EXTENDED REPORT

Immunogenicity, adalimumab levels and clinical response in ankylosing spondylitis patients during 24 weeks of follow-up

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ABSTRACT

Background Immunogenicity influences adalimumab levels and therefore clinical response in patients with rheumatic diseases.

Objectives To study the relationship between clinical response, adalimumab levels and antidrug antibodies (ADAb) in ankylosing spondylitis (AS).

Methods Observational cohort study of 115 consecutive AS patients treated with adalimumab in the Netherlands (n=85) and Taiwan (n=30), monitored during 24 weeks. Adalimumab levels and ADAb titres were determined using an ELISA and an antigen binding test (ABT), respectively, designed by Sanquin Research, Amsterdam. Response to adalimumab treatment was defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) response, and disease activity was measured using the Ankylosing Spondylitis Disease Activity Score using C-reactive protein (CRP) (ASDAS).

Results At baseline, median BASDAI (IQR) was 6.4 (4.5–7.6) and mean ASDAS (SD) was 3.5 (1.0). After 24 weeks, 49 (42.6%) patients were BASDAI50 responders and mean ASDAS (SD) for responders was 1.5 (1.0) vs 2.6 (1.0) for non-responders (p<0.001). Thirty-one (27.0%) patients had detectable ADAb. After 24 weeks, adalimumab levels (mg/L) (IQR) were significantly higher in ADAb-negative patients than in ADAb-positive patients (12.7 (8.2–18.0) vs 1.2 (0.0–2.0), (p<0.001)). A significant association was demonstrated between adalimumab levels and ASDAS (p=0.02; RC −1.1; 95% CI −2.0 to −0.2). Eleven (9.6%) patients had no detectable adalimumab levels and high detectable ADAb titres (>100 AU/mL). In these patients, CRP and erythrocyte sedimentation rate remained elevated during treatment.

Conclusions Adalimumab levels are related to clinical response in AS patients measured with ASDAS and are influenced by ADAb detectable with an ABT.

INTRODUCTION

Approximately 40% of ankylosing spondylitis (AS) patients do not respond to tumour necrosis factor (TNF) inhibitors.1 Part of the non-response cannot be explained; however, an important reason for non-response is low drug levels as a result of the development of antidrug antibodies (ADAb). Previous studies of adalimumab treatment in AS patients showed percentages of detectable ADAb around 30% during 6–12 months of follow-up, leading to low or undetectable adalimumab levels and assessment of spondyloarthritis (ASAS) non-response.2–4 A diminished treatment response associated with ADAb development has been described for rheumatoid arthritis (RA) to a larger extent.4–8 These studies, from three different medical centres, observed different proportions of patients that developed ADAb. In patients with AS, the frequency of ADAb might be higher compared with patients with RA due to the lack of concomitant disease modifying antirheumatic drugs (DMARDs) (particularly methotrexate) in the treatment of AS. In RA, methotrexate has been shown to reduce the percentage of detectable ADAb.9 10 Currently, there is no firm evidence to support a significant benefit of methotrexate monotherapy in the treatment of AS.11 Several randomised controlled trials (RCTs) have studied the beneficial effect of methotrexate in addition to infliximab in AS patients; however, a significant difference in disease activity or infliximab levels could not be demonstrated by these trials.12–15

Previous studies showed that serum drug levels may vary widely between patients, but despite these observed variations,2 4 5 pharmacokinetics of TNF inhibitors is currently not taken into account when treating AS patients. Considering the high costs of TNF inhibitors, there is a need to optimise TNF inhibitor treatment by identifying causes for non-response and preventing overtreatment in responders. The aim of this study was to investigate the relationship between clinical response, adalimumab levels and ADAb in AS in order to explore the utility of drug level and ADAb testing for the optimisation of adalimumab treatment in AS patients.

