Tumour necrosis factor (TNF)-blocking agents in juvenile psoriatic arthritis: are they effective?


Published in:
Annals of the Rheumatic Diseases

DOI:
10.1136/ard.2010.135731

Citation for published version (APA):
Tumour necrosis factor (TNF)-blocking agents in juvenile psoriatic arthritis: are they effective?

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ABSTRACT

Objectives To evaluate the effectiveness of tumour necrosis factor (TNF) blockers in juvenile psoriatic arthritis (JPsA).

Methods The study was a prospective ongoing multicentre, observational study of all Dutch juvenile idiopathic arthritis (JIA) patients using biologicals. The response of arthritis was assessed by American College of Rheumatology (ACR) paediatric response and Wallace inactive disease criteria. The response of psoriatic skin lesions was scored by a 5-point scale.

Results Eighteen JPsA patients (72% female, median age onset 11.1 (range 3.3–14.6) years, 50% psoriatic skin lesions, 39% nail pitting, 22% dactylitis) were studied. The median follow-up time since starting anti-TNFα was 26 (range 3–62) months. Seventeen patients started on etanercept and one started on adalimumab. After 3 months of treatment 83% of the patients achieved ACR30 response, increasing to 100% after 15 months. Inactive disease reached in 67% after 39 months. There was no discontinuation because of inefficacy. Six patients discontinued treatment after a good clinical response. However, five patients flared and restarted treatment, all with a good response. During treatment four patients (two JPSA and two JIA patients with other subtypes) developed de novo psoriasis. In four of the nine patients the pre-existing psoriatic skin lesions improved. In the remaining five patients the psoriatic skin lesions did not respond well and four patients developed de novo psoriasis.

Conclusion Anti-TNFα therapy in JPsA seems effective in treating arthritis. However, in most patients the arthritis flared up after treatment discontinuation, emphasising the need to investigate optimal therapy duration. The psoriatic skin lesions did not respond well and four patients developed de novo psoriasis.

INTRODUCTION

Juvenile psoriatic arthritis (PsA), a subgroup of juvenile idiopathic arthritis (JIA), is defined by the International League of Association of Rheumatology (ILAR) as arthritis with a typical psoriatic rash, or when this rash is absent with at least two of the following: dactylitis, nail pitting or onycholysis, or psoriasis (PsA) in a first-degree relative.1 In adults the psoriatic rash appears to precede the onset of arthritis, but in children the occurrence of arthritis or psoriasis as the first symptom seems to be divided evenly.2 It remains debatable whether this subtype (accounting for 2–11% of JIA patients) represents a clearly defined entity.3

Tumour necrosis factor (TNF) blockers have led to dramatic improvements in JIA patients with a poly-articular course not responding to the maximum (tolerated) dose of methotrexate (MTX).4 5 However, no studies have explored JPsA only. In adult-onset PsA, anti-TNFα agents are highly effective and safe.6 7 As well as the beneficial effects on joints, they are also effective in paediatric psoriatic skin lesions.8 In contrast, there are reports on induction or exacerbation of PsA during anti-TNFα therapy, which seems contradictory since these agents are successful in the treatment of psoriasis.9 In children only two cases of new-onset psoriatic skin lesions during anti-TNFα therapy have been reported.10 11

The present study evaluates the effectiveness of TNF-blocking agents in JPsA patients on both arthritis and psoriatic skin lesions.

METHODS

This study is part of the Arthritis and Biologicals in Children project, an ongoing prospective multicentre, observational study, which includes all Dutch JIA patients using biologicals since 1999.12 In the register, patient and disease characteristics are collected at baseline. Data on the JIA core set (physician’s global assessment of disease activity by visual analogue scale (VAS) (range 0–100 mm, 0 best score), Childhood Health Assessment Questionnaire (range 0–3, 0 best score) by patients/parents, including global assessment of well-being by VAS, number of active and limited joints and erythrocyte sedimentation rate (ESR)) are retrieved at the start, and then at 3, 15 months and yearly thereafter.

From the patients included in the register until 2010 we selected JPsA patients and JIA patients with subtypes other than JPsA that developed psoriatic skin lesions. Additional data on the diagnostic ILAR criteria for JPsA were collected retrospectively (ie, presence and type of psoriatic skin lesions, dactylitis, nail pitting or onycholysis and PsA in a first-degree relative).1

The response of arthritis was assessed using the American College of Rheumatology (ACR) paediatric 30, 50 and 70 criteria (ACRpedi30/50/70), defined as at least 30% (50% and 70%, respectively) improvement from baseline in three or more variables of the JIA core set with no more than one variable worsening by >50%.13 Inactive disease was defined as: no active arthritis, no uveitis, normal ESR (values under 16 mm/h) and physician’s global assessment indicating no disease activity (defined as a score below 10 mm).14 Responses in
JPsA patients were compared with the results of the first 146 JIA patients from our register. The response of psoriatic skin lesions was scored from the patients’ records using a 5-point scale: markedly improved, improved, no change, worse and markedly worse.

