Preliminary evidence that etanercept may reduce radiographic progression in juvenile idiopathic arthritis

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Abstract

Objective

To investigate the rate of radiographic progression, as measured with the carpo-metacarpal ratio (Poznanski score), during etanercept (ETN) therapy in children with polyarticular juvenile idiopathic arthritis (JIA).

Methods

Patients included in the Italian ETN registry who had a standard radiograph of both hands and wrists in the posteroanterior view made at start of treatment and after 1 year were included in the study. The clinical response was assessed by means of the ACR Pediatric definition of improvement. Radiographic progression was determined by calculating the change in the Poznanski score between the baseline and the 1-year radiographs.

Results

A total of 40 patients were studied. The frequency of ACR pediatric 30, 50, and 70 response at 1 year was 77%, 72%, and 50%, respectively. The median change in the Poznanski score between baseline and 1 year was + 0.3 units, meaning that, on average, patients experienced improvement in radiographic progression.

Conclusion

Our pilot study provides evidence that ETN is potentially capable of reducing the progression of radiographic joint damage in JIA. This finding deserves confirmation in a controlled trial.

Key words

Juvenile idiopathic arthritis, etanercept, tumor necrosis factor inhibitors, radiographic progression, carpo-metacarpal ratio.

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Introduction

In recent years, the biologic response modifier etanercept (ETN) has become the drug of first choice in children with polyarticular juvenile idiopathic arthritis (JIA) who show an inadequate response to, or are intolerant of, methotrexate (MTX) (1-3). ETN is currently the only biologic agent that is licensed for the treatment of children and adolescents aged 4 to 17 years with active polyarticular JIA who have had an inadequate response to, or who have proved intolerant of, MTX. The efficacy and safety of ETN in JIA have been demonstrated in a randomized clinical trial in 69 patients who were intolerant or refractory to MTX (4). Long-term extension studies of the original trial cohort have documented sustained clinical benefit and acceptable safety profile after 2 and 4 years (5, 6). These findings were confirmed in several non controlled analyses and in reports from national registries (7, 8), although some investigators observed a less encouraging safety profile (7) or noticed that patients with systemic-onset disease did not respond as well to ETN as those with other forms of JIA (7-9). Recently, knowledge on the effectiveness of this drug in JIA was further expanded by the demonstration of its favorable impact on growth velocity and bone status (10, 11). However, no information still exists regarding whether ETN has the ability to prevent progression of radiographic damage to joints. This detracts from the evidence of its effectiveness in JIA because it does not allow to fully establish whether it possesses a disease-modifying potential (12). Studies in adult patients with rheumatoid arthritis have shown that ETN slows the rate of radiographic progression when given as monotherapy, and that this effect is more pronounced when it is given in combination with MTX (13, 14).

The aim of the present study was to investigate the rate of radiographic progression, as measured with the carpometacarpal ratio (Poznanski score) (15, 16), during ETN therapy in children with JIA.

Patients and methods

Patient selection

The study cohort was composed by JIA patients who were treated with ETN between March 1999 and January 2004 in the centers belonging to the Italian Pediatric Rheumatology Study Group and were included in a registry aimed to collect data on the efficacy and safety of the drug. The registry was sponsored by the Italian Ministry of Health (anti-TNF therapy in rheumatoid arthritis ANTARES registry) and was managed by the Paediatric Rheumatology International Trials Organization (PRINTO) (17). Patients were candidate to receive ETN if they had JIA by the International League of Associations for Rheumatology (ILAR) criteria (18), had a polyarticular course of arthritis, and were refractory to, or intolerant of, MTX. Patients in the registry who had involvement of wrist joints and had a standard radiograph of both hands and wrists in the posteroanterior view made at treatment start (baseline) and after 1 year were included in the present study. All films were done with identical projection and were of sufficient quality to enable measurement of the Poznanski score components (see below).

