Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study
Bartelds, G.M.; Wijbrandts, C.A.; Nurmohamed, M.T.; Stapel, S.; Lems, W.F.; Aarden, L.; Dijkmans, B.A.C.; Tak, P.P.; Wolbink, G.J.

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Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study

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ABSTRACT

Objective To investigate how antibodies against anti-tumour necrosis factor (anti-TNF) agents influence response after switching from infliximab to adalimumab in rheumatoid arthritis (RA).

Methods This cohort study consisted of 235 patients with RA, all treated with adalimumab. At baseline 52 patients (22%) had been previously treated with infliximab (‘switchers’), and 183 (78%) were anti-TNF naive. Disease activity (using the 28-joint count Disease Activity Score (DAS28)) and presence of antibodies against infliximab and adalimumab were assessed. Clinical response to adalimumab was compared between switchers and anti-TNF naive patients and their anti-infliximab and anti-adalimumab antibody status.

Results After 28 weeks of adalimumab treatment the decrease in DAS28 (ΔDAS28) for the 235 patients was 1.6±1.5 (mean±SD). Anti-adalimumab antibodies were detected in 46 patients (20%). ΔDAS28 was 1.8±1.4 in patients without anti-adalimumab and 0.6±1.3 in patients with anti-adalimumab (p<0.0001). Thirty-three of the 52 switchers (63%) had anti-infliximab antibodies. Patients with anti-infliximab more often developed anti-adalimumab than anti-TNF naive patients (11 (33%) vs 32 (18%); p=0.039). ΔDAS28 was greater for anti-TNF naive patients (1.7±1.5) than for switchers without anti-infliximab antibodies (ΔDAS28=0.9±1.4) (p=0.009). ΔDAS28 for switchers with anti-infliximab was 1.2±1.3 and did not differ significantly from anti-TNF naive patients (p=0.262).

Conclusion Switchers with anti-infliximab antibodies more often develop antibodies against adalimumab than anti-TNF naive patients. Response to adalimumab was limited in switchers without anti-infliximab antibodies, which raises the question whether a second anti-TNF treatment should be offered to patients with RA for whom an initial treatment with an anti-TNF blocker fails, in the absence of anti-biological antibodies.

INTRODUCTION

Biological agents directed against tumour necrosis factor (TNF) have greatly improved the treatment of chronic inflammatory diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis, Crohn’s disease and psoriasis. However, in RA, the proportion of patients who do not respond to anti-TNF treatment is substantial and varies between 30% and 40%. The lack of response can partly be explained by an immunogenic antibody response against these drugs, but there are also non-responding patients in whom an immunogenic reaction cannot be demonstrated. Lack of response to TNF blockade in these patients might to a certain extent be related to mechanisms that are not primarily driven by TNF. Hence, there seem to be different types of non-responders with different underlying pathogenic mechanisms causing non-response. Currently, these mechanisms and their consequences are not completely understood and it is unclear whether patients for whom one TNF blocker fails should switch to another TNF antagonist or to a drug with a different mechanism of action.

At present the TNF antagonists that are available for the treatment of RA: infliximab, adalimumab and etanercept; their mechanisms of action have recently been reviewed in detail. Personalised treatment regimens in the field of TNF blocking treatment are still far from optimal and most importantly, the factors influencing treatment outcomes in individual patients are unclear.

In RA it is common to try another TNF blocker after treatment with the first has failed. Previous studies on switching from one TNF blocker to another after non-response have focused on whether switching was useful or not.

These studies have also shown that there is considerable variation in response after switching; however, the contributing factors influencing this response have not been investigated.

To achieve a better understanding of factors determining response after switching from one TNF blocker to another, we prospectively studied a cohort of consecutive patients with RA receiving adalimumab treatment, for some of whom prior treatment with infliximab had failed. We compared clinical response as well as anti-antibody formation for infliximab–adalimumab switchers and TNF blockade naive patients. The ultimate goal is to understand the variation in clinical response after switching in different patient groups and to identify these different types of (non-) responders.

