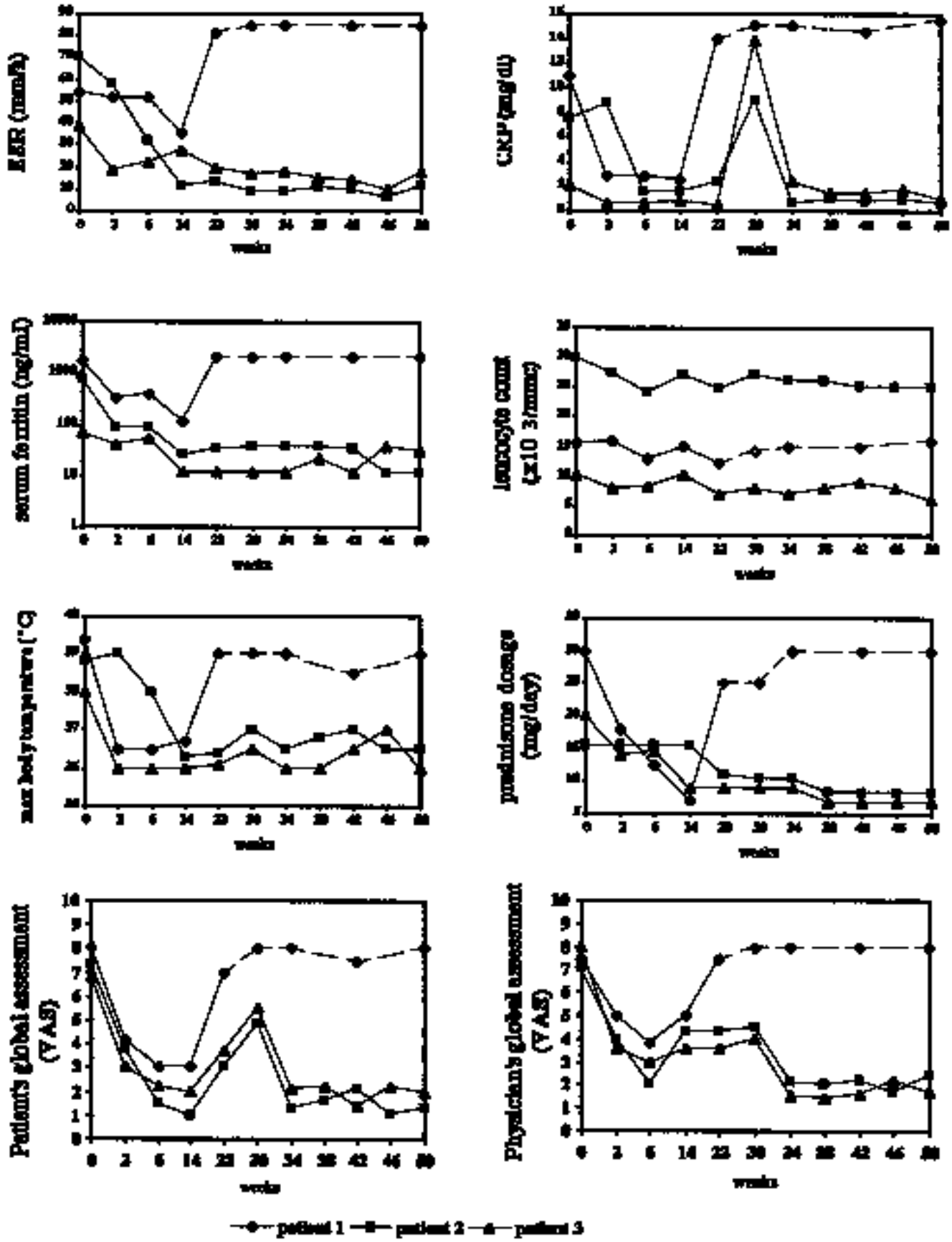

Fig. 1. Variation of laboratory parameters, maximal body temperature, prednisone dosage, and patient's and physician's global assessment during follow-up (patient 1 suspended treatment at 22 weeks).

sent paper is the first report of the use of infliximab in refractory ASD. The treatment led to a rapid control of systemic symptoms and a decrease in ESR, CRP and serum ferritin in all cases, whereas the white blood cell count did not vary significantly. In our patients the number of swollen or tender joints was low at baseline (see Table I); in all cases infliximab infusion resulted in a regression of the patients' arthritis.

During follow-up, patient 1 relapsed at 18 weeks and dropped out of the study at week 22 due to an adverse reaction (see below). Patients 2 and 3 showed a relapse of arthralgias and sore throat at weeks 20 and 28, i.e. 6 weeks after the last infliximab infusion; drug reinfusion led in both cases to the complete control of symptoms. This fact could have been due to an excessively long interval between the infusions, since a reduction in this interval from 8 to 4 weeks led to persistent clinical improvement in both patients. As a matter of fact, in rheumatoid arthritis the recommended dosage ranges from 3 mg/kg every 8 weeks to 10 mg/kg every 4 weeks (7). Our study does not give any indication as to the optimal duration of infliximab therapy in ASD. However, treatment should not be stopped prematurely since relapses were common in our patients after drug discontinuation or when infusions were given at 8-week intervals.

Previous reports showed the usefulness of serum ferritin levels as a marker of ASD activity (14,15). In all of our patients serum ferritin decreased during treatment, even if in patient 3 baseline values were within normal limits, suggesting the presence of concomitant true iron deficiency (16, 17). Indeed, in patient 3 the clinical response was associated with reduction in serum ferritin levels, which reached values as low as those observed in iron deficiency.

Few cases of cutaneous rash and urticaria have been reported in patients with rheumatoid arthritis treated with Infliximab (7), while they were observed in two of our three patients. Patient 1 presented a severe diffuse urticarioid reaction soon after the beginning of the fifth infusion, so that Infliximab was stopped. Patient 3 developed a mild diffuse cutaneous rash in correspondence with the first and second infusions; pre-medication with oral chlorpheniramine prevented this side effect. Further studies are needed to ascertain whether allergic cutaneous reactions to infliximab do occur more frequently in ASD than in RA. During follow-up our patients did not present any infection and we did not find the occurrence of antinuclear and anti-dsDNA antibodies, previously reported in some RA patients treated with infliximab (7, 9).

In conclusion, infliximab may be regarded as a useful tool in the treatment of relapse of the disease refractory to conventional therapy and requiring continuous high dose corticosteroid medication. Further controlled studies on a larger number of patients are needed to evaluate the optimal schedule of infusion as well as long-term efficacy and safety of this treatment.

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