Clinical assessment

Patient information recorded at baseline included: onset age, sex, ILAR category, and disease duration. The following clinical assessments made at baseline and after 1 year were also recorded: physician's global assessment of disease activity on a 10-cm visual analogue scale (VAS; 0 = no activity; 10 = maximum activity); parent's global assessment of the child's well-being on a 10-cm VAS (0 = very good; 10 = very poor); parent's rating of the intensity of the child's on a 10-cm VAS (0 = no pain; 10 = very severe pain), count of joints with swelling, pain on motion/tenderness, and restricted motion; count of joints with active arthritis (*i.e.*, joints with swelling or, if no swelling was present or detectable, with restricted motion and either pain upon movement or tenderness) (19); functional ability assessment through the Italian version of the Childhood Health Assessment Questionnaire (CHAQ) (20) (0 = best; 3 = worst); and erythrocyte sedimentation rate (ESR) (Westergren method).

Assessment of therapeutic response

The clinical response at 12 months after the beginning of ETN therapy was assessed by means of the ACR Pediatric definition of improvement (21). This definition is based on a core set of 6 outcome measures (physician's global assessment, parent's global assessment, active and restricted joint counts, functional ability assessment, and an acute phase reactant) and requires, to enable classification of a patient as responder at the end of a trial, an improvement of at least 30% with respect to baseline in at least 3 of the 6 core set items, with no more than 1 of the remaining worsened by more than 30%. Patients were also evaluated for 50% and 70% improvement (50% and 70% improvement in at least 3 of the 6 response variables and a worsening of 30% or more in no more than 1 of the 6 response variables).

Radiographic assessment

Radiographic joint damage was scored according to the Poznanski method (16) by 2 independent investigators (FR and SMM) who were unaware of the clinical data. This method is based on the measurement of the radiometacarpal length (RM) and of the length of the second metacarpal bone (M2). Patients with advanced bone destruction or radiographic closure of the growth plates of the second metacarpal, which precludes application of the Poznanski method, were excluded from the analysis.

For each wrist, the number of standard deviations (SD) between the expected and the observed RM for the measured M2 was calculated according to the formulae reported by Poznanski *et al*. (16). The RM/M2 ratio, which constitutes the Poznanski score, reflects the amount of radiographic damage in the wrist. The more negative the Poznanski score is, the more severe the radiographic damage. The radiographic progression in the first year was determined by calculating the change in the Poznanski score between the baseline and the 1-year radiographs. A positive value of radiographic progression indicates improvement, whereas a negative value reveals worsening.

Intraclass inter and intra-reader correlation coefficients for RM and M2 measurements were very high, ranging from 0.93 to 0.99. The independent scores of the 2 observers for each radiograph were then averaged, and this average was used for the analyses. In each patient, the Poznanski score was expressed as the mean of the 2 wrists.

Statistics

Quantitative variables were reported as medians and interquartile ranges, whereas qualitative variables were reported as frequencies. Comparison of clinical features between patients included and excluded from the study was made by the Mann-Whitney U-test, in case of quantitative variables, and by the chi-square test or Fisher's exact test, as appropriate, in case of qualitative variables. Correlation between the length of disease before ETN therapy and the change in Poznanski score during treatment was calculated using the Spearman rank correlation coefficient.

Table I. Comparison of the demographic and clinical features of patients included or not included in the study. Values are medians (interquartile range) unless otherwise indicated.

	Patients included (n=40)		Patients not included (n=171)		*p*-value
	N		N		
No. (%) female	40	25 (62.5)	171	124 (75.6)	0.21
No. (%) male		15 (37.5)		47 (27.4)	
ILAR category, no. (%)	40		171		
Oligoarthritis extended		7 (17.5)		48 (28.1)	0.1
Polyarthritis[#]		21 (52.5)		75 (43.9)	
Systemic arthritis		11 (27.5)		41 (24)	
Psoriatic arthritis		1 (2.5)		7 (4.1)	
Age at onset (years)	40	2.9 (2.2; 4.3)	166	3.6 (2; 8.1)	0.04
Disease duration (years)	40	4.4 (2.6-7.0)	166	7 (3.3; 11.3)	0.002
Physician's global assessment[§]	39	6.5 (5.0; 8.8)	166	5.7 (4.3; 7)	0.004
Parent's global assessment[§]	36	6.0 (4.6; 7.3)	147	5.1 (2.7; 7)	0.04
Parent's pain assessment[§]	36	5.7 (4.3; 7.9)	144	4.9 (2.5; 6.7)	0.01
CHAQ score[†]	36	1.4 (1.0; 1.9)	147	1 (0.4; 1.5)	0.007
Active joint count	40	9.5 (6.0; 17.5)	171	8 (5; 15)	0.43
Swollen joint count	39	6.0 (4.0; 15.0)	171	6 (3; 11)	0.50
Tender joint count	39	9.0 (5.0; 14.0)	171	7 (2; 13)	0.20
Restricted joint count	39	8.0 (6.0; 19.0)	171	9 (5; 16)	0.56
ESR, mm/hour[¶]	40	49.5 (25.0; 70.5)	170	44 (29; 66)	0.61
Poznanski score, units°	40	- 2.0 (-3.3; -0.7)	53	-2.2 (-4.1; -1.1)	0.57
No. (%) previously treated with econd-line drugs	40	40 (100%)	198	198 (100%)	1
Patients who took other second-line drugs during ETN administration	40	30 (75%)	171	99 (57.9%)	0.05
Patients who took corticosteroid therapy during ETN administration	40	18 (45%)	171	66 (38.6%)	0.46
No. (%) of ACR Pediatric 30 responders					
at 3 months	36	26 (72.2%)	147	94 (63.9%)	0.35
at 6 months	36	24 (66.7%)	129	96 (74.4%)	0.36
at 12 months	31	24 (77%)	93	66 (71%)	0.49