PATIENTS AND METHODS

Study design and patients

This prospective observational cohort study consisted of 126 consecutive adult patients with AS (according to the 1984 modified New York Criteria) who received adalimumab therapy at the department of Rheumatology of the Jan van Breemen Research Institute | Reade, Amsterdam, and Chung Shan Medical University Hospital, Taichung. All patients had failed to respond to at least two non-steroid anti-inflammatory drugs (NSAIDs) in the maximal tolerable dosage or had contraindications for the use of NSAIDs before
start of TNF inhibitors according to the ASAS consensus statement of initiation and continuation of TNF-inhibiting therapy in AS.\textsuperscript{17} Patients were treated either with adalimumab and concomitant NSAID or DMARD therapy or with adalimumab monotherapy. All patients started with adalimumab 40 mg subcutaneously every other week. If mandatory, as judged by the treating rheumatologist, the dosing frequency of adalimumab could be adapted to 40 mg per week or every 3 weeks. The study was approved by the Medical Ethics Committee of both institutes. All patients gave written informed consent.

**Clinical response**

At the Jan van Breemen Research Institute | Reade, Amsterdam, disease activity was assessed at baseline, 4, 12 and 24 weeks. In the Chung Shan Medical University Hospital, Taichung, disease activity was assessed at baseline, 8 and 20 weeks. For analysis, weeks 8 and 12 and weeks 20 and 24 were combined. Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)\textsuperscript{18} and Ankylosing Spondylitis Disease Activity Score using C-reactive protein (CRP) (ASDAS).\textsuperscript{19} Active disease was defined as a BASDAI \(\geq 4\)\textsuperscript{20} or an ASDAS \(\geq 2.1\).\textsuperscript{21 22} Response to adalimumab treatment was defined according to the international ASAS consensus statement for the use of TNF inhibitors in AS and was defined as a 50% improvement or an absolute improvement of two points of the BASDAI (0–10 scale), further mentioned here as BASDAI\textsubscript{50} response.\textsuperscript{17}

**Measurements of adalimumab concentrations**

Trough serum samples were taken at each visit, and adalimumab concentrations were measured by ELISA based on the principle that adalimumab is captured via its ability to bind TNF. Serum concentrations were measured by ELISA based on the principle that adalimumab is captured via its ability to bind TNF. The lower limit of quantitation of this assay is 0.01 mg/L.

Measurements of ADAb

ADAb titres were determined using an antigen binding test (ABT) as described previously.\textsuperscript{24 23} Patients were defined as positive for ADAb if titres were above 12 AU/ml on at least one occasion, in combination with serum adalimumab levels below 5.0 mg/L, as previously described by Bartelds \textit{et al.}\textsuperscript{4}

**Statistical analysis**

For statistical analysis, statistical package for the social sciences (SPSS) V17.0 was used. For differences between groups, we used independent sample t test, Mann–Whitney U test or \(\chi^2\) test as appropriate. The threshold for significance was set at \(p<0.05\). The generalised estimating equation (GEE) approach was used to investigate the association between adalimumab levels and disease activity or response over time. The influence of confounders on this association was investigated. Variables considered as potential confounders were chosen from all available baseline variables if unrelated to ASDAS (hence, not in analysis: CRP, erythrocyte sedimentation rate (ESR) and BASDAI) and validated as potential confounders if unrelated to ASDAS (hence, not in analysis: CRP, erythrocyte sedimentation rate (ESR) and BASDAI) and considered as potential confounders were chosen from all available baseline variables if unrelated to ASDAS (hence, not in analysis: CRP, erythrocyte sedimentation rate (ESR) and BASDAI).

**RESULTS**

**Patient characteristics**

Of 126 suitable patients, 115 (91.3%) were included in this study and 11 (8.7%) were excluded because only baseline samples were available. The demographic data and the baseline characteristics are shown in table 1. For an additional 11 patients, the assessment of response status was not possible due to missing baseline BASDAI (n=8) or missing follow-up BASDAI (n=3). Forty-nine patients were BASDAI\textsubscript{50} responder.