PATIENTS AND METHODS

Patients

Between February 2004 and February 2006, 255 consecutive patients with RA were included in a prospective observational cohort at the outpatient clinics of the departments of rheumatology of the Jan van Breemen Institute and the Academic Medical Centre in Amsterdam. All patients fulfilled the American College of Rheumatology 1987 revised criteria.
for RA, and had active disease, indicated by a disease activity score in 28 joints (DAS28) of $\geq 3.2$ despite earlier treatment with two disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), at a dosage of 25 mg weekly or at the maximal tolerable dosage, according to the Dutch consensus statement on the initiation and continuation of TNF blocking treatment in RA. Patients were treated with either adalimumab and concomitant DMARD treatment or adalimumab monotherapy. All patients used adalimumab 40 mg subcutaneously every other week. In patients with an inadequate response as judged by the treating rheumatologist, the dosing frequency of adalimumab could be increased to 40 mg/week.

Eligible patients for this study were all patients who had previously been treated with infliximab and anti-TNF naive patients. A total of 235 patients fulfilled these criteria; 52 of these patients had previously been treated with infliximab, and are referred to as ‘switchers’, and 183 were anti-TNF naive patients. The study was approved by the medical ethics committee of the Slotervaart Hospital, Boerijn Hospital, the Jan van Breemen Institute and the Academic Medical Centre/University of Amsterdam. All patients gave written informed consent.

Clinical response to adalimumab

Disease activity was assessed at baseline and after 4, 16 and 28 weeks of treatment using the DAS28 score. Clinical response was assessed by the decrease in DAS28 score ($\Delta$DAS28) and the European League Against Rheumatism (EULAR) response criteria. The 52 patients who had previously been treated with infliximab and for whom infliximab was stopped were qualified as non-responders to infliximab.

Measurement of antibodies against infliximab and adalimumab

Serum samples were collected at baseline and just before an injection with adalimumab after 4, 16 and 28 weeks. The presence of anti-infliximab antibodies was determined at baseline before the start of adalimumab. The presence of anti-adalimumab antibodies was determined at all time points between baseline and 28 weeks. Anti-infliximab and anti-adalimumab antibodies were detected by radioimmunoassay as more extensively described previously. The assays measure specific high avid IgG antibodies against adalimumab and infliximab by an antigen binding test. Serum ($1 \mu l/test$) was preincubated with Sepharose-immobilised protein A ($1 mg/test$; Pharmacia, Uppsala, Sweden) in Freeze buffer (Sanquin, Amsterdam, The Netherlands). Non-bound serum components were removed by washing before 50 $\mu l$ of $^{125}$I-labelled F(ab')2 fragment of adalimumab/infliximab was added. $^{125}$I F(ab')2 fragment of adalimumab/infliximab was added as two separate incubations. After overnight incubation, non-bound radiolabel was washed away and Sepharose-bound radioactivity was measured. Test results were converted into arbitrary units per millilitre (AU/ml) by comparison with dilutions of a reference serum. The mean cut-off value was set at 12 AU/ml, which was derived from 100 healthy donors. Assay specificity was demonstrated by the absence of anti-adalimumab in 25 serum samples containing high-titre anti-infliximab antibodies. In the assays we did not find cross reactivity. Recently, patient serum samples were tested in a bioassay, which confirmed the specificity and validity of the radioimmunoassay.

Clinical response

The mean decrease in DAS28 after 16 weeks of adalimumab treatment for the whole patient population was 1.7±1.4. There were 55 (23%) non-responders, 95 (40%) moderate responders and 85 (36%) good responders according to the EULAR response criteria. After 28 weeks of adalimumab treatment the mean decrease in DAS28 was 1.6±1.5. There were 57 (24%) non-responders, 100 (43%) moderate responders and 78 (33%) good responders at that time point (figure 1).

There was a difference in response between anti-TNF naive patients and patients who were treated with infliximab before adalimumab treatment. The improvement in DAS28 was larger for anti-TNF naive patients than for infliximab switchers ($\Delta$DAS28 1.7±1.5 vs 1.1±1.4; $p=0.007$) in a univariate analysis, and after adjustment for confounding variable DAS28 at baseline in multivariate regression analysis (95% CI 1.166 to 0.351; $p<0.0001$).

