Etanercept in systemic juvenile idiopathic arthritis

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ABSTRACT

Objective

To evaluate the effectiveness of etanercept in patients with systemic juvenile idiopathic arthritis (SJIA) refractory to methotrexate (MTX) therapy in a pediatric rheumatology practice.

Methods

Fifteen patients with SJIA with active polyarthritis refractory to higher dose MTX (≥ 20 mg/m²/week) for at least 3 months were included. Patients received etanercept 0.4 mg/Kg twice weekly concomitantly with MTX. Observed period of treatment ranged from 5 to 12 months (median 9 months).

Results

Improvement of ESR, swollen and limited joint counts, functional capacity, and general wellbeing was achieved by 14/15 patients. The most significant impact on these variables was observed 3 to 5 months after treatment onset. Mean time to improvement was 2 months. In the 4 patients who presented fever and rash, these signs disappeared after the beginning of etanercept treatment and reappeared during flares. Three patients showed sustained clinical and biochemical remission on low dose MTX (≤ 5 mg/m²/week). Thirteen relapses were observed in 9 (60 %) patients at a mean of 7.6 months after therapy was begun. Etanercept was discontinued due to lack of efficacy in 7 patients, only after higher dose (1 mg/kg/dose) was used. MTX and corticosteroid doses were decreased during the observation period. No serious side effects were observed.

Conclusions

Etanercept, in combination with MTX, demonstrated benefit soon after initiation of treatment in patients with refractory SJIA, but flares and progressive loss of effectiveness were observed with continued treatment in most patients. Sharp decreases in the dose of MTX and corticosteroids may have contributed to subsequent occurrence of flares. Changes in MTX and corticosteroids doses should probably need to be made gradually, and it is possible that patients on SJIA should continue on therapeutic doses of MTX while being on etanercept in order to maintain therapeutic benefit.

Introduction

Systemic juvenile idiopathic arthritis (SJIA) is probably the most severe form of juvenile arthritis, frequently leading to severe dissability and significant mortality (1). Most patients with SJIA need to be treated with NSAIDs as well as disease modifying drugs. For the past decade, methotrexate (MTX) has been the drug of choice for the disease, but some children do not respond satisfactorily to this treatment (2). Etanercept, a dimeric fusion protein that binds tumour necrosis factor (TNF) α inhibiting its activity, has demonstrated short-term efficacy and safety in the treatment of polyarticular JIA that failed to respond to MTX in one placebo-controlled study (3). Since its publication, only small series of patients with different subsets of JIA treated with etanercept have been reported (4-8). In these series, patients with SJIA showed infrequent, mild or transient improvement, and frequent flares. However, a retrospective study based on a wide survey revealed a significant benefit in 60% of patients on this treatment (9). Although no controlled studies have been conducted, many pediatric rheumatologists share the impression that etanercept is not particularly effective in patients with SJIA (1). We performed this study to evaluate the effectiveness of etanercept in the treatment of patients with SJIA with active polyarthritis who did not achieve remission with MTX in a pediatric rheumatology clinic.

Patients and methods

Patients

All children with a diagnosis of SJIA (10) who were non-responders to MTX (persistence of active polyarthritis despite the use of higher-dose MTX [≥ 20 mg/m²/week] for at least three months) were included. All patients needed to have active polyarthritis to enter the study. They were followed at the Rheumatology Section of a tertiary hospital in the period December 1999 - September 2001. Patients with concurrent major infections were excluded.

Study design

All patients started etanercept therapy

at 0.4 mg per kilogram of body weight, subcutaneously twice weekly, concomitantly with MTX. Changes in the dose of etanercept and MTX were allowed according to the course of the disease. Treatment with corticosteroids (up to 0.8 mg per kilogram per day of prednisone, or up to 1.2 mg/kg/day of deflazacort) and NSAIDs was permitted. Patients were followed periodically and data were registered prospectively. Intervals between visits varied between one and three months. Clinical and biochemical examinations (hematologic, serum chemical, and urine analysis) were performed on each visit. Clinical data included: age at disease onset, initial and final MTX and steroid doses, presence of systemic signs (fever, rash), pain according to the patient or parents, measured on a visual analogue scale (VAS) (score ranging from 0 to 10), and response variables for the definition of improvement and flare: 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) (11), IV. disease activity according to the physician measured on a VAS (score ranging from 0 to 10), and V. patient wellbeing according to the patient or parents measured on a VAS (score ranging from 0 to 10).