### RESULTS

Patient characteristics

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<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total patient population (n=115)</th>
<th>BASDAI\textsubscript{50} responder (n=49)</th>
<th>BASDAI\textsubscript{50} non-responder (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years±SD</td>
<td>42±11</td>
<td>40±10</td>
<td>44±12</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>78 (68)</td>
<td>34 (69)</td>
<td>35 (64)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.9 (22.8–27.8)</td>
<td>24.1 (22.7–26.7)</td>
<td>25.4 (22.7–26.9)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years (median)</td>
<td>8 (3–15)</td>
<td>8 (3–16)</td>
<td>7 (2–15)</td>
</tr>
<tr>
<td>HLA-B27-positive, no. (%)</td>
<td>95 (83)</td>
<td>42 (86)</td>
<td>45 (82)</td>
</tr>
<tr>
<td>CRP, mg/L (median)</td>
<td>7 (3–17)</td>
<td>8 (3–18)</td>
<td>6.5 (3–17)</td>
</tr>
<tr>
<td>ESR, mm/h (median)</td>
<td>25 (9–40)</td>
<td>28 (14–40)</td>
<td>14 (7–40)</td>
</tr>
<tr>
<td>ASDAS CRP±SD</td>
<td>3.5±1.0</td>
<td>3.4±1.0</td>
<td>3.5±1.0</td>
</tr>
<tr>
<td>BASDAI (median)</td>
<td>6.4 (4.5–7.6)</td>
<td>6.3 (4.2–7.5)</td>
<td>6.6 (5.2–7.5)</td>
</tr>
<tr>
<td>GDA VAS (median)</td>
<td>7 (5–8)</td>
<td>6 (5–8)</td>
<td>7 (5–8)</td>
</tr>
<tr>
<td>BASFI (median)</td>
<td>5.2±2.5</td>
<td>4.5±2.6**</td>
<td>5.8±2.6**</td>
</tr>
<tr>
<td>DMARD therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior biologicals, no. (%)</td>
<td>21 (18.3)</td>
<td>6 (12.2)</td>
<td>9 (16.4)</td>
</tr>
<tr>
<td>Methotrexate use, no. (%)</td>
<td>5 (4.3)</td>
<td>2 (4.1)</td>
<td>2 (3.6)</td>
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<tr>
<td>Sulfasalazine, use no. (%)</td>
<td>34 (29.6)</td>
<td>16 (32.7)</td>
<td>16 (29.1)</td>
</tr>
<tr>
<td>NSAID use, no. (%)</td>
<td>75 (65.2)</td>
<td>33 (67.3)</td>
<td>36 (65.5)</td>
</tr>
</tbody>
</table>

*Mean values±SD, median (IQR) or numbers (percentages) are shown. There was a significant difference between patients with and without BASDAI\textsubscript{50} response for **BASFI (p=0.01). ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GDA VAS, general disease activity on a visual analogue scale (0–10); HLA-B27, human leucocyte antigen B27; NSAID, non-steroid anti-inflammatory drugs.
after 24 weeks, and 55 patients were BASDAI50 non-responders. Baseline characteristics did not differ significantly for responders and non-responders except for Bath Ankylosing Spondylitis Functional Index (BASFI) (p=0.02).

Patients from Taiwan had a more severe and long-standing disease as shown in table 2.

**Discontinuation of treatment**
Nine patients (7.8%) dropped out before 24 weeks, five patients due to treatment failure in the opinion of the patient or physician, three patients due to adverse events (palmpantar pustular psoriasis, increased liver enzymes and multiple myeloma) and one patient due to follow-up. Of the patients dropping out due to failure, one patient had detectable ADAb.

**Clinical response**
After 24 weeks, 106 (92.2%) patients were still on adalimumab treatment. In one patient, dosing frequency was increased to adalimumab once a week and in four patients adalimumab dosing frequency was decreased to once per 3 weeks. Mean ASDAS for BASDAI50 responders was 1.5 (SD 1.0) vs 2.6 (SD 1.0) for non-responders (p<0.001). There was no significant difference in BASDAI response between patients from the Netherlands and Taiwan (47.3% vs 46.7%, respectively; p=0.93).

Six patients did not have 24 weeks of follow-up yet, and response data at 24 weeks of 20 (17.4%) patients were missing. To exclude bias due to missing data, a sensitivity analysis was performed for patients who completed 6 months of adalimumab treatment; this did not alter the results. More information on the method we used for the sensitivity analysis can be found in the online supplementary file.