Among the anti-TNF naive patients 38% were good responders, 39% were moderate responders and 22% were non-responders. In the infliximab-switchers group 15% of the patients were good responders, 54% were moderate responders and 31% were non-responders ($p=0.008$; figure 1).

Post hoc analysis showed that only the percentage of good responders was significantly different between anti-TNF naive patients and infliximab switchers ($p=0.002$).

Immunogenicity

Anti-adalimumab antibodies were determined in 233 patients; for two patients appropriate serum samples were not available. During 28 weeks’ follow-up, anti-adalimumab antibodies were detected in 46 patients (20%). Mean $\Delta$DAS28 was 1.8±1.4 in patients without anti-adalimumab antibodies and 0.6±1.3 in...
Table 1  Demographic and clinical characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Total population (N=235)</th>
<th>Anti-TNF naive patients (n=183)</th>
<th>IFX switchers (n=52)</th>
<th>IFX switchers with anti-IFX (n=33)</th>
<th>IFX switchers without anti-IFX (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>53±12</td>
<td>53±12</td>
<td>52±12</td>
<td>54±10</td>
<td>49±13</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>185 (79)</td>
<td>142 (78)</td>
<td>43 (83)</td>
<td>27 (82)</td>
<td>16 (84)</td>
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<td>DMARD treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prior DMARDs</td>
<td>3.5±1.7</td>
<td>3.2±1.4*</td>
<td>4.4±2.2*</td>
<td>4.3±2.2†</td>
<td>4.7±2.1†</td>
</tr>
<tr>
<td>Methotrexate use, n (%)</td>
<td>193 (82)</td>
<td>150 (82)</td>
<td>43 (83)</td>
<td>28 (85)</td>
<td>15 (79)</td>
</tr>
<tr>
<td>Prednisone use, n (%)</td>
<td>80 (34)</td>
<td>56 (31)*</td>
<td>24 (46)</td>
<td>13 (39)</td>
<td>11 (58)</td>
</tr>
<tr>
<td>Prednisone dose (mg/day)</td>
<td>7.5 (5-10)</td>
<td>7.0 (5-10)*</td>
<td>7.5 (5-10)</td>
<td>5 (4-6)†</td>
<td>10 (5-10)†</td>
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<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>9 (4–17)</td>
<td>8 (4–17)</td>
<td>12 (6–18)</td>
<td>13 (6–18)</td>
<td>9 (3–17)</td>
</tr>
<tr>
<td>Rheumatoid factor positive, n (%)</td>
<td>171 (73)</td>
<td>130 (71)</td>
<td>41 (79)</td>
<td>28 (85)</td>
<td>18 (68)</td>
</tr>
<tr>
<td>Erosive disease, n (%)</td>
<td>182 (77)</td>
<td>140 (77)*</td>
<td>42 (61)*</td>
<td>28 (85)</td>
<td>14 (74)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>29±23</td>
<td>26±22</td>
<td>36±26</td>
<td>37±27</td>
<td>35±23</td>
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<tr>
<td>C-reactive protein (mg/dl)</td>
<td>11 (5–24)</td>
<td>11 (5–24)</td>
<td>10 (3–35)</td>
<td>8 (2–36)</td>
<td>14 (5–35)</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.2±1.2</td>
<td>5.1±1.2</td>
<td>5.4±1.3</td>
<td>5.3±1.2</td>
<td>5.7±1.4</td>
</tr>
</tbody>
</table>

Mean values ± SD, median (IQR) or percentages are shown. *There were significant differences between anti-TNF naive patients and switchers for prior DMARDs (p=0.000), prednisone use (p=0.037) and erythrocyte sedimentation rate (ESR) (p=0.025). †There were significant differences between anti-TNF naive patients and switchers with anti-infliximab for prior DMARDs (p=0.009), prednisone dose (p=0.013) and ESR (p=0.027). ‡Between anti-TNF naive and switchers without anti-IFX for prior DMARDs (p=0.009) and prednisone use (p=0.016) and dose (p=0.007).