Laboratory variables included: haemoglobin levels, white blood cell count (WBC), platelet (plt) count, erythrocyte sedimentation rate (ESR), rheumatoid factor and antinuclear antibodies. Improvement was defined according to the criteria of Giannini *et al.* (12), as follows: improvement of 30% or more in three of the six response variables (I to V plus ESR) with worsening of 30 percent or more in no more than one of these variables.

Flare was defined according to the criteria used by Lovell *et al.* (3), as follows: worsening of 30% or more in three of the six response variables (a minimum of two active joints required) with improvement of 30% or more in no more than one of these variables. Patients were evaluated for 30, 50, and 70% improvement. Patients in whom the treatment with etanercept was suspended for any reason were withdrawn from the study. Observation period varied between 5 and 12 months (median 9 months). Written informed consent was obtained from all subjects prior to the beginning of the study.

Results

Demographic and base-line data

Fifteen patients were included in the study. All patients were receiving MTX and corticosteroids at the time of etanercept treatment onset. Three patients had also received other second-line drugs prior to entrance to the study (cyclosporine in 1, gammaglobulin in 1, and both in 1). At the time of this evaluation, 15 patients had received etanercept for over 5 months, 13 for over 7 months, 9 for over 9 months, and 5 for over 12 months. Demographic and clinical data at baseline are presented in Table I.

Efficacy of etanercept

Fourteen of the 15 (93%) patients showed improvement at one moment of their follow-up. Seven and 11 patients achieved improvement 1 and 3 months after the beginning of the study respectively. Mean time to improvement was 2 months. Changes in the different variables along the time of treatment as well as achievement of 30, 50, and 70 percent improvement are shown in Table II.

The most pronounced improvement was observed at the third and fifth months after the beginning of etanercept. In those patients who had presented with fever and rash prior to the beginning of the etanercept treatment, these signs disappeared and later reappeared during flares. Three patients reached sustained remission (no joint swelling, limitation, morning stiffness or pain, normal ESR, and full functional capacity), and have presented no relapses after 12 months of follow-up. They were receiving MTX at a dose ≤ 5 mg/m^2/week concomitantly.

Thirteen flares were observed in 9 (60%) patients during treatment, and these occurred at a mean time of 7.6 months after therapy with etanercept was begun. Flares occurred in 7 of the 9 patients who had received the drug for over 7 months. The drug had to be discontinued due to lack of efficacy in 7 patients, only after having increased its dose to 1 mg per kilogram per injection for one month (maximum dose 25 mg) (Fig. 1). This discontinuation occurred at 5 months in 1 patient, and at 7, 9 and 12 months in 2 patients each after initiation of treatment. These 7 patients did not show any clinical or biochemical features at base line that could have allowed differentiation from the other subjects. Additionally, 3 patients were withdrawn from the study due to intermittences in etanercept supply and administration (at 5 and 7 months after initiation of treatment).

MTX was maintained in all patients: its dose was progressively reduced to 5 mg/m^2 weekly in 14 patients, and it

Table I. Demographic and clinical data at baseline.

Age (yr)	9.3 (+/- 4.2)
Sex	
female, no. of pts. (%)	10 (67)
male, no. of pts. (%)	5 (33)
Age at SJIA onset (yr)	5.5 (+/- 3.4)
Duration of SJIA (yr)	3.8 (+/- 2.4)
Methotrexate therapy at study entry (mg/m^2/week)*	27
Corticosteroid therapy	
Prednisone (no. of pts.) (mg/Kg/day)*	12 (0.3)
Deflazacort (no. of pts.) (mg/Kg/day)*	3 (0.6)
No. of pts. with systemic features	4

Values are expressed as means or *medians (+/- 1 SD).
pts: patients.

Table II. Disease activity measures at base-line and visits.

Measure	Base-line	mo 1	mo 3	mo 5	mo 7	mo 9	mo 12
no. of patients at follow-up	15	15	15	15	13	9	5
No. of active joints	17	12 (29)	10 (41)	4 (76)	11 (35)	10 (41)	4 (76)
No. of limited joints	15	7 (47)	4 (73)	4 (73)	11 (27)	10 (33)	4 (73)
Physician's assessment of disease severity*	4.6	2.3 (50)	1.3 (72)	1.2 (74)	2.5 (46)	2.2 (52)	2.5 (46)
Patient's assessment of well-being*	5	2 (60)	2.8 (44)	2.7 (46)	1.8 (64)	2.4 (52)	0.4 (92)
CHAQ score^	1.1	1.1 (0)	0.7 (36)	0.9 (18)	0.9 (18)	1.1 (0)	0.6 (45)
ESR (mm/h)	65	45 (31)	26 (60)	23 (65)	32 (49)	61 (6)	34 (48)
Pain*	3.9	1.7 (57)	1.8 (54)	2.6 (33)	2.6 (33)	3.6 (8)	4.7 (0)
Flares	-	-	1	2	5	3	2
Patients who reached 30% improvement	-	7	11	10	8	6	3
Patients who reached 50% improvement	-	4	7	9	7	5	3
Patients who reached 70% improvement	-	2	6	5	5	3	3
Patients who withdrew due to inefficacy (cummulative)	-	-	-	1	3	5	7
MTX dose (mg/m2/week)	27	25	7	7	5	5	5
Prednisone dose (mg/Kg/day)	0.3	0.1	0.1	0.1	0.15	0.2	0.1

