Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation

Mirjam K de Vries, Gerrit Jan Wolbink, Steven O Stapel, Henk de Vrieze, J Christiaan van Denderen, Ben A C Dijkmans, Lucien A Aarden and Irene E van der Horst-Bruinsma

Ann Rheum Dis 2007;66;1252-1254; originally published online 1 May 2007; doi:10.1136/ard.2007.072397

Updated information and services can be found at:
http://ard.bmj.com/cgi/content/full/66/9/1252

These include:

References
This article cites 12 articles, 5 of which can be accessed free at:
http://ard.bmj.com/cgi/content/full/66/9/1252#BIBL

2 online articles that cite this article can be accessed at:
http://ard.bmj.com/cgi/content/full/66/9/1252#BIBL

Rapid responses
You can respond to this article at:
http://ard.bmj.com/cgi/eletter-submit/66/9/1252

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Notes

To order reprints of this article go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to Annals of the Rheumatic Diseases go to:
http://journals.bmj.com/subscriptions/
Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation

Mirjam K de Vries, Gerrit Jan Wolbink, Steven O Stapel, Henk de Vrieze, J Christiaan van Denderen, Ben A C Dijkmans, Lucien A Aarden, Irene E van der Horst-Bruinsma

Methods: In accordance with the international ASsessment in Ankylosing Spondylitis (ASAS) consensus statement, patients were treated with infliximab (5 mg/kg) every 6 weeks after a starting regimen. Preinfusion sera were collected at baseline, 24 and 54 weeks. At every visit, the 20% improvement response (ASAS-20) was assessed and laboratory tests performed.

Results: 24 of the 38 (63%) patients fulfilled ASAS-20 response criteria after 24 weeks of treatment and 21 (53%) after 54 weeks. After 54 weeks, 11 (29%) patients showed undetectable serum trough infliximab levels and detectable anti-infliximab; six of these patients developed an infusion reaction. Anti-infliximab was found significantly more often (p = 0.04) in ASAS-20 non-responders compared with responders at week 54. Serum trough infliximab levels were significantly (p < 0.0001) lower in patients with (mean 0.02 mg/l) than in those without (12.7 mg/l) anti-infliximab.

Conclusions: In ankylosing spondylitis, high levels of serum trough infliximab correlated with a good clinical response. Detection of anti-infliximab within 54 weeks is associated with undetectable serum trough infliximab levels, reduced response to treatment and increased risk of developing an infusion reaction.

Large randomised clinical trials have shown that tumour necrosis factor blocking agents such as infliximab are very effective in ankylosing spondylitis. It is unknown why >30% of patients with ankylosing spondylitis fail to respond, or why some initial responders lose responsiveness during treatment and in some cases even develop an infusion reaction. The non-responsiveness to infliximab might be due to the development of antibodies against it, which has been described in patients with rheumatoid arthritis and Crohn disease. In ankylosing spondylitis, we recently showed in a small group of patients that detection of anti-infliximab was associated with undetectable serum trough infliximab levels, a reduced response to treatment and a higher risk of infusion reactions.

The aim of this study was to evaluate these data in a larger group of patients with ankylosing spondylitis who were treated for a longer period of time and to specify the influence on infliximab levels.

Methods

All consecutive patients with ankylosing spondylitis (according to the 1984 modified New York Criteria) who received treatment with infliximab in our centre were included in this study.

Disease activity was measured with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the ASsessment in Ankylosing Spondylitis 20% response criteria (ASAS-20). Active disease was defined as a BASDAI score ≥4. Response to treatment with infliximab was defined as fulfilment of the ASAS-20 response criteria.

Patients with ankylosing spondylitis were treated with intravenous infliximab, 5 mg/kg bodyweight at baseline, weeks 2 and 6, and every 6 weeks thereafter. This treatment was initiated in accordance with the international ASAS consensus statement. In case of decrease of clinical response, the dose of infliximab was increased to 7.5 mg/kg.

At each visit, the presence of infections, side-effects or infusion reactions, and the cause for discontinuation of therapy were recorded. Questionnaires and routine laboratory tests were obtained. Preinfusion sera were collected at baseline, weeks 24 and 54, before any dose escalation and at two consecutive visits after dose escalation. After 24 weeks of treatment, serum samples were collected from 15 patients to measure infliximab levels 2 weeks after the infliximab infusion.

Validated immunosassays (Sanquin Research, Amsterdam, the Netherlands) were used for detection of anti-infliximab and serum trough infliximab levels. Trough serum infliximab levels were measured by ELISA, based on the principle that infliximab is captured through its ability to bind tumour necrosis factor-α. The assay, which was described previously, was modified recently. It currently uses specific polyclonal rabbit antibodies to infliximab for detection instead of the monoclonal human IgG that was previously used. The sensitivity of detection is 0.0003 mg/l.

A radioimmunosassay was used for anti-infliximab detection. Arbitrary units per ml (AU/ml) were expressed as absolute amounts of infliximab-specific IgG (mg/l) (1 AU = 12 ng of infliximab-specific IgG). The cut-off value for IgG anti-infliximab was determined by assaying in our anti-infliximab test 100 plasma samples from blood donors sent to Sanquin for IgG anti-tetanus toxoid testing. The average result (AU/ml) + 6 SD was 12 AU/ml (0.144 mg/l).

