When and how to stop etanercept after successful treatment of patients with juvenile idiopathic arthritis

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Currently, little is known about when or how to stop etanercept in patients with juvenile idiopathic arthritis (JIA) when a good clinical response is reached, and therefore no guidelines are available.[1] We evaluated the disease course of patients with JIA who discontinued etanercept because of a sustained good clinical response.

This study is embedded in the Arthritis and Biologicals in Children (ABC) project, a prospective ongoing multicentre, observational study that includes all Dutch patients with JIA who used etanercept since 1999.[2 3] We selected all patients who discontinued etanercept because of sustained good clinical response determined by the treating doctor. The outcome measures to assess disease activity consisted of the JIA core set of six response variables.[4] To evaluate the disease course we used the criteria for inactive disease on medication (IDM) or off medication (ID) and the criteria for clinical remission on medication (CRM) or off medication (CR) by Wallace.[5 6] We defined erythrocyte sedimentation rate (ESR) values under 16 mm/h as normal and stated that a doctor's overall assessment score below 10 mm on a visual analogue scale (VAS) indicated no disease activity.[7] Differences were tested with the Mann–Whitney U test using level of significance $p<0.05$.

In all, 19 patients on the ABC register discontinued etanercept because of a sustained good clinical response. Most data on these patients were prospectively collected in the register, more detailed data on disease activity after etanercept discontinuation were collected retrospectively.

Characteristics and disease course of each individual patient are shown in table 1.

After discontinuation 10 patients (53%) retained remission over a median of 0.8 years (interquartile range (IQR) 0.5 to 2.8). They used etanercept longer (3.5 vs 2.1 years, $p = 0.21$) and showed a longer median period of CRM (1.5 vs 0 years, $p = 0.004$) compared to the nine patients who experienced flares. None of the juvenile arthritis psoriatica patients had psoriatic lesions and the enthesitis-related arthritis patient had no enthesitis. At last observation 4 of the 10 had reached the criteria for CR.

Four out of five patients who discontinued etanercept without tapering experienced flares. In total nine patients developed a disease flare within a median of 0.7 years (IQR 0.1 to 1.1) after discontinuation of etanercept. All eight patients who resumed etanercept use after experiencing flares reacted promptly to treatment.

This explorative study shows some important indicators for successful discontinuation of etanercept: prolonged CRM and careful tapering of etanercept. Rheumatoid factor positivity seems to be negatively related with sustained remission. This is all inline with data from rheumatoid arthritis treatment.[8 9] We suggest that patients with JIA should meet the criteria of CRM for at least 1.5 years before considering discontinuation of etanercept, and then taper it carefully.

It is reassuring that patients regained effectiveness of etanercept after experiencing flares. A promising result is that four out of five patients with systemic JIA retained ID after discontinuation of etanercept. This last finding indicates that etanercept can be successful in systemic JIA, as we previously showed in results from our ABC register in which the same percentages of patients with systemic JIA meet the criteria of CRM compared to other subtypes after prolonged treatment.[2]

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Table 1 Individual characteristics and disease course of patients with juvenile idiopathic arthritis (JIA) with a sustained good clinical response who discontinued etanercept

Patient	JIA subtype	Sex	Age at onset of JIA (years)	Disease duration at start of ETN (years)	Time on ETN therapy (years)	Tapering of ETN before stopping	IDM* (years)	CRM* (years)	ID* (years)	CR* (years)	Time to flare after stopping ETN (years)	Disease course and therapy after stopping ETN
1	sJIA	M	4.0	4.0	5.2	Y	2.4	1.9	1.6	0.6		Remission
2	sJIA	F	3.0	3.2	5.3	Y	2.6	2.1	0.8	0	0.76	Flare; restart NSAID and ETN
3	sJIA	M	9.0	2.8	3.7	Y	3.0	2.5	0.4	0		Remission
4	sJIA	M	5.2	11.5	5.1	Y	4.4	3.9	0.6	0		Remission
5	sJIA	M	5.5	5.2	6.5	Y	4.7	4.2	0.5	0		Remission
6	JIA RF+	F	11.2	4.8	0.6	N	0	0	0	0	0.25	Flare; restart NSAID, MTX and ETN
7	JIA RF+	F	14.0	2.0	1.1	N	0	0	0	0	0.18	Flare; restart ETN and continue MTX
8	JIA RF−	M	4.2	5.2	3.8	Y	0	0	1.3	0.3	2.25	Flare; hospitalisation, restart NSAID and prednisolone
9	JIA RF−	M	4.8	5.3	1.0	N	0	0	0	0	0.04	Flare; restart prednisolone and ETN
10	JIA RF−	F	7.5	0.5	2.4	Y	0.7	0.2	2.8	1.8		Remission
11	JIA RF−	F	10.0	1.6	2.1	Y	1.6	1.1	0.4	0		Remission
12	JIA RF−	F	5.0	11.1	3.6	Y	2.9	2.4	2.8	1.8		Remission
13	oJIA ext	M	4.0	8.8	2.1	Y	0.3	0	0.1	0	0.05	Flare; restart NSAID and ETN
14	oJIA ext	F	3.4	3.4	1.6	Y	0.8	0.3	4.5	3.5		Remission
15	oJIA ext	F	8.1	1.4	1.7	N	1.4	0.9	1.0	0		Remission
16	PsJIA	F	13.1	0.4	2.5	N	0	0	0	0	0.62	Flare; hospitalisation, restart prednisolone, MTX and ETN
17	PsJIA	M	7.7	2.8	2.0	Y	0.8	0.3	0.5	0		Remission
18	PsJIA	M	9.9	4.6	1.6	Y	0.8	0.3	0	0	0.03	Flare; restart ETN
19	ERA	M	9.5	0.8	3.7	Y	0	0	0	0	0.68	Flare; restart NSAID and ETN

*According to the criteria of Wallace *et al*.[5 6]

CR, clinical remission off medication; CRM, clinical remission on etanercept medication; ERA, enthesitis-related arthritis; ETN, etanercept; ID, inactive disease off medication; IDM, inactive disease on etanercept medication; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; oJIA ext, oligoarticular extended JIA; pJIA RF+/−, polyarticular rheumatoid factor positive/negative JIA; PsJIA, juvenile arthritis psoriatica; sJIA, systemic JIA.