Monitoring serum etanercept levels in juvenile idiopathic arthritis: a pilot study

Sirs,

Etanercept (ETN) has shown to be effective in the treatment of non-systemic juvenile idiopathic arthritis (JIA). Serum levels of ETN and anti-drug antibodies (ADAbs) have been elsewhere determined in JIA (1). However, it is generally agreed that these antibodies are non-neutralising and do not influence drug safety or efficacy, at least in adults with rheumatoid arthritis (2).

Our aim was to investigate the usefulness of monitoring serum ETN levels and ADAbs in a retrospective chart review. All patients included were required to: 1) meet JIA criteria, according to the International League of Associations for Rheumatology (ILAR) (3), 2) have responded succesfully to ETN and consequently show inactive or little active disease, otherwise etanercept would have been withdrawn and switching to a different biologic agent indicated; and 3) have serum drug levels and ADAbs measurements. Weight in kg, ETN dose in mg, and interval dosing (from once or twice a week to every two weeks or longer) should be available. Several patients were receiving an ETN weekly dose less than 0.8 mg/kg, due to achievement of inactive disease.

Serum ETN levels were determined by capture ELISA using Progenika SL (Derio, Vizcaya, Spain) reactives, while ADAbs expressed in arbitrary units (AU)/ml were quantified with an in-house bridging ELISA (ETN-coated plates, incubation with serum, detection with biotin-labelled ETN) developed by the laboratory of our own hospital. The cut-off points for positivity were 50 ng/ml and 50 AU/ml respectively. Samples were obtained within 24 hours before drug administration. Albeit these tests are part of the hospital standard routine services, patients and their parents were informed.

Disease activity was evaluated with Juvenile Arthritis Disease Activity Score (JADAS)-71 (4). Inactive disease was considered in the absence of active arthritis and uveitis, normal erythrocyte sedimentation rate and C-reactive protein, physician visual analogue scale of 0, and no morning stiffness. The illness was considered to be little activity when JADAS-71 was below 15.

Statistical analysis was carried out using SPSS v. 11.0. Frequency data were compared by Fisher's exact test. Differences in quantitative variables between groups were calculated with the Mann-Withney U or Kruskal-Wallis tests.

Table I summarizes the characteristics of 40 patients (27 girls, 13 boys) with one measurement of serum ETN levels, 34 with two determinations and 22 with three. None of them had detectable ADAbs. The ILAR subsets of JIA were represented as follows: oligoarticular in 20 cases, polyarticular in 13, enthesitis related arthritis in 5 and psoriatic arthritis in 2. Mean age at diagnosis was 4.4 years (S.D 2.8, range 1–10.8). Mean age at the time of the first determination was 11.3 years (S.D 3.5, range 4–18.6). Treatment duration refers to the continued administration of ETN.

This study has two considerable limitations, it is retrospective and the sample is small. But, as it could be expected, serum ETN levels were associated with the weekly dose stratified into three ranges, corresponding to each of the measurements (Fig. 1). The most extreme case was that of a patient who while receiving 0.15 mg/kg/w presented 0 ng/ml of ETN. However, serum ETN levels did not show association with the little activity.

Adverse effects were minor (small local reactions and mild uveitis flares). They were not associated with serum ETN levels or treatment duration, and did not lead to drug withdrawal. ETN was interrupted in 6 children by clinical decision, always in case of inactive disease. All of them experienced a flare between 1 and 15 months later (mean 6.5). They received ETN a mean of 2.3 years, being the mean of serum drug levels of 1094 ng/ml at discontinuation. All patients responded favourably to reintroduction.

In an initial study (5) our results suggested, as they do in the present research, that low doses may be sufficient in maintaining remission, although then we did not have serum ETN measurements. Previous investigations in rheumatoid arthritis show similar conclusions (6).

These results showed that drug levels were associated with the dose received and the absence of ADAbs. Further prospective investigations are required to determine both the minimum dose to keep disease remission, and the serum drug levels associated with this minimum dosage.

Key message

In patients with inactive or little JIA, serum ETN levels were associated with the dose that patients received and ADAbs were not detected in any case.

Table I. Characteristics of 40 patients with JIA responders to etanercept, having three serum drug levels and anti-drug antibodies measurements.

Determinations	1	2	3
Number of patients	40	34	22
ETN previously	6 (15)	10 (29)	10 (45)
Treatment duration (y)	1±0.9 (0.09-4.3)	1.5±1.4 (0.2-5.6)	2±1.4 (0.3-6)
ETN doses (mg/kg/w)	0.8±0.2 (0.3-1.6)	0.7±0.2 (0.2-1)	0.7±0.2 (0.3-0.8)
ETN levels (ng/ml)	1553±1065 (57-5861)	1842±1062 (50-4030)	1933±1239 (0-4708)
ADAbs (AU/ml)	0	0	0
Concomitant MTX	8 (20)	8 (24)	6 (27)
JADAS-71 score (0-101)	1.7±3 (0-13)	1±2 (0-7)	0±1.3 (0-5)
Little active disease	13 (32)	9 (26)	5 (23)
Inactive disease	27 (68)	25 (74)	17 (77)
Discontinuation/Relapse	2/2 (100)	2/2 (100)	2/2 (100)
Adverse effects	3 (8)	4 (12)	2 (9)

Values are expressed as n (%) unless otherwise specified. JIA: juvenile idiopathic arthritis; ETN: etanercept; ADAbs: Anti-ETN antibodies; JADAS: Juvenile Arthritis Disease Activity score; MTX: methotrexate.

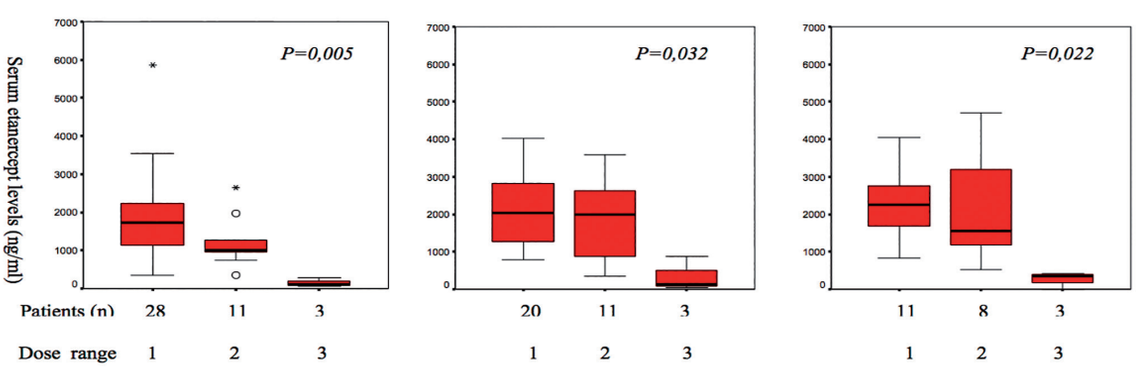

Fig. 1. Serum etanercept levels (ng/ml) *vs* dose range that patients received (1 ≥0.7 mg/kg/w; 2 <0.7 and ≥0.5 mg/kg/w; 3 <0.5 mg/kg/w) in the three determinations.

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