Clinical and synovial tissue studies in psoriatic arthritis
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Citation for published version (APA):

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Chapter 8

Relationship between the clinical response to adalimumab treatment and serum levels of adalimumab and anti-adalimumab antibodies in patients with psoriatic arthritis

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While the majority of patients with psoriatic arthritis (PsA) responds well to treatment with adalimumab, some patients lose response (1). An explanation might be the development of anti-adalimumab antibodies, which has been reported in rheumatoid arthritis (RA) (2;3). Therefore, we studied the incidence of anti-adalimumab antibodies in PsA, and the relationship with serum adalimumab concentration and clinical response.

Twenty-two patients with active PsA, fulfilling CASPAR classification criteria (4), started adalimumab treatment (Table 1). The patients met the requirements of the Dutch consensus on initiation of TNF blocking therapy in PsA (5), and were seen at baseline, and after 3 and 12 months. Serum samples were collected just before the next injection with adalimumab. The Disease Activity Score in 28 joints (DAS28), which has been shown to discriminate between active drug and placebo in clinical trials in PsA, was chosen to monitor clinical disease activity, and EULAR response criteria were applied (6-8).

Trough serum adalimumab concentrations were measured by ELISA, and anti-adalimumab antibodies were detected with a radioimmunoassay, as previously described (2). The antibody test was considered positive when antibody concentrations exceeded 12 AU/ml and adalimumab concentration was below 5 mg/l.

All patients continued adalimumab 40 mg every other week for 12 months. Mean ± standard error of the mean (s.e.m.) DAS28 decreased from 4.92 (0.3) at baseline to 2.91 (0.3) after 3 months, and 2.92 (0.3) after 12 months (P< 0.001 for both). At 3 months there were 12 moderate and 10 good responders. At 12 months there were 4 non-responders, 8 moderate and 10 good responders.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>value</th>
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<tbody>
<tr>
<td>Male / Female</td>
<td>14 / 8</td>
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<tr>
<td>Mean age (range)</td>
<td>43.3 (21-61)</td>
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<tr>
<td>Median disease duration psoriasis, years (range)</td>
<td>12.7 (1-53)</td>
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<tr>
<td>Median disease duration PsA, years (range)</td>
<td>6.3 (1-18)</td>
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<tr>
<td>Clinical phenotype: PA / OA / DIP (9)</td>
<td>15 / 6 / 1</td>
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<tr>
<td>Concomitant MTX use, no (%)</td>
<td>12 (55%)</td>
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<tr>
<td>Median MTX dose in mg/week (range)</td>
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<tr>
<td>Mean DAS28 (s.e.m.)</td>
<td>4.92 (0.25)</td>
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<tr>
<td>Median PASI (IQR)</td>
<td>5.7 (1.5-7.0)</td>
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<tr>
<td>Median ESR in mm/hour (IQR)</td>
<td>17.5 (7.8-31)</td>
</tr>
<tr>
<td>Median CRP in mg/l (IQR)</td>
<td>6.2 (2.6-25.7)</td>
</tr>
</tbody>
</table>

PsA, psoriatic arthritis; PA, polyarticular; OA, oligoarticular; DIP, distal interphalangeal joint; MTX, methotrexate; DAS28, Disease Activity Score in 28 joints; PASI, Psoriasis Area and Severity Index; ESR, erythrocyte sedimentation rate; IQR, interquartile range; CRP, C-reactive protein
In four patients (18%) anti-adalimumab antibodies were detected at any time point. After 3 months, three patients had low concentrations anti-adalimumab antibodies (<100 AE/ml), two of those developed high concentrations (>100 AE/ml) at 12 months. In the 3rd patient the antibodies had disappeared at 12 months, but a 4th patient demonstrated low concentration antibodies at 12 months.

Figure 1. Clinical response to adalimumab treatment presented by DAS28 over time
A. Mean DAS28 in patients who developed anti-adalimumab antibodies versus those without such antibodies. The patients without anti-adalimumab antibodies (n=19) showed sustained clinical improvement, while the patients with such antibodies (n=3) lost the initial good response to adalimumab. After 12 months the mean DAS28 ± s.e.m. was higher in the anti-adalimumab positive patients compared to the anti-adalimumab negative patients: 5.05 ± 0.84 vs 2.58 ± 0.32 (P= 0.01).
B. DAS28 in the three patients with anti-adalimumab antibodies at 12 months, demonstrating a loss of the initial clinical response to adalimumab treatment. At 3 months these patients were moderate (n=1) or good (n=2) responder, at 12 months they were non-responder (n=2), or moderate responder (n=1).
The median adalimumab concentration at 3 months was 7.8 mg/l (range 0.9-16.7), and 7.0 mg/l (undetectable-21.8) at 12 months. Patients with anti-adalimumab antibodies had lower median adalimumab concentrations than patients without: 1.7 vs 8.1 mg/l (P= 0.007) at 3 months, and 1.7 vs 9.8 mg/l (P= 0.031) at 12 months. Adalimumab concentration was undetectable in patients with high concentrations antibodies. The reduction in adalimumab concentration may be caused by formation and increased clearance of adalimumab-anti-adalimumab immune complexes. This may explain the loss of response in some patients, but not all, as demonstrated by the fact that 2 of 4 non-responders at 12 months had anti-adalimumab antibodies and low adalimumab concentrations. One non-responder had a low adalimumab concentration (3.8 mg/l) without detectable antibodies; the 4th had a normal adalimumab levels.

Patients with antibodies appeared to lose their initial good response (Figure 1). Our study was not designed to examine whether concomitant methotrexate treatment could reduce the formation of anti-adalimumab antibodies.

In conclusion, anti-adalimumab antibodies develop in a minority of patients with PsA, but are associated with lower serum levels of adalimumab and diminished clinical response to treatment.
References