ILAR: International League for Associations of Rheumatology; CHAQ: Childhood Health Assessment Questionnaire; ESR; erythrocyte sedimentation rate; [#]3 and 7 patients in the included and not included group, respectively, were rheumatoid-factor positive; [§]range 0 (best) to 10 (worst); [†]range 0 (best) to 3 (worst); [¶]normal < 15 mm/hour; °normal < 0.3 mg/dl.

Results

Up to June 2004, a total of 211 JIA patients treated in 17 centers had been enrolled in the Italian ETN registry. Forty of these patients, enrolled in 7 centers, who had a hand/wrist radiograph made at treatment start and after 1 year available for review were included in the

Table II. Absolute values and changes in JIA outcome measures in the first year of etanercept therapy.

	Baseline value	1 yr value	Change baseline - 1 yr	
	Median (IQR)	Median (IQR)	Median	Percentage
Physician's global assessment	6.5 (5.0; 8.8)	2.4 (0.6; 3.5)	-4.8	-72
Parent's global assessment	6.0 (4.6; 7.3)	1.4 (0.4; 2.8)	-4.3	-72.2
Parent's pain assessment	5.7 (4.3; 7.9)	1.1 (0.4; 2)	-4.7	-84.7
CHAQ score	1.4 (1.0; 1.9)	0.6 (0; 1)	-0.9	-66.7
Active joint count	9.5 (6.0; 17.5)	2.5 (1; 6)	-8.5	-78.4
Swollen joint count	6.0 (4.0; 15.0)	1 (0; 4)	-6.0	-88.9
Tender joint count	9.0 (5.0; 14.0)	1 (0; 5)	-8	-87.5
Restricted joint count	8.0 (6.0-19.0)	4 (1; 8)	-6.0	-60
ESR, mm/hour	49.5 (25.0-70.5)	21 (12; 49)	-19	-46.6
Poznanski score, units	- 2.0 (-3.3; -0.7)	-1.8 (-3.4; -0)	0.3§	-16

See Table I for abbreviations and normal ranges. §For the Poznanski score a positive change means improvement, as opposed to all other outcome measures.

present study. Of the 171 patients not included, 99 had no radiographs available, 53 had only a baseline radiograph, and 21 had advanced bone destruction or radiographic closure of the growth plates in the wrists that precluded a reliable assessment of the Poznanski score. The baseline demographic and clinical features of patients included and not included in the study are shown in Table I. Patients included and not included were comparable for female/male ratio, distribution of ILAR categories, severity of joint disease, ESR, Poznanski score, and frequency of previous second-line drug therapy. Compared with patients included, patients not included were older at disease onset, had longer disease duration, had greater physician and parent global assessments and C-HAQ score, and were more likely to have received other second-line medications concomitantly with ETN. The frequency of active arthritis in the wrist at treatment baseline in patients included and not included was 78% and 56%, respectively. The frequency of ACR Pediatric 30 response at 3, 6, and 12 months was comparable across patients included or not included.