**Figure 1** The EULAR response in anti-tumour necrosis factor (anti-TNF) naïve patients and switchers. Of the 235 patients, 57 (24%) were non-responders, 100 were moderate responders (43%) and 78 were good responders (33%). Of the 183 anti-TNF naïve patients, 41 (22%) were non-responders, 72 were moderate responders (39%) and 70 were good responders (38%). Of the 52 switchers, 16 patients were non-responders (31%), 28 were moderate responders (54%) and 8 were good responders (15%).

Immunogenicity and clinical response

Improvement in DAS28 was significantly greater for anti-TNF naïve patients than for switchers without anti-infliximab antibodies (p=0.016) and greater than for switchers with anti-infliximab antibodies; however, this difference did not reach statistical significance (p=0.079; table 2). After adjusting for confounding variables prednisone dose and DAS28 at baseline, the difference in ΔDAS28 for anti-TNF naïve patients compared with switchers without anti-infliximab antibodies remained (95% CI −0.934 to −0.096; p=0.017), but the trend towards significance disappeared for the difference in ΔDAS28 when anti-TNF naïve patients were compared with switchers with anti-infliximab antibodies (95% CI −1.410 to 0.316; p=0.210). Since the presence of antibodies against infliximab was associated with a higher frequency of anti-adalimumab antibody formation we performed an additional adjustment for the possible intermediate anti-adalimumab; the difference in ΔDAS28 for anti-TNF naïve patients compared with switchers with anti-infliximab antibodies remained (95% CI −1.410 to 0.316; p=0.210). Since the presence of antibodies against infliximab was associated with a higher frequency of anti-adalimumab antibody formation we performed an additional adjustment for the possible intermediate anti-adalimumab; the difference in ΔDAS28 for anti-TNF naïve patients compared with switchers without anti-infliximab antibodies (p<0.001). Of all patients without anti-adalimumab antibodies 89% used concomitant MTX treatment compared with 54% of the patients with anti-adalimumab antibodies (p<0.001).

Clinical response to adalimumab did not differ significantly between prior infliximab-treated patients with and without anti-infliximab antibodies (p=0.556). Adjustment for prednisone dose, DAS28 at baseline and number of prior DMARDs (95% CI −1.861 to 0.046; p=0.091)
MTX reduces the risk of forming anti-adalimumab antibodies.

levels.23

immune response leads to immune complex formation (thera-
tications, leading to antidrug antibody formation. This antidrug
or humanised, injected into humans can incite immune reac-
tion in the patient group receiving 1 mg/kg compared with the
10 mg/kg group.24 High levels of biologically active TNF could
lead to patients with a high disease activity at baseline having
a greater risk of developing antidrug antibodies, however, the
baseline characteristics of our patient groups do not support
this hypothesis.

The data show that anti-TNF naive patients had a better response
to adalimumab treatment than prior infliximab non-responders.
Prior infliximab non-responders without anti-infliximab antibodies
had the least improvement with subsequent adalimumab treatment.
Previous studies on switching biological agents also identified differ-
ent patient groups based on their response after switching; patients
in whom there was primary failure of previous infliximab treatment
(that is, no response/intolerance, unlike secondary failure—that is,
loss of response) had a poor response to subsequent adalimumab
treatment.10–12 It was suggested by some that there may be a sub-
population of patients with RA that does not respond to anti-TNF
treatment.11,13 Further evidence for the latter is given by a study that
showed that high levels of circulating TNFα bioactivity was associ-
ated with a good clinical response to infliximab.7 A possible expla-
nation is that TNF may not be the crucial cytokine instigating RA
nation is that TNF may not be the crucial cytokine instigating RA
processes.7,25

to 2.032; p=0.928) and additional adjustment for anti-adalimumab
status (95% CI −1.972 to 1.900; p=0.969) did not influence this.