Values are expressed as medians (improvement percentage is in parenthesis)
* scores ranging from 0 (best) to 10 (worst); ^scores ranging from 0 (best) to 3 (worst).

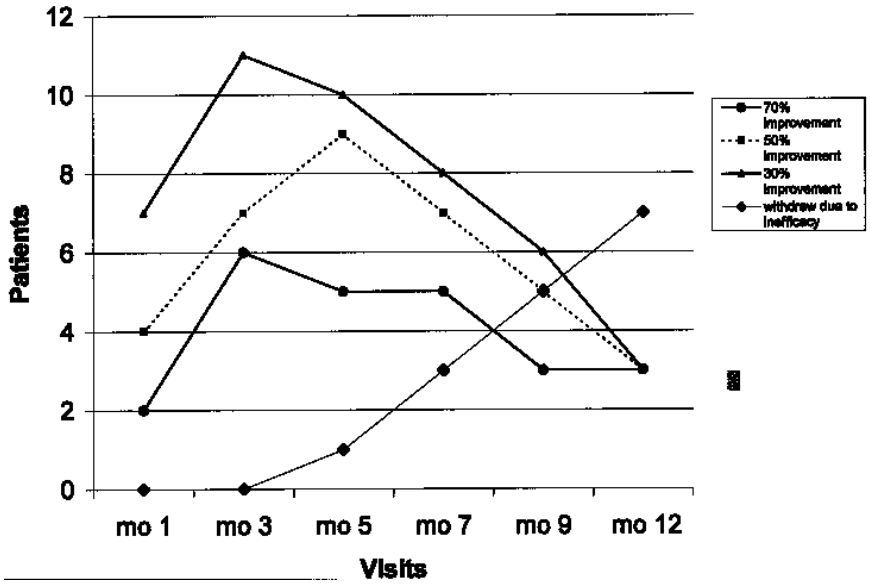

Fig. 1. Achievement of 30,50,and 70% improvement and withdrawals due to efficacy in selected visits.

was kept at 30 mg/m^2 weekly in 1 patient. In 14 (93%) patients corticosteroids dose was tapered or stopped (median dose of prednisone at last visit 0.1 mg per kg daily). No therapeutic arthrocentesis were performed. No side effects were observed with the use of etanercept, except for local pain and bruising in 2 patients, and nausea and vomiting in 1 patient.

Discussion

While MTX is currently the mainstay of therapy for JIA, etanercept is becoming a valid alternative therapy for the treatment of cases refractory to MTX. According to a controlled study on patients with JIA, improvement rates in children with SJIA are inferior to those observed in patients with polyarticular onset JIA after treatment with etanercept (3). Other smaller series showed that patients with SJIA experienced infrequent, mild or transient improvement, and frequent flares (4-8). A survey conducted by Kimura *et al.* (9) revealed that over 60% of patients with SJIA treated with etanercept showed improvement in both their joint and systemic features, but failed to inform about long-term loss of efficacy or concomitant treatment with MTX. Our study shows that the majority of patients with SJIA refractory to MTX benefit from the use of the drug in the first months of treatment, but their improvement is not sustained and both relapses and loss of efficacy occur in many cases.

In his report, Lovell *et al.* (3) included 22 patients with SJIA with polyarticular course of a total of 69 patients with JIA: 77% of patients with SJIA improved after 3 months of etanercept treatment, but 44% of the 9 children who continued the drug for 7 months experienced a flare. Similarly, 93% of our patients improved but 60% experienced a flare, and this event occurred in 7 of 9 patients who continued on etanercept for more than 7 months. Additionally, almost half of our patients needed to discontinue etanercept treatment due to inefficacy in the first 12 months of therapy. It is possible that neutralizing autoantibodies directed against etanercept are synthesized, although they have not been found in previous studies (3).