**Adalimumab concentration and antibodies against adalimumab**
Thirteen (11.3%) patients had detectable ADAb at week 12 after start of treatment and 31 (27.0%) at week 24. There was no significant difference in the proportion of patients with ADAb for BASDAI50 responders and non-responders (14 (28.6%) and 14 (25.5%), respectively; p=0.56). Of the 5 patients who used concomitant methotrexate, none had ADAb, and of the 34 patients using concomitant sulfasalazine at baseline 10 had ADAb.

After 24 weeks, median adalimumab level was 9.7 mg/L (3.9–15.7) and varied from undetectable to 56.7 mg/L in patients with adalimumab in a dose of 40 mg every other week. Adalimumab levels (mg/L) were significantly different for patients without and with ADAb (12.7 (IQR 8.2–18.0) and 1.2 (IQR 0.0–2.0), respectively; p<0.001 (figure 1)).

At 24 weeks of follow-up, median adalimumab levels were significantly higher for Dutch patients (12.6 (5.9–18.5) vs Taiwanese patients (6.1 (1.1–11.4) mg/L) (p=0.001); this was a result of the higher percentage of ADAb-positives among Taiwanese patients (12 (40.0%) vs Dutch patients (19 (22.4%)) (p=0.06).

Patients could be divided into four groups according to the height of the ADAb titre and adalimumab level: 77 (67.0%) patients with high adalimumab levels (median 12.7 mg/L; IQR 7.1–16.5) and no ADAb, 20 (17.4%) patients with adalimumab levels <5 mg/L (median 2.0 mg/L; IQR 1.6–3.6) and intermediate ADAb (12–100 AU/mL) titres (median 35 AU/mL; IQR 21–57), 11 (9.6%) patients with no detectable adalimumab levels (0.0 mg/L; IQR 0.0–0.0) and high ADAb (>100 AU/ml) titres (median 670 AU/mL; IQR 319–13600) and 7 (6.1%) patients with transient ADAb titres (fluctuating over time and >12 AU/mL on at least one visit) (median 14 AU/mL; IQR 0–32) but adalimumab levels (median 7.4 mg/L; IQR 5.1–18.6) remained at >5 mg/L (figure 1).

Although a lower percentage of Dutch patients tested positive for ADAb as compared with Taiwanese patients, among the 11 patients with high ADAb levels and no detectable adalimumab most patients were Dutch (n=8).

**Clinical response and adalimumab concentrations**
There was no statistically significant difference in adalimumab levels between BASDAI50 responders and non-responders (12.0

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**Table 2**  
Demographics and clinical characteristics at baseline between patients from the Netherlands and Taiwan*

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total population (n=115)</th>
<th>Netherlands (n=85)</th>
<th>Taiwan (n=30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>42±11</td>
<td>43±12</td>
<td>37±12</td>
<td>0.01</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>78 (68)</td>
<td>52 (61)</td>
<td>26 (87)</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>24.9 (22.8-27.8)</td>
<td>24.8 (22.9-27.8)</td>
<td>25.0 (22.7-27.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years (median)</td>
<td>8 (2.5–15)</td>
<td>7 (2–14)</td>
<td>12 (5.7–16.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>HLA-B27-positive, no. (%)</td>
<td>95 (82.6)</td>
<td>65 (76.5)</td>
<td>30 (100)</td>
<td>0.003</td>
</tr>
<tr>
<td>CRP, mg/L (median)</td>
<td>7.0 (3–17)</td>
<td>5.0 (2–11.5)</td>
<td>15.6 (12–28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESR, mm/h (median)</td>
<td>25 (8.5–39.5)</td>
<td>15 (7–31)</td>
<td>38 (30.5–54.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASDAS CRP (mean)</td>
<td>3.5 (1)</td>
<td>3.1 (2.4–3.8)</td>
<td>4.3 (3.7–4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BASDAI (median)</td>
<td>6.4 (4.5–7.6)</td>
<td>6.1 (4.3–7.3)</td>
<td>7.4 (6.5–8)</td>
<td>0.001</td>
</tr>
<tr>
<td>GDA VAS (median)</td>
<td>7 (5–8)</td>
<td>6 (5–8)</td>
<td>7 (5–8)</td>
<td>0.15</td>
</tr>
<tr>
<td>BASFI (median)</td>
<td>5.2±5.2</td>
<td>4.7±2.5</td>
<td>6.5±2.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mean values±SD, median (IQR) or numbers (percentages) are shown.

ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GDA VAS, general disease activity on a visual analogue scale (0–10); HLA-B27, human leucocyte antigen B27; NSAID, non-steroid anti-inflammatory drugs.

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As shown in table 3, GEE analysis demonstrated a significant association between adalimumab and disease activity, measured with ASDAS and BASDAI. There were no confounders for the association between adalimumab and ASDAS. BASFI was the only confounder for the association between adalimumab and BASDAI, and after correction significance (p=0.05) it decreased but a trend in favour of BASDAI remained. Also, there was a statistically significant association of adalimumab with ESR in GEE (table 3).

Figure 1 Median adalimumab trough levels (mg/L), Bath Ankylosing Spondylitis Disease Activity Index score (0–10), erythrocyte sedimentation rate (mm/h) and C-reactive protein (mg/L) for ankylosing spondylitis patients divided into four groups: no detectable adalimumab levels and antidrug antibodies (ADAb) titres with normal adalimumab levels (>5 mg/L), mediate detectable ADAb titres with low adalimumab levels (<5 mg/L) and high detectable ADAb titres with low adalimumab levels (<5 mg/L) and patients with transient ADAb during 24 weeks of follow-up.

DISCUSSION

Our results show that adalimumab levels vary widely among patients, and ADAb were detected in 27% of AS patients. Adalimumab levels were significantly lower for patients with ADAb compared with patients without ADAb. A significant association between adalimumab and ASDAS, BASDAI and ESR was established with GEE analysis. In particular in patients with high ADAb titres, the adalimumab levels were absent and in these patients CRP and ESR remained elevated throughout 24 weeks of follow-up.

In this study, we combined two populations in which baseline characteristics were different between both cohorts (table 2). We found a higher ADAb percentage in patients from Taiwan, who had a more severe and long-standing disease with more physical limitations at baseline, compared with patients from the Netherlands. Probably patients with high levels of inflammation...
and a more severe and long-standing disease are more prone to extensively develop ADAb as is shown in RA.7

Although CRP levels at baseline are elevated only in a proportion of AS patients, it might be helpful in assessing disease activity and response in AS because suppression of inflammation is the mechanism of action of TNF inhibition therapy.

First, CRP and ESR at baseline have been described as a predictor for BASDAI50 response.26 In our study, CRP and ESR were higher for BASDAI50 responders compared with non-responders, although this difference was not significant.

Second, at 24 weeks of treatment, ESR was significantly higher in ADAb-positive patients. Additionally, in patients with high ADAb titres and no adalimumab level, CRP and ESR remained elevated throughout 24 weeks of treatment, although the number of patients with high ADAb titres and no adalimumab levels was too small to analyse separately. To study the association between adalimumab and disease activity, clear measurements for disease activity and response are needed. BASDAI is a validated measurement of disease activity and the most used, but this is a patient-reported questionnaire only. ASDAS using CRP (or ESR as an alternative) has been introduced as an alternative measurement for assessing disease activity in AS19 21 and might be a more objective measurement because it includes inflammatory parameters.

Data on adalimumab level and immunogenicity are limited. A previous study in 60 AS patients of whom 20 patients were treated with adalimumab showed that adalimumab levels were negatively correlated with BASDAI and ESR after 6 months, with CRP after 12 months and with ASDAS CRP after 3 months (p<0.05). Median adalimumab levels at 6 months of treatment were 6.8 μg/mL (5.9–11.4) and 1.6 μg/mL (0.0–2.4) for patients without and with adalimumab, respectively. ADAb was detected in 30% of patients at 1 year of treatment.2 de Vries et al3 found an ADAb percentage of 31 in AS patients treated with adalimumab for 6 months, in correspondence with diminished or undetectable adalimumab levels. In our study, ADAb detectable with an ABT were found in 27% of patients. These results show that the percentage of patients developing ADAb within 6 months of adalimumab treatment is higher for AS patients compared with RA patients at 6 months, which might be due to the differences in pathophysiology or rather due to the differences in cofactors such as concomitant DMARD use or differences in ADAB testing.27