Examination of the EULAR response to subsequent adali-
mumab treatment for switchers without anti-infliximab anti-
odies showed that there were no good responders and 42% of
the patients were non-responders.

**DISCUSSION**

The results from this study show that formation of antibodies
against adalimumab is associated with a diminished treatment
response in patients with active RA. Second, our data indicate
that switchers with anti-infliximab antibodies more often form
antibodies against adalimumab than anti-TNF naive patients.
Finally, there are different types of non-responders, which may
be relevant in the context of individualised medicine.

These data underscore initial data that immunogenicity
against monoclonal antibodies is associated with a diminished
response.3 Several studies have shown a relationship between
the development of antibodies against infliximab and a dimin-
ished response to treatment in Crohn’s disease, ankylosing
spondylitis and RA.4–10,12–20

Data on the immunogenicity of humanised and ‘fully human’
monoclonal antibodies are still limited. However, it is becom-
ing more and more clear that these antibodies can also cause
a clinically relevant immune response. Three studies have
shown an association between anti-adalimumab antibodies
and a diminished clinical response in RA.5,20 21 Approximately
6% of the patients receiving natalizumab, a humanised mono-
clonal antibody against cellular adhesion molecule α4-integrin
approved for the treatment of multiple sclerosis and Crohn’s
disease, developed persistent antibodies to the drug with sub-
sequent loss of efficacy.22 Our data contribute to the evidence
that all biologically active molecules, even being ‘fully human’
or humanised, injected into humans can incite immune reac-
tions, leading to antidrug antibody formation. This antidrug
immune response leads to immune complex formation (thera-
peutic drug antibody bound to antidrug antibody) which may
promote the rapid clearance of the drug resulting in low trough
levels.23

An important question is why an immunogenic response
is triggered in some patients but not in others. Concomitant
immunosuppressive treatment is an important factor in reduc-
ing immunogenicity.4,5,15 Current data confirm that concomitant
MTX reduces the risk of forming anti-adalimumab antibodies.
This might be of significance for the treatment of diseases where
it is not common to give concomitant MTX—for example,
in the treatment of psoriasis and ankylosing spondylitis. An
important new finding from this study is that patients who
previously formed antibodies against infliximab are more likely
to develop antibodies against adalimumab. There are three
possible explanations why people develop antibodies against
both drugs. Cross reactivity between the assays seems a logi-
cal explanation, but this could not be demonstrated. It is more
likely that some patients are more prone to develop an immune
response, possibly related to the genetic background. Another
option is that too low dosing could lead to immunogenicity,
and high dosing to the induction of immunotolerance. Initially,
every patient receives the same dosage of infliximab or adali-
mumab, but in some patients with high levels of biologically
active TNF the standard dose may be too low. For example,
for infliximab there was more anti-infliximab antibody forma-
tion in the patient group receiving 1 mg/kg compared with the
10 mg/kg group.24 High levels of biologically active TNF could
lead to patients with a high disease activity at baseline having
a greater risk of developing antidrug antibodies, however, the
baseline characteristics of our patient groups do not support
this hypothesis.

The results from this study show that formation of antibodies
to infliximab treatment was significantly different for different
patient groups. From our results a first step can be made in defi-
cing these patient groups based on their response to anti-TNF
therapy. Further research is needed to identify potential
markers, which may be useful in individualising treatment.

