

A combination of etanercept and methotrexate for the treatment of refractory juvenile idiopathic arthritis: a pilot study

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Abstract

Objective—To study the efficacy of combination therapy with etanercept and methotrexate in patients with refractory juvenile idiopathic arthritis.

Methods—Seven children with active juvenile idiopathic arthritis refractory to at least combination therapy with methotrexate and sulfasalazine or cyclosporin A were studied. Concomitant treatment, consisting of non-steroidal drugs, corticosteroids, and methotrexate, remained unchanged.

Results—Six patients continued the treatment for at least 24 weeks. In the child with systemic arthritis, etanercept was stopped because of persisting spiking fever, joint pain, and rash. In the remaining children an immediate significant decrease in joint pain ($p < 0.05$), disappearance of morning stiffness, and regression of joint swelling ($p < 0.05$) were observed. Improvement was apparent after two injections. An immediate significant ($p < 0.05$) decrease in erythrocyte sedimentation rate, C reactive protein, and interleukin 6 was observed. Side effects consisted of mild reactions at the injection site in two children.

Conclusions—In this observational study, etanercept in combination with methotrexate was well tolerated and highly effective in treating juvenile polyarthritis but not in the patient with systemic arthritis. Combination treatment appears to be feasible in terms of toxicity and may enhance efficiency.

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The term juvenile idiopathic arthritis (JIA) was coined in 1996 and includes juvenile rheumatoid and chronic arthritis according to the earlier ARA and EULAR classification criteria.¹⁻³

Seven groups were defined, depending on presentation during the first six months of the disease. Prognosis depends on the subgroup, with systemic and polyarticular onset JIA having the worst outcome.^{4,5} Pharmacotherapy consists of multiple drug combination treatment including non-steroidal drugs, corticosteroids, and various disease modifying drugs.⁵ As double blind, controlled studies in JIA showed efficacy only with sulfasalazine and methotrexate, these two compounds are currently used most often.^{6,7} However, in a significant proportion of children, the disease activity cannot be controlled even with combinatory regimens.

Although the cause of JIA is not well understood, evidence exists that proinflammatory cytokines such as interleukin (IL)1, IL6, and tumour necrosis factor α (TNF α) play an important role in the pathogenesis of the disease. Biologically active molecules targeting proinflammatory cytokines have been successfully applied for rheumatoid arthritis.⁸⁻¹⁰ TNF α can be neutralised by monoclonal antibodies or by etanercept, a genetically engineered construct consisting of the extracellular domains of p75 TNF receptor molecules and the human immunoglobulin gamma chain Fc fragment. A placebo controlled trial using etanercept in polyarticular JIA has been published very recently.¹¹ In this study, methotrexate was discontinued because of intolerance or lack of efficacy. The present observational study reports the first experience using etanercept in combination with methotrexate to treat children with active and refractory JIA.

Methods

PATIENTS

Table 1 outlines the patient characteristics. All children had active non-remittent disease that had been refractory to multiple treatment regimens for 2.5-7 years.

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Table 1 Characteristics of patients with juvenile idiopathic arthritis (JIA)

Sex	Age at onset (years)	Disease duration (years)	JIA subtype*	Previous DMARD†	Concomitant medication	Current treatment
1 Male	7	7	VI	MTX,SUL , AUR	NSAIDs, MTX, prednisone 7.5 mg	NSAIDs, MTX, prednisone 7.5 mg
2 Female	4	4	II	MTX,SUL , AUR	NSAIDs, MTX, prednisone 5 mg	NSAIDs, MTX, prednisone 2.5 mg/48 h
3 Female	3	2.5	II	MTX,SUL	NSAIDs, MTX, prednisone 5 mg	NSAIDs, MTX, prednisone 2.5 mg/48 h
4 Female	2.5	4	IVb	MTX,SUL , AUR, ivIGG	NSAIDs, MTX, prednisone 2.5 mg	NSAIDs, MTX,
5 Female	7	4	III	MTX,SUL , AUR	NSAIDs, MTX, prednisone 5 mg	NSAIDs, MTX, prednisone 2.5 mg/48 h
6 Female	3	8	IVb	MTX,SUL , AUR, ivIGG, CHL	NSAIDs, MTX, prednisone 2.5 mg	NSAIDs, MTX,
7 Male	9	2.5	I	MTX, AZA, CSA, pulse prednisolone , ivIGG	NSAIDs, MTX, prednisone 7.5 mg,	