The clinical data and presence of HLA B27 were used to correlate disease activity with serum trough infliximab levels and anti-infliximab levels. Differences between groups were tested with the Mann–Whitney U test. Associations were calculated with logistic regression. The threshold for significance was set at p < 0.05. The last observation was carried forward for patients who dropped out before week 54.

Results

Demographic and clinical characteristics of the 38 patients included are shown in table 1. Four patients were lost to follow-up before week 54: one wanted to become pregnant, one...
After correction for probable confounding variables such as gender and human leucocyte antigen B27 (HLA-B27), the absence of anti-infliximab remained a significant determinant for ASAS-20 response, with an odds ratio (OR) of 100 (95% CI 5.2 to 1000). Remarkably, the presence of anti-infliximab was significantly associated with the absence of HLA-B27 (OR = 7.1; 95% CI 1.1 to 47.6; Pearson χ², p = 0.03).

Two weeks after the infusion of week 24, significantly lower infliximab levels were measured (20 mg/l compared with 51 mg/l; p<0.01) in patients who developed anti-infliximab within 54 weeks of treatment.

In 12 patients, dose was increased within the 54 weeks, because of insufficient clinical response. Nine (75%) of these patients showed anti-infliximab antibodies. Increase in dose did not result in a significant increase of the serum trough infliximab level (p = 0.33), or a significant decrease in the anti-infliximab level (p = 0.90) and BASDAI (p = 0.39). However, 2 of 12 patients reported longer duration of effect.

Infusion reactions occurred in six patients. Most reactions were mild, and all patients recovered after supportive therapy. Treatment with infliximab was stopped in each case. Every infusion reaction was preceded by development of anti-infliximab and consequently undetectable serum trough infliximab levels. All antibodies to infliximab consisted of IgG1 and IgG4 subtypes. Although these infusion reactions resemble a type 1 allergic reaction, no IgE was detected. One patient’s pre-infusion serum contained an anti-infliximab level of 6.4 g/l, indicating that approximately half of his total serum IgG consisted of infliximab-specific antibodies.

DISCUSSION
A good clinical response of ankylosing spondylitis to treatment with infliximab was correlated with the presence of high serum trough infliximab levels and the absence of anti-infliximab antibodies, and inefficacy with the reverse. Moreover, these data demonstrate that anti-infliximab antibodies precede an infusion reaction.

The mechanism of the decrease in efficacy can be explained by the lower serum trough infliximab levels, probably caused by enhanced clearance due to immune complex formation of anti-infliximab antibodies and infliximab. A recent study in RA showed an enhanced clearance as a consequence of this process and an accumulation in the macrophage–phagocyte system (liver and spleen).

Remarkably, absence of HLA B27 shows significant correlation with anti-infliximab formation. Further genetic evaluation will be performed to unravel this interesting observation.

It also has to be investigated whether coadministration of immunosuppressive drugs inhibits anti-infliximab formation, and whether infliximab levels can be used for determination of the optimum dose of infliximab in ankylosing spondylitis.

In accordance with our previous report, the efficacy of infliximab in ankylosing spondylitis is clearly related to infliximab levels and the formation of anti-infliximab antibodies. Detection

### Table 1 Demographic and clinical variables at baseline, week 24 and at week 54 of patients with ankylosing spondylitis (n = 38)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Week 24</th>
<th>Week 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>26 (68)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40 (10)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HLA B27+ (%)</td>
<td>32 (84)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IBD (%)</td>
<td>6 (16)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Use of corticosteroids (%)</td>
<td>3 (8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Use of other</td>
<td>6 (16)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>immunosuppressives (%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BASDAI</td>
<td>6.4 (1.2)</td>
<td>3.6 (2.6)†</td>
<td>4.1 (3.0)†</td>
</tr>
<tr>
<td>Morning stiffness†</td>
<td>6.3 (2.2)</td>
<td>3.0 (2.5)†</td>
<td>3.5 (3.2)†</td>
</tr>
<tr>
<td>GDA</td>
<td>6.8 (1.3)</td>
<td>4.3 (2.9)†</td>
<td>4.9 (3.4)†</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>37 (34.2)</td>
<td>9.3 (10.7)†</td>
<td>15.8 (21.1)*</td>
</tr>
<tr>
<td>(normal: &lt;8.0 mg/l)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Detectable serum</td>
<td>0</td>
<td>31 (82)</td>
<td>27 (71)</td>
</tr>
<tr>
<td>trough infliximab (%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anti-infliximab (%)</td>
<td>0</td>
<td>7 (18)</td>
<td>11 (29)</td>
</tr>
</tbody>
</table>

Except when indicated otherwise, the values are the mean (SD).

†Mean of item 5+6 of the BASDAI (0–10 cm).

### Figure 1 Serum trough infliximab level for responders (n = 21; 8.2 mg/l) and non-responders (n = 17; 6.3 mg/l) according to the ASAS-20 response criteria, at week 54 (p = 0.018).
of anti-infliximab antibodies within 54 weeks is associated with undetectable serum trough infliximab levels, reduced response to treatment and increased risk of development of an infusion reaction.

Figure 2  Percentage of patients (n = 38) with (9%) and without (74%) ATI fulfilling ASAS-20 response criteria at week 54 (*p<0.001).

REFERENCES