**Table 2** Frequency of anti-ADA antibodies and clinical response (ΔDAS28) after 28 weeks of adalimumab treatment

<table>
<thead>
<tr>
<th>Anti-ADA status, n (%)</th>
<th>Total population (N = 235)</th>
<th>Anti-TNF naive patients (n = 183)</th>
<th>IFX switchers (n = 52)</th>
<th>IFX switchers with anti-IFX (n = 33)</th>
<th>IFX switchers without anti-IFX (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ADA status, n (%)</td>
<td>46 (20)</td>
<td>32 (18)</td>
<td>14 (27)</td>
<td>11 (33)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>ΔDAS28 all</td>
<td>1.6 ± 1.5</td>
<td>1.7 ± 1.5</td>
<td>1.1 ± 1.4</td>
<td>1.2 ± 1.3</td>
<td>0.9 ± 1.4</td>
</tr>
<tr>
<td>ΔDAS28 anti-ADA –</td>
<td>1.8 ± 1.4*</td>
<td>2.0 ± 1.4*</td>
<td>1.3 ± 1.3*</td>
<td>1.6 ± 1.1*</td>
<td>0.9 ± 1.4</td>
</tr>
<tr>
<td>ΔDAS28 anti-ADA +</td>
<td>0.6 ± 1.3</td>
<td>0.6 ± 1.3</td>
<td>0.5 ± 1.4</td>
<td>0.4 ± 1.4</td>
<td>0.7 ± 1.4</td>
</tr>
</tbody>
</table>

Results are shown as n (%) or mean ± SD.

Anti-adalimumab status could not be determined in two of the anti-TNF naive patients owing to missing serum samples. The difference in ΔDAS28 between anti-adalimumab-negative (anti-ADA−) and -positive (anti-ADA+) patients was significant for the total population (p = 0.000), anti-TNF naive patients, switchers and infliximab (IFX) switchers with anti-infliximab (anti-IFX) (p = 0.019). The difference in ΔDAS28 between anti-adalimumab-positive and -negative patients did not reach significance in infliximab switchers without anti-infliximab (p = 0.809).

ADA, adalimumab, DAS28, Disease Activity Score in 28 joints; IFX, infliximab.
response to subsequent adalimumab for patients with anti-infliximab antibodies (who probably had low serum infliximab levels during infliximab treatment) did not differ significantly from that of TNF naive patients. Prior infliximab non-responders without anti-infliximab antibodies (who did not respond to infliximab despite presumably adequate infliximab levels) had a significantly worse response to subsequent adalimumab than anti-TNF naive responders. We could not demonstrate a difference in response between switchers with and without anti-infliximab in a direct analysis, but this is probably owing to a type II error. Most switchers without anti-infliximab antibodies did not respond to subsequent adalimumab despite not having antiadalimumab antibodies. Since immunogenicity did not cause non-response in these patients, it is possible that these patients are refractory to anti-TNF treatment. Therefore, our study suggests that non-responders to TNF blockers should be treated differently according to their anti-drug antibody status. Antibody-positive patients probably benefit most from switching to a less immunogenic drug acting on the same principle, or from optimising concomitant DMARD (MTX) treatment. Furthermore, it is likely that in non-responders without anti-TNF blocker antibodies it is more useful and cost-effective to start treatment based on a mechanism of action other than TNF blockade.

This study is limited by the number of patients and the consequences of the observational cohort study design. The patient population had severe RA: long disease duration and many prior DMARDs; therefore, possibly, treatment effects are more difficult to the interval and the presence of anti-infliximab antibodies (data showed). The frequency of anti-infliximab antibodies is higher than the level we measured. The first adalimumab injection it might be that the frequency of anti-infliximab antibodies is higher than the level we measured. However, we did not find an association between the length of the interval and the presence of anti-infliximab antibodies (data not shown). In addition to these limitations, our study provides unique insight into the role of immunogenicity in treatment with biological agents. In daily practice in RA switching to another biological agent after non-response is often a random decision rather than an evidence-based decision. To our knowledge, this is the first study providing more information on the underlying mechanisms contributing to the possible success of switching. Further studies are necessary to provide more conclusive data on this subject. However, we show that determining the immunogenic status of a non-responding patient may be important for further decision-making and might assist in developing an optimised treatment for the individual patient.

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Competing interests BACD, PPT and WF are members of the advisory board of Abbott and BACD and PPT have received honoraria for lectures. PPT has served as a consultant to Abbott, Amgen, Centocore, Schering-Plough, UCB and Wyeth.

Ethics approval The study was approved by the medical ethics committee of the Slotervaart Hospital, BovenIJ Hospital, the Jan van Breemen Institute and the Academic Medical Centre/University of Amsterdam.

Provenance and peer review Not commissioned; externally peer reviewed.

References


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