*JIA subtypes: I, systemic onset; II, seronegative polyarticular onset; III, seropositive polyarticular onset; IV, oligoarticular onset, IVb, oligoarticular onset and polyarticular course; VI, psoriasis and arthritis.⁷

†DMARD = disease modifying drugs: MTX = methotrexate; SUL = sulfasalazine; AUR = injectable gold salts; CHL = chlorambucil; ivIGG = high dose intravenous immunoglobulins; CSA = cyclosporin A; AZA = azathioprine; NSAIDs = non-steroidal anti-inflammatory drugs. DMARDs used directly before entry to the study are printed in bold. The dose of methotrexate was 10-15 mg/m² body surface per week.

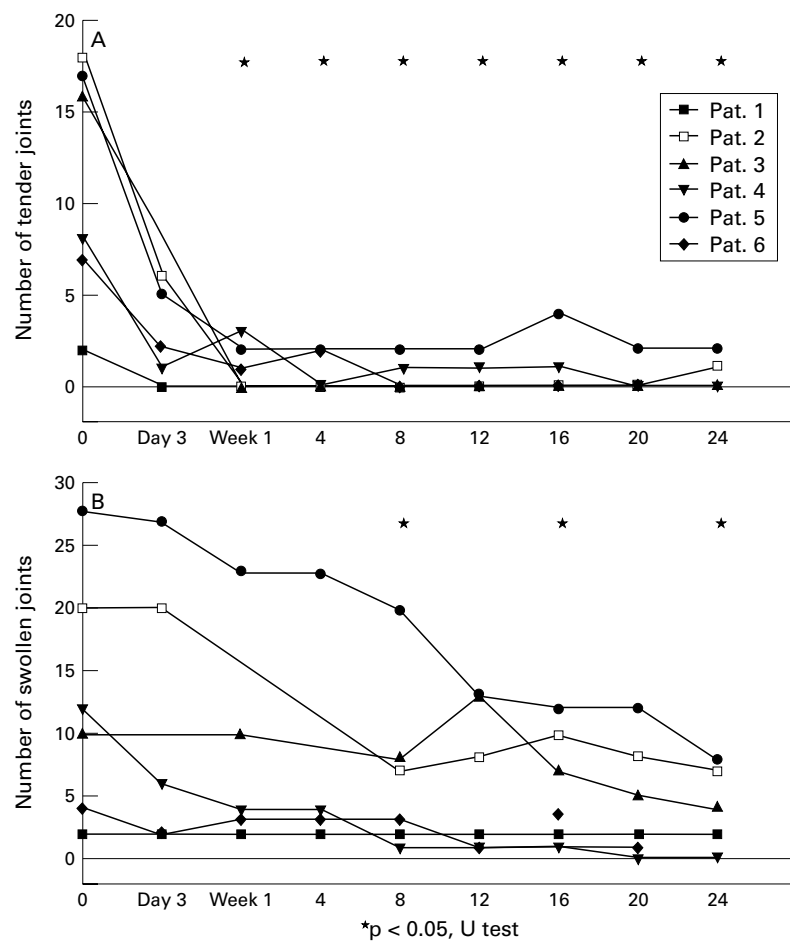


Figure 1 Clinical outcome parameters. (A) The tender joint count and (B) the number of swollen joints decreased significantly ($p < 0.05$, indicated by asterisks). Morning stiffness disappeared in all children after one week of treatment (data not shown).

TREATMENT PROTOCOL

Etanercept was given subcutaneously at a dose of 0.4 mg/kg body weight twice a week as recommended. In the boy with systemic arthritis, the dose was increased to 1 mg/kg. All except this boy were discharged after the first injections. The number of swollen and tender joints and the duration of morning stiffness were recorded monthly. Routine laboratory variables—erythrocyte sedimentation rate (ESR), serum levels of C reactive protein (CRP) and IL6 (enzyme linked immunosorbent assay (ELISA); Immulite; Biermann, Bad Nauheim, Germany)—were monitored.