ETN was started in all patients at the standard dose of 0.4 mg/kg twice a week and was given subcutaneously. In the first year of treatment, 30 of the 40 patients were simultaneously given another second-line medication, which was MTX in 26 (87%) of them. Table II shows the median values of the JIA outcome measures at treatment start and after 1 year, and their median and percentage change. All clinical measures showed a marked improvement, which ranged from 47% to 89%. The median change in Poznanski score between baseline to 1 year was + 0.3 units, which means that, on average, patients experienced improvement in radiographic progression. The frequency of ACR pediatric 30, 50, and 70 response at 1 year was 77%, 72%, and 50%. Correlation between length of disease before ETN therapy and change in the Poznanski score during ETN treatment was not significant (r=0.29; p=0.12), meaning that the two parameters were not interrelated

Discussion

Our study is the first to investigate the rate of radiographic progression during ETN therapy in children with JIA. We used the Pozanski score to measure radiographic progression in our patients because this score was specifically developed for use in children (16) and was previously demonstrated to be valid for the assessment of progression of radiographic damage in JIA patients (22). We found that, on average, our patients with polyarticular-course disease experienced an improvement (*i.e.*, a positive change) in the carpometacarpal ratio (Poznanski score) during the first year of ETN administration, which suggests that this drug is potentially capable of halting the progression of radiographic joint damage in JIA. Although a control group was not available, the observed progression rate compares favorably with that seen by the authors in a historical group of 94 patients with polyarticular JIA, 93% of whom had received MTX (and only 3% ETN) (22). Indeed, the median +0.3 change seen in the present study is greater than both the mean change in Poznanski score during the first year of observation (-0.5) and the mean yearly change in Poznanski score during the entire follow-up period (-0.1) observed in the historical patient cohort. These findings suggest that ETN may have a greater disease-modifying effect than MTX in JIA. That the rate of radiographic progression may improve in children with JIA is not surprising because it is well known that the regenerative capacity of articular cartilage is better in growing children than in adults (23-26). This phenomenon might, thus, be the result of a combination of cartilage repair and halting of radiographic progression.

Because our study was not controlled, we cannot exclude that patients included in the analysis had a more benign disease than those not included due to the lack of radiographs available for review. However, the values of all JIA outcome measures at treatment start were comparable between patients included or not included, or worse in patients included. Furthermore, the study patients had severe, long-standing polyarticular disease that was not controlled in spite of previous administration of one or more traditional second-line agents and had bilateral wrist involvement. It has been suggested that patients with polyarthritis and wrist disease are at high risk of experiencing radiographic progression (22, 27). Since the study patients had, on average, a long disease duration at baseline and the sensitivity of the Poznanski score can be reduced in case of advanced cartilage thinning, we cannot exclude the possibility that a ceiling effect could partly account for the observed improvement in radiographic progression. However, the latter phenomenon was paralleled by a marked improvement in clinical signs and symptoms, which suggests that it was, at least partially, secondary to an effect on the disease process (Table II).

Harel *et al*. (23) and Ravelli *et al*. (28) previously found that MTX, given as monotherapy, was capable of reducing radiographic progression in JIA. MTX is currently the standard comparator in clinical trials of biologic response modifiers in patients with chronic arthritis. It would have been, therefore, important to compare our findings with those obtained in patients treated with MTX as monotherapy. However, a control group with comparable disease duration at baseline was not available because in the study period it was common practice to introduce ETN only after the failure of MTX in controlling disease activity. Because most of our patients received concomitant therapy with MTX, we could not compare the efficacy of ETN alone versus that of ETN and MTX in combination. A randomized trial is needed to investigate the relative effect of ETN and MTX on the progression or structural joint damage or to establish whether the combination with MTX is more advantageous than the administration of ETN alone.

Our study should be viewed in the light of several potential limitations, which include its retrospective and non controlled nature, the small sample size, the wide variability in disease duration, and the heterogeneity in disease-modifying antirheumatic therapies. Future investigations should include more patients, extend the duration of the observational period, and be designed in a prospective way. We should also recognize that the historical cohort of MTX-treated patients was not entirely comparable to the study group and that, therefore, the observed difference in radiographic progression should be regarded with caution. Nevertheless, our study is the first to investigate radiographic progression under ETN therapy in JIA and provides useful clinical information that can be of help in assessing and interpreting the effectiveness of this drug in children with JIA.

We conclude that our pilot study suggests that ETN may reduce radiographic progression in JIA. This finding should be further explored in the context of a controlled trial.

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