A follow-up study of patients with juvenile idiopathic arthritis who discontinued etanercept due to disease remission

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Abstract

Objectives.

Assessment of the post-etanercept (ET) disease course in patients with juvenile idiopathic arthritis (JIA) who discontinued the drug due to disease remission, using a recently developed tool that scores the disease activity.

Methods.

Eleven patients (F/M 9/2, median age 9.2 years), with either a polyarthritis' (9) or an oligoarthritis' (2) disease course were followed up for 12.25–27 months after ET withdrawal. The median treatment period under ET was 36 months. The Juvenile Arthritis Disease Activity Score (JADAS) was used to grade the JIA activity at the time of ET commencement, at discontinuation and at the time of the flare.

Results.

All 11 patients flared during the follow-up period. Compared to the time of ET initiation, JADAS was significantly reduced at ET discontinuation as well as at the time of the flare (26.3 to 0 and to 9.5 respectively, $p<0.001$). The median remission following ET discontinuation lasted 3 months. The flares were controlled with methotrexate±cyclosporine A in 10 patients and methotrexate plus anti-TNF in the remaining one.

Conclusion.

All patients after ET withdrawal flared but they had a minor disease activity score compared to the time of ET initiation. Flares were mostly controlled by the administration of 1 or 2 disease modifying anti-rheumatic drugs. JADAS was found to be a useful and handy tool for assessing and following-up the JIA activity over the disease course.

Key words

juvenile idiopathic arthritis, anti-TNF, etanercept, outcome, Juvenile Arthritis Disease Activity Score

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Introduction

The current management of juvenile idiopathic arthritis (JIA) with anti-tumour necrosis factor agents (anti-TNF), aims to induce a long-term inactive and off medication disease (1-4). Very recently, sporadic data have been published regarding the disease course following discontinuation of etanercept (ET) due to disease remission in adults with either ankylosing spondylitis (AS) or rheumatoid arthritis (RA) and only one similar report in JIA (5-7).

To date, in contrast to RA, the disease course in JIA is qualitatively assessed and compared to a baseline (3, 4, 8). Thus, patients with JIA, even among the same centre, may have incomparable disease activity at baseline.

The aim of the study was to assess and follow up the disease course in our patients with JIA after ET discontinuation due to disease quiescence, by ranking their disease activity at certain disease stages with respect to the time of ET initiation using a quantitative tool (9).

Materials and methods

Patients with JIA who discontinued ET treatment and fulfilled the criteria of disease remission until October 2008 (4) were enrolled in the study. The criterion for ET initiation was a non-response to a disease modifying anti-rheumatic drugs (DMARDS) combination (including methotrexate) or to another anti-TNF.

Both their parents and the Ethics Board of the Hospital had previously given approval for anti-TNF studies in JIA patients (no. 22/year 2004).

The patients' demographics are shown in Table I. The Centre's current policy is ET with or without concurrent DMARD withdrawal, at least 1 year after disease remission escorted by the absence of minimal disease activity (8). In detail, discontinuation of MTX was mainly decided on a short disease prior to ET initiation (less than 2 years) and the physician's global estimation.

The disease activity score was retrospectively measured with a relevant and recently developed tool, the Juvenile Arthritis Disease Activity Score (JADAS) at pre-defined disease points: at ET initiation, at the time of ET discontinuation and at the time of the flare thereafter. This validated composite disease activity score (Table II) is similar to the tools already used to quantify the disease activity in RA, such as the Disease Activity Score (DAS), the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) (9). The components of JADAS have been selected from the 6 variables included in the ACR Pedi (3). The version of JADAS-71 that counts all 71 joints was selected and used in this study.

All patients were followed up for at least 12 months after the post-ET flare.

Statistics

Descriptive statistics for the comparison of the Disease Activity Indices were used. ANOVA was applied for comparisons between nominal and continuous data and *p*-values less than 0.05 were considered statistically significant. The statistical package used was JMP® 8.0 (SAS Institute).

Results

During the study period, among the 36 patients who received ET for at least 12 months (range 12.25–27 months), 11 fulfilled the criteria of JIA remission (4) and were enrolled in the study. Nine patients had a polyarticular JIA course and 2 an oligoarticular course.

ET was abruptly discontinued in 9 of the 11 patients, and tapered over a 3-month period by expanding the interval of two consecutive injections in the remaining 2 patients.