In our study, seven patients had transient ADAb titres (fluctuating ADAb titres over time and >12 AU/mL on at least one visit); possibly these patients develop tolerance for adalimumab, which was described earlier.28

Several factors can influence drug levels of TNF inhibitors, of which ADAb development, dosage and concomitant methotrexate use are the most important. The number of patients with concomitant methotrexate or sulfasalazine use in our study was too small to detect a significant relationship between the development of ADAb and the use of concomitant DMARDs, as well as detect a significant difference in drug levels between patients with adalimumab monotherapy or in combination therapy. Previous studies have shown that RA patients with ADAb significantly less often used concomitant methotrexate,7 9 which has appeared to be an important factor in reducing immunogenicity in a dose-dependent manner.10 Also, a better clinical response and higher drug levels of biologics have been described for TNF inhibitors with concomitant methotrexate compared with TNF inhibitor monotherapy in RA.29 Currently, there is not enough evidence to support any benefit of methotrexate in the treatment of AS. Therefore, it is also not used as concomitant therapy with TNF inhibitor treatment.11 30 Several RCTs studied the beneficial effects of methotrexate (varying from 10 to 15 mg/week) in addition to infliximab, but no significant difference in disease activity or infliximab levels was found.12–15 In these studies, response was defined according to ASAS20 or BASDAI50 response criteria; patient numbers varied between 26 and 76, and follow-up was relatively short.12–15 Possibly these factors influenced the results of these studies.

Previous studies described lower infliximab levels for RA as reported for AS.10–33 Possibly beneficial effect of additional methotrexate is only seen when TNF inhibitor drug levels reach a critical level. This is an adalimumab level that is low enough for the immune system to overcome by the production of ADAb and therefore cause loss of response. If TNF inhibitor dosage can be lowered when methotrexate is added in the treatment of AS patients, this might save costs. It would be interesting to study the effect of methotrexate on the immunogenicity and drug levels of TNF inhibitors in AS patients prospectively.

There are some limitations to this study. First, the missing data, although a sensitivity analysis did not alter the results. This was mostly due to the fact that patient questionnaires were not completed. Second, a small amount of the samples might not have been exactly trough level since adalimumab is an at-home administered drug.

In conclusion, adalimumab levels varied widely among patients; however, some patients improved based on clinical measurements such as BASDAI or ASDAS CRP despite low adalimumab levels. Currently, the variation in pharmacokinetics of TNF inhibitors is not taken into account in the treatment of AS. TNF inhibitor treatment is expensive, and due to the large observed variations in drug levels a personalised treatment strategy is necessary to identify undertreatment and overtreatment. This is especially important in AS, where the treatment options are limited and clear clinical measurements for disease activity are lacking.

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Contributors All authors were responsible for study concept and design, clinical revision and drafting of the manuscript for important intellectual content, and approved the final version of the manuscript to be published. ELK, JC-CW, K-JY, CYC and CLMK were responsible for acquisition of data. ELK, GW and CLMK were responsible for analysis and interpretation of data. MTN, GW and CLMK obtained funding. TN, GW and CLMK supervised the study.

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Competing interests MTN reports having received consultancy fees from Abbott, Roche, Pfizer, MSD, UCB, SOBI and BMS, payment for lectures from Abbott, Roche and Pfizer. GW reports having received a research grant from Pfizer (Wyeth) (paid to the institution) and payments for lectures from Pfizer and Amgen.

Patient consent Obtained.

Ethics approval The study was approved by the medical ethics committee of Reade Slotenvaart and the Institutional Review Board, Chung Shan Medical University Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

Clinical and epidemiological research


Immunogenicity, adalimumab levels and clinical response in ankylosing spondylitis patients during 24 weeks of follow-up

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