CONCOMITANT TREATMENT

Long term treatment with sulfasalazine was terminated in five children before etanercept was instituted. Weekly oral methotrexate, non-steroidal drugs, and stable low dose corticosteroids (7.5 mg/day in the boy with systemic JIA) were continued.

STATISTICAL ANALYSIS

This was performed using SPSS software (SPSS Inc, Chicago, Illinois, USA). Changes in outcome parameters were analysed by non-parametric testing (Mann-Whitney U test).

Results

In six patients, treatment was performed for at least 24 weeks. Patient 7, a boy with systemic arthritis, continued to show spiking fever,

malaise, weakness, arthritis of both wrists, polyarticular joint pain, and a rheumatoid rash despite treatment with etanercept. Therefore the dose was increased to 25 mg (1 mg/kg body weight) for eight weeks without any clinical improvement. There was also no improvement in the laboratory variables (ESR, 58 and 90 mm/h; CRP, 103 and 75 mg/l; IL6 133 and 1278 pg/ml; before and at the end of treatment). Therefore etanercept was discontinued and corticosteroids were increased to 1.5 mg/kg body weight.

In the remaining six patients, tender joint count decreased significantly ($p < 0.05$ at week 1, months 1–6). In four children tenderness in the joints disappeared completely, whereas in the remaining two, the tender joint count decreased from eight to one and from 17 to four. In all children, morning stiffness had disappeared completely at the end of the first week. The number of swollen joints significantly regressed in all children with polyarticular disease (fig 1; $p < 0.05$ at months 2, 4, 6; $p = 0.08$ at month 3; $p = 0.06$ at month 5). In three of five children with polyarticular arthritis, complete remission was evident after one to two months of treatment. In the remaining two, joints remained swollen but without pain. All children were able to resume physical treatment. In two children, corticosteroids could be withdrawn, and they were tapered off in three children.

Patient 1 presented with highly active arthritis of both knee joints with a flexion contracture of 30° refractory to intensified physiotherapy and several intra-articular injections of triamcinolone. On etanercept treatment, his symptoms disappeared and he gained full joint function during the first month of treatment. Joint swelling regressed considerably, but effusions persisted for up to eight months by which time they had completely disappeared in the right knee. Of interest, at months 6 and 7, his left knee required arthrocentesis because of a pronounced effusion, although pain, inflammation, and morning stiffness were absent.

Figure 2 gives the laboratory results. Before treatment, all children had elevated ESR, CRP, and IL6 levels except for patient 5, who presented with active joint disease despite a normal ESR. On treatment, the ESR decreased to normal levels (< 10 mm/h) in four children after one month, and in five children after two, three, and four months respectively. At four months, one child showed a transient increase in ESR to 60 mm/h without any clinical signs of a disease flare. CRP levels persistently showed considerable decreases after one or two injections only, reaching almost normal levels (below 10 mg/l) after one month in five children and after two months in the remainder. IL6 levels were considerable elevated in three cases (50 ng/l to 140 ng/l) and moderately elevated in the other three. IL6 levels normalised after one to two injections (< 10 ng/l; data not shown).

The change in ESR from baseline to week 1, month 1, 2, 5 and 6, and the change in CRP and IL6 from baseline to week 1, months 1–6, were significant ($p < 0.05$).