The profile of the flares

Remission after ET withdrawal lasted 1–15 months, over a median of 3 months, (Interquartile Range (IQR) 2-8 months, Table I). About half of the patients (n=5) flared when they were off all medication, namely MTX plus ET. These patients flared 1, 6, 8 and 15 (n=2) months off treatment. The patient with the shortest interval had a systemic onset with an oligoarthritis' course and the feature of the flare was oligoarthritis without systemic manifestations. The remaining 6 patients flared while they were still on MTX. One patient with a history of recurrent uveitis had also eye activity at the time of the flare.

Table I. Demographics of the 11 patients enrolled in the study.

Sex: F/M	9/2
JIA type	
Polyarthritis RF negative	6
Extended oligoarthritis	2
Systemic with a polyarticular course	1
Systemic with an oligoarticular course	2
ANA positive	5/11
Age of JIA onset, median, SD (years)	3.6 (2.1)
Age at etanercept (ET), median, SD (years)	6.22 (2.83)
Disease duration prior to ET initiation, median, SD (years)	2.62 (2.2)
Duration of ET administration*, median, SD (months)	36 (14)

*All patients concomitantly received methotrexate per os, in a dose of 15mg/m^2/w and follinic acid supplementation on the consecutive day.

Table II. The Juvenile Arthritis Disease Assessment Score (JADAS)-71.

Domain	Scoring system visual analogue scale (VAS, range in cm)
Physicians' global assessment	0–10
Parent/patient's global assessment on well being	0–10
No of active joints	0–71
ESR converted: (ESR mm/hour-20) /10	0–10
Sum of JADAS	0–101

Table III. JADAS estimation in respect to etanercept administration over the study.

Domains	ET initiation	Flare in the post-ET era	*p*-value
Physicians' global assessment (median, IQR)	4.5 (3–7)	2 (0.5–3)	<0.001
Parent/patient's global assessment on well being (median, IQR*)	5 (2–7)	1 (0.5–2)	<0.001
No. of active joints (median, IQR*)	7 (5–14)	2 (1–4)	<0.001
ESR converted, (median, IQR*)	3.5 (1–6)	1.7 (0–4.3)	<0.01
Sum of JADAS (median, IQR*)	26.3 (13–29.5)	9.5 (2.5–17.1)	<0.001

*Interquartile range.

The interval between ET discontinuation and the flare was not related either to the disease course (poly- or oligoarthritis, p=0.72) or to the way of ET discontinuation (abruptly or tapering, p=0.30). However, the disease-free interval was longer in the 5 patients who were free off medication as compared to the 6 patients who were still under MTX (median 8 *vs*. 2.5 months, p=0.04).

Medication to control flares

The introduction of DMARD monotherapy with MTX (n=1) or cyclosporine A(CSA, n=1) or the combination of MTX plus CSA (n=8) led to disease remission in 10 of the 11 patients. Only 1 patient required a regimen of MTX plus adalimumab after a 6-month poor response (ACR Pedi<30) to MTX plus CSA. At that time, restart of ET was not decided due to the concomitant uveitis (10).

Application of JADAS in the periodical assessment of disease activity

At the time of ET discontinuation, as expected, all indices decreased to 0 and this reduction was highly significant compared to ET initiation (p<0.001). At the time of a flare in the post-ET era, JADAS was significantly lower, compared to the time of ET initiation. Impressively, each individual JADAS component was also significantly lower as compared to the time of ET initiation (Table III).

Discussion

This exploratory study aimed to evaluate the post-ET era in patients with JIA who achieved disease remission and discontinued the agent. Additionally, the impact of ET in the disease activity was investigated, by applying a quantification tool named JADAS (9). JADAS has not been serially evaluated in receivers of anti-TNFs over the JIA course so far.

It was found that in patients who discontinued ET due to persistent disease remission, the chance of a flare was similar to patients who had discontinued all medication or were still under MTX. The failure of MTX administration before ET initiation followed by a subsequent favourable response to MTX plus ET in our patients, allow us to postulate that their remission can be attributed to ET. Similarly, a multicentre Italian study has reported that a 12-month ET therapy reduced clinical and radiographic progression in JIA patients (11).