RESULTS
In total 18 JPsA-patients were included. Table 1 shows patient and disease characteristics. Most JPsA patients (94%) were initially treated with etanercept. One patient switched from etanercept to adalimumab because of a severe course of uveitis, but switched back to etanercept after 6 weeks due to a relapse of arthritis. No other patients switched between TNF blockers or to other biologicals.

Psoriatic skin lesions were present in nine patients (50%): in four patients the arthritis preceded the psoriatic skin lesions by 5 (range 2–10) months, and five patients had psoriatic skin lesions 15 (range 8–62) months before onset arthritis. Two JPsA patients (with arthritis, dactylitis and nail pitting) developed psoriatic skin lesions after introduction of etanercept. These de novo psoriatic skin lesions were confirmed by a dermatologist (one plaque psoriasis and one guttate psoriasis). No relationship with discontinuation of MTX was found. Table 2 shows the physician-reported response of psoriatic skin lesions to TNF blockers.

De novo plaque psoriasis during etanercept treatment also occurred in one patient diagnosed with rheumatoid factor negative poly-articular JIA, and one patient with rheumatoid factor positive poly-articular JIA.

Figure 1 presents data on ACRpedi30/50/70 improvement and inactive disease during a follow-up period of 39 months in JPsA patients compared with JIA subtypes. In these first 146 JIA patients no differences in responses were seen between poly-articular rheumatoid factor positive, poly-articular rheumatoid factor negative, and oligo-articular subtypes. At 5 months of treatment, 15 of the 18 JPsA patients achieved an ACRpedi30 response, which increased to 100% in the patients that reached 15 months of treatment. Inactive disease was seen in five out of nine JPsA patients with 27 months of follow-up, and four out of six patients with 39 months of follow-up.

During follow-up MTX was discontinued in 10 patients (59% with concomitant MTX at start) and systemic glucocorticoids and other disease-modifying anti-rheumatic drugs (DMARDs) in all. Six patients discontinued etanercept because of good clinical response after 22 (range 13–55) months of etanercept treatment. At time of discontinuation no patients used concomitant DMARDs or prednisone and four patients fulfilled criteria of inactive disease. Of the six patients who discontinued etanercept, five (83%) flared and needed to restart etanercept after a median 2 months (range 19 days to 10 months). After re-introduction of etanercept all patients regained a good response, and four patients reached inactive disease again. Discontinuation of anti-TNFα treatment due to inefficacy did not occur.

Table 1 Patient and disease characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>JPsA (n=18)</th>
<th>All JIA* (n=146)</th>
<th>All non-systemic JIA* (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>13 (72)</td>
<td>101 (69)</td>
<td>82 (77)</td>
</tr>
<tr>
<td>Age onset arthritis (years) (median, range)</td>
<td>11.1 (3.3–14.6)</td>
<td>11.2 (3.3–18.6)</td>
<td>12.5 (3.3–18.6)</td>
</tr>
<tr>
<td>Age onset psoriatic skin lesions (years) (median, range)</td>
<td>12.2 (2.8–15.2)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median disease duration before start anti-TNFα (months) (median, range)</td>
<td>24 (2–55)</td>
<td>49 (1–190)</td>
<td>53 (4–190)</td>
</tr>
<tr>
<td>Median follow-up duration since start anti-TNFα (months) (median, range)</td>
<td>26 (3–62)</td>
<td>30 (1–88)</td>
<td>25 (1–83)</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 active joints at start anti-TNFα (n (%))</td>
<td>3 (17)</td>
<td>6 (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>&gt;5 active joints at start anti-TNFα (n (%))</td>
<td>15 (83)</td>
<td>140 (96)</td>
<td>103 (96)</td>
</tr>
<tr>
<td>Psoriatic skin lesions (%)</td>
<td>9 (50)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Plaque psoriasis</td>
<td>6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Guttate psoriasis</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Inverse psoriasis</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Dactylitis (n (%))</td>
<td>4 (22)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nail pitting or onycholysis (n (%))</td>
<td>7 (39)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Relative with psoriatic skin lesions (n (%))</td>
<td>13 (72)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>First-degree relative (%)</td>
<td>10</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anti-TNFα agent (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>17 (94)</td>
<td>146 (100)</td>
<td>107 (100)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1 (6)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Medication history before start of anti-TNFα (n (%))</td>
<td>7 (39)</td>
<td>90 (62)</td>
<td>52 (49)</td>
</tr>
<tr>
<td>Systemic glucocorticoids</td>
<td>6 (33)</td>
<td>60 (41)</td>
<td>44 (41)</td>
</tr>
<tr>
<td>Intra-articular glucocorticoids</td>
<td>17 (94)</td>
<td>146 (100)</td>
<td>107 (100)</td>
</tr>
<tr>
<td>MTX</td>
<td>11 (61)</td>
<td>74 (51)</td>
<td>67 (63)</td>
</tr>
<tr>
<td>Other DMARDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications at start of anti-TNFα (n (%))</td>
<td>4 (22)</td>
<td>67 (46)</td>
<td>34 (32)</td>
</tr>
<tr>
<td>Systemic glucocorticoids</td>
<td>15 (83)</td>
<td>113 (77)</td>
<td>81 (76)</td>
</tr>
<tr>
<td>MTX</td>
<td>3 (17)</td>
<td>13 (9)</td>
<td>12 (12)</td>
</tr>
</tbody>
</table>