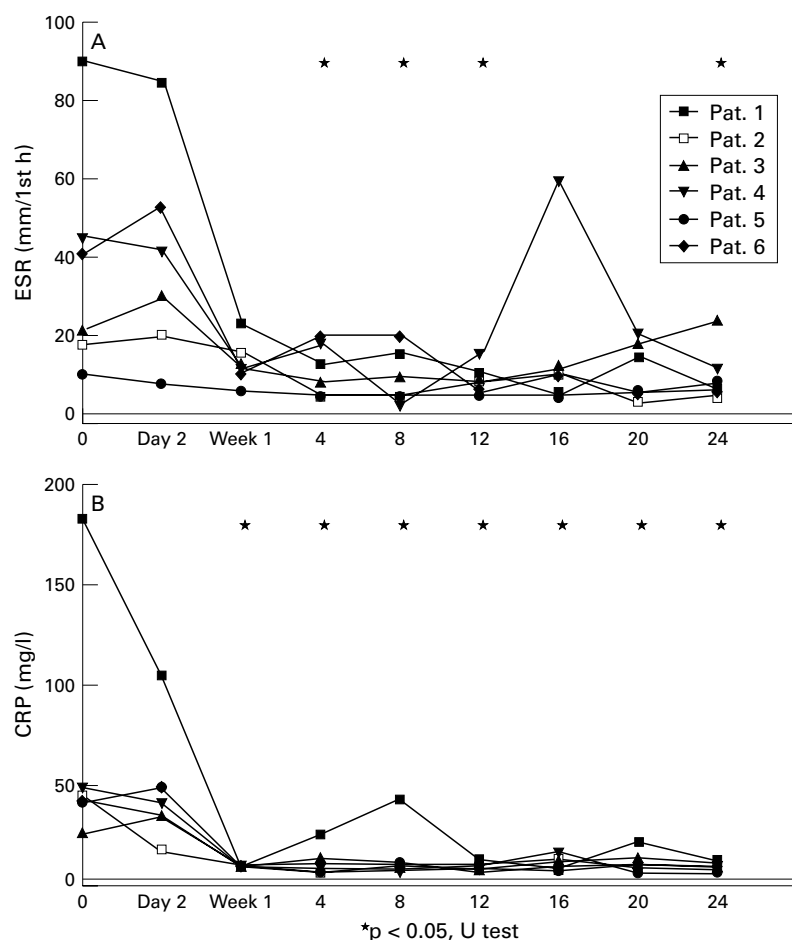


Figure 2 Laboratory outcome parameters. The median erythrocyte sedimentation rate (ESR) decreased significantly from 31 to 8, 7.5, 9, and 12.5 mm/h after one, two, three, and six months respectively ($p < 0.05$, indicated by asterisks). The median C reactive protein (CRP) level significantly decreased from 41.3 to 5.5, 7.1, 6.5, and 6.9 mg/l after one, two, three, and six months respectively ($p < 0.05$, indicated by asterisks). The median IL6 level decreased from 34.2 to 6.3 pg/ml, after one month. Thereafter it remained undetectable in sera from five of the six patients (data not shown).

Injection site related side effects were noted in two children and consisted of an itching erythema lasting for up to one week after the injection. However, no patient dropped out of the study because of skin reactions. No further side effects, especially infections, were observed.

Discussion

The first trial of etanercept in JIA was published very recently.¹¹ During the first open part of this study, improvement was seen in 51 of 69 children with JIA (74%). The responders took part in a placebo controlled trial that confirmed the efficacy of the drug by achieving at least 50% improvement in 70% of children compared with 25% of patients on placebo. This study included children who failed or did not tolerate methotrexate. Our patients received a combination of etanercept and methotrexate because prior studies in adult patients with rheumatoid arthritis have shown synergistic effects of methotrexate and etanercept.¹⁰

Our patients showed a rapid and impressive improvement in joint tenderness and morning stiffness. However, the persistence of joint swelling and effusions in half of the patients, albeit at a low level, indicates that the drug did not induce complete remission.

Only minor side effects were observed. Injection site reactions did not require termination of treatment. However, the observation period is too short for evaluation of long term tolerance. In patients with JIA, corticosteroids are given only for highly active uncontrolled disease. The sparing use of corticosteroids is a major aim of the antirheumatic treatment. Treatment with etanercept allowed discontinuation or tapering off of corticosteroids in all six patients.

In our patients, the combination of etanercept with methotrexate did not result in increased toxicity. The long term efficacy remains to be determined in further multicentre controlled trials. In addition, the impact of TNF inhibition on the development of erosive disease in JIA has not been confirmed. However, the delay in radiographic progression seen in patients with rheumatoid arthritis treated with TNF inhibitors raises hope that this phenomenon may also occur in JIA. Furthermore, it will be of interest to investigate whether etanercept is effective for two major problems of paediatric rheumatology, rheumatoid uveitis and systemic arthritis. Our attempt to treat with etanercept a boy with systemic arthritis was unsuccessful, in contrast with our patients with other onset subtypes of JIA. This observation is in agreement with the results of Lovell *et al*¹¹: while on etanercept, four of nine patients with systemic onset JIA showed a flare of the disease activity, but only three of 14 patients with polyarticular onset and none of two patients with oligoarticular onset JIA. It will be an important future task to identify patients who are likely to improve on etanercept.

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