The disease-free interval did not differ between patients with a polyarthritis' or an oligoarthritis' course. The finding that MTX receivers had a shorter disease-free interval obviously indicates that they had a difficult- to treat disease course requiring continuation of a DMARD.

The median disease-free period was about 3 months and much shorter than the interval reported by the very recent Dutch publication reporting on the outcome of 19 patients with JIA (7). Moreover, they had reported that tapering ET before withdrawal in 13 of the 19 patients was associated with a prolonged disease-free period, which was not confirmed in our study. Further direct comparisons between these 2 studies were not feasible due to their different designs. Another recent study in adults, involving 2 patients with RA reported also a longer (over 1 year) disease-free interval after gradual withdrawal of ET and subsequent continuation of MTX (6).

JADAS, which is already familiar to paediatric rheumatologists as it contains indices of the ACR Pedi (3), proved to be a useful and handy tool in assessing our 11 patients with JIA

during the anti-TNF and post anti-TNF era (9). It was retrospectively applied to our registry and significantly contributed to the evaluation of our patients in the post-ET disease course. Despite the indication of JADAS for selected JIA types, we had enrolled 3 patients with a systemic onset and either an oligo-or a polyarticular course, because they had no systemic manifestation at the time of the post-ET flare. The novel observation that the disease flares had a lower disease activity score as compared to the time of ET initiation was further confirmed by the finding that the vast majority of our patients (10 of the 11) were successfully managed with only DMARDS. We assume that the lower disease activity could be attributed to the sustained impact of previous long-term ET administration. On the same line, a previous study on the outcome of adults with AS had also reported disease control and a significant reduction of their Disease Activity Index (BASDAI) after 24 months of ET treatment (5).

A limitation of the study was the relatively small number of patients enrolled. Therefore, these findings need to be further validated with larger series of JIA patients. Thus, no conclusion could be derived about the optimal duration of ET treatment following disease remission for our Centre with respect to the scores of disease activity.

In conclusion, this exploratory study demonstrated that all patients who discontinued ET flared, but that all had a lesser disease activity as compared to the time of ET initiation. This finding was supported by the subsequent response of all but one patient to DMARDs. It can be cautiously postulated that ET had a lasting impact on the disease activity, and that JADAS could be incorporated in the patient's global evaluation, not only in the post-anti-TNF follow-up JIA trials but also in daily practice.

References

1. HAYWARD K, WALLACE CA: Recent developments on anti-rheumatic drugs in pediatrics: treatment of Juvenile Idiopathic Arthritis. *Arthritis Res Ther* 2009; 11: 216-27.
2. RAVELLI A, MARTINI A: Juvenile idiopathic arthritis. *Lancet* 2007; 369: 767-78.
3. 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.
4. RINGOLD S, WALLACE CA: Measuring clinical response and remission in Juvenile Idiopathic Arthritis. *Curr Opin Rheumatol* 2007; 19: 471-6.
5. BARALIAKOS X, BRANDT J, LISTING J *et al*.: Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. *Arthritis Rheum* 2005; 53: 856-63.
6. MIYAMURA T, SONOMOTO K, NAKAMURA M *et al*.: Discontinuation of etanercept in patients with rheumatoid arthritis who were in clinical remission. *Clin Rheumatol* 2010; 29: 87-90.
7. PRINCE FHM, TWILT M, SIMON SC: *et al*.: When and how to stop etanercept after successful treatment of patients with juvenile idiopathic arthritis. *Ann Rheum Dis* 2009; 68: 1228-9
8. MAGNI-MANZONI S, RUPERTO N, PISTORIO A *et al*.: Development and Validation of a Preliminary Definition of Minimal Disease Activity in patients with Juvenile Idiopathic Arthritis. *Arthritis Rheum* 2008; 59: 1120-7.
9. CONSOLARO A, RUPERTO N, BAZSCO A *et al*.: Development and validation of a Composite Disease Activity Score for Juvenile Idiopathic Arthritis. *Arthritis Rheum* 2009; 61: 658-66.
10. PIAN CE, MCCANN LJ: Challenges in the management of juvenile idiopathic arthritis with etanercept. *Biologics* 2009; 3: 127-39.
11. NIELSEN S, RUPERTO N, GERLONI V *et al*.: Preliminary evidence that etanercept may reduce radiographic progression in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2008; 26: 688-92.