DMARDs, disease-modifying anti-rheumatic drugs; JIA, juvenile idiopathic arthritis; JPsA, juvenile psoriatic arthritis; MTX, methotrexate; TNFα, tumour necrosis factor α.

Range is presented as minimum – maximum.

*Characteristics of the first 146 JIA patients (107 non-systemic JIA patients) as published from our register. 5
been shown in adult-onset PsA: 37% reached remission after non-systemic JIA patients only, TNF blockers seem to be more effective in JPsA patients than in all non-systemic JIA patients. Thus, even compared with data from our register and the German register, the response rate in JPsA patients increased to 100% at 15 months of treatment, indicating a delayed clinical response in some patients, as previously shown in JIA patients treated with etanercept. The rapid ACRpedi30 response seems to persist after discontinuation. However, the majority of our JPsA patients in clinical remission who discontinued etanercept flared thereafter. This emphasises the need to establish the optimal duration of therapy, and to develop strategies to discontinue anti-TNFα treatment. It is reassuring that all patients who re-started etanercept after flaring had a good clinical response.

Surprisingly, besides the excellent effect of etanercept on joints, the psoriatic skin lesions improved in only four of our nine patients with pre-existing skin lesions, and two patients even had a worsening of the lesions during anti-TNFα treatment. However, the retrospective documentation of the course of the psoriatic skin lesions made it impossible to use validated indices (eg, the Psoriasis Area and Severity Index). Nevertheless, it is noteworthy that, since TNF blockade is approved for psoriasis, the pre-existing psoriatic skin lesions improved in a minority of the JPsA patients and some even worsened.

In the present study, four patients (two JPsA and two JIA patients with subtypes other than JPsA) developed de novo psoriatic skin lesions after starting anti-TNFα treatment. Development of new-onset psoriatic skin lesions during anti-TNFα treatment has frequently been reported in adults, but only twice in children. Whether there is a causal relation to etanercept is unclear; it could be a paradoxical adverse event, a late-onset skin manifestation in JPsA, or a coincidental combination, since the prevalence of psoriatic skin lesions in the general population is considerable.

Classification into the JIA subtypes is based upon clinical and laboratory findings within the first 6 months after onset of JIA. Whether patients in whom the ILAR criteria changes after 6 months from onset JIA should switch to another subtype is debatable. A prospective re-evaluation of the ILAR criteria after 6 months should be recommended, mainly since in JPsA arthritis precedes psoriatic skin lesions in about 50% of the cases and psoriatic skin lesions may occur even years after onset of arthritis.

In conclusion, this is the first study to show that anti-TNFα treatment is highly effective in patients with JPsA, of whom 67% reached inactive disease after 39 months of therapy. Therapy could not be discontinued in the majority of the patients. Psoriatic skin lesions improved in the minority of the JPsA patients and de novo psoriatic skin lesions were observed in four patients.

**Acknowledgements** We would like to thank Drs Joost Swart and Dr Merlijn van den Berg for their participation in the ABC Register.

**Funding** Board of Health Insurances from 2003 until 2006, and Wyeth International from 2007 until 2010.

**Competing interests** Wyeth International supported the development and maintenance of the web-based register unconditionally from 2007 until 2010.

**Ethics approval** This study was conducted with the approval of the Erasmus MC Board of Health Insurances from 2003 until 2006, and Wyeth International.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*Ann Rheum Dis* 2011 70: 337-340 originally published online November 10, 2010
doi: 10.1136/ard.2010.135731

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