Other drugs used in concomitance with etanercept, and the changes in their doses, are important factors to be considered when evaluating the effectiveness of this drug. All patients in our study received etanercept and MTX

simultaneously, and this combination may have accounted for the improvement observed at different points. The combination of both drugs is probably synergistic and more efficacious than each of its components alone (13). However, flares were observed in nearly half of our studied population. It should be noted that the modification of MTX and corticosteroid doses performed along the observation period may have certainly exerted some effects over the disease expression in our patients. Both MTX and corticosteroid doses were tapered early after the introduction of etanercept treatment in all our patients. There is a possibility that the observed flares in our study could be related to significant decreases in the dose of concomitant medications and not to a loss of efficacy of etanercept. Sustained higher doses of MTX (and possibly corticosteroids) than those used in our study, or a more gradual tapering of their doses, may contribute to sustained effectiveness of etanercept in patients with SJIA.

In our study etanercept at 0.4 mg/Kg/ dose associated with MTX was of definite benefit to 3 patients who entered sustained remission. In 7 other children who presented flares, higher dose (1 mg/Kg/day) was used but it failed to achieve control of the disease course. High dose etanercept has proven ineffective in patients with JIA in a recent study (5). Of interest, most of the patients included in this study had systemic arthritis.

In summary, etanercept -in combination with MTX- was initially effective in almost all patients with SJIA who had not showed a satisfactory response to MTX, but flares and progressive loss of effectiveness were observed after the first five months of treatment in most patients. Sharp decreases in the dose of MTX and corticosteroids performed in our patients may have contributed to subsequent occurrence of flares. Consequently, changes in MTX and corticosteroids doses should probably need to be made slowly and gradually, and it is also possible that patients on SJIA should continue on therapeutic doses of MTX while being on etanercept in order to maintain clinical benefit.

References

1. WULFFRAAT NM, KUIS W: Transplantation in JRA. *J Rheumatol* 2001; 28: 929-31.
2. REIFF A,SHAHAM B, WOOD BP, BERNSTEIN BH, STANLEY P, SZER IS: High dose methotrexate in the treatment of refractory juvenile rheumatoid arthritis. *Clin Exp Rheuma - tol* 1995; 13: 113-18.
3. LOVELL DJ, GIANNINI EH, REIFF A *et al*.: Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 2000; 342: 763-9.
4. SCHMELING H,MATHONY K, JOHN V, KEYBER G, BURDACH S, HORNEFF G A combination of etanercept and methotrexate for the treatment of refractory juvenile idiopathic arthritis:A pilot study. *Ann Rheum Dis* 2001; 60: 410-12.
5. TAKEI S, GROH D, BERNSTEIN B, SHAHAM B, GALLAGHER K, REIFF A: Safety and efficacy of high dose etanercept in the treatment of juvenile rheumatoid arthritis. *J Rheumatol* 2001; 28: 1677-80.
6. HIGGINS GC, JONES K, RENNEBOHM RM: Variable response of systemic juvenile rheumatoid arthritis to etanercept. *Arthritis Rheum* 2000; 43 (Suppl.): S257.
7. PRIEUR AM, MOUY R, DEBRÉ M, QUARTIER P: Enbrel (etanercept) in juvenile idiopathic arthritis (JIA). *Ann Rheum Dis* 2000; 59: 745-6.
8. KIETZ DA, PEPMUELLER PH, MOORE TL: Clinical response to etanercept in polyarticular course juvenile rheumatoid arthritis. *J Rheumatol* 2001; 28: 360-2.
9. KIMURA Y, LI S, EBNER LYON L, IMUNDO L: Treatment of systemic JIA with etanercept: results of a survey. *Arthritis Rheum* 2000; 43 (Suppl.): S257.
10. PETTY RE, SOUTHWOOD TR, BAUM J *et al*.: Revision of the proposed classification criteria for Juvenile Idiopathic Arthritis: Durban, 1997. *J Rheumatol* 1998: 25: 1991-4.
11. MOROLDO MB, DECUNTO C, HUBSCHER O, *et al*.: Cross-cultutral adaptation and validation of an Argentine-Spanish version of the Stanford Childhood Health Assesment Questionnaire (CHAQ). *Arthritis Care* 1998; 11: 382-90.
12. GIANNINI EH, RUPERTO N, RAVELLI A, LOVELL DJ, FELSON DT, MARTINI A: Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997; 40: 1202-9.
13. WEINBLATT ME, KREMER JM, BANKHURST AD *et al*.: A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340: 253-9.