Concise report

Drug trough levels predict therapeutic responses to dose reduction of adalimumab for rheumatoid arthritis patients during 24 weeks of follow-up

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Abstract

Objective. To evaluate the impact of adalimumab (ADA) dose-halving on therapeutic responses and drug levels, the differences in drug levels among patients with different therapeutic responses and the optimal baseline cut-off ADA levels for predicting persistent remission or low disease activity (LDA) at week 24 of dose-halving therapy in 64 RA patients who had already achieved LDA or remission at baseline.

Methods. Anti-ADA antibody levels were determined by bridging ELISA, ADA levels were evaluated using sandwich ELISA and therapeutic responses were assessed by the 28-joint DAS change. The optimal cut-off drug levels for predicting persistent remission were determined by receiver operating characteristic curve analysis.

Results. At baseline, 25 (39.1%) and 39 (60.9%) patients had achieved remission and LDA, respectively. After 24 week ADA dose-halving, persistent remission was observed in 23 patients, remission turned LDA in 2 patients, persistent LDA in 24 patients and disease flare in 15 (23.5%) patients. Three patients who developed anti-ADA antibodies at week 24 of dose-halving had very low drug levels and disease flare. Among 61 anti-ADA antibody-negative patients, ADA levels declined by half after 24 weeks of dose-halving (median 5.5 vs 2.6 \(\mu g/ml\)). Baseline ADA levels were significantly higher in patients with persistent remission (median 10.5 \(\mu g/ml\)) or LDA (4.5 \(\mu g/ml\)) than in those with disease flare (0.9 \(\mu g/ml\)), indicating associations of ADA levels with therapeutic responses. An ADA level above the cut-off value of 6.4 \(\mu g/ml\) might predict persistent remission after dose-halving with high sensitivity and specificity.

Conclusion. ADA dose-halving is feasible for patients who have achieved remission and sufficient drug levels. Drug level monitoring may help clinicians optimize the dosing regimen and prevent overtreatment for patients receiving anti-TNF-\(\alpha\) therapy.

Key words: dose reduction, drug trough level, adalimumab, therapeutic responses, rheumatoid arthritis.

Rheumatology key messages

- Adalimumab dose-halving is feasible in remitted RA patients with an adalimumab trough level above 6.4 \(\mu g/ml\).
- Therapeutic drug monitoring may help clinicians optimize dosage in RA patients receiving anti-TNF-\(\alpha\) therapy.

Introduction

TNF-\(\alpha\) inhibitors have been an effective therapy for RA patients, and disease remission is well-recognized as an
appropriate goal [1]. However, the feasibility of dose reduction or discontinuation of TNF-α inhibitors for patients who have already achieved clinical remission should be considered based on concerns such as dose-dependent adverse effects and economic burden [2]. Although most patients with established RA flare upon discontinuation of TNF-α inhibitors [3], proper dose reduction after attainment of remission or low disease activity (LDA) allows good outcomes to be sustained [4]. Therefore the Taiwan Health Insurance Bureau put forward a dose-reducing policy for biologic therapy in April 2013, in which a half dose reduction (dose-halving) of TNF-α inhibitors should be conducted in patients with LDA after at least 2 years of therapy. However, there has been no well-established dose-reducing strategy for biologics in RA patients.

Recently a few studies have indicated that RA patients who have a good therapeutic response and a trough drug level above the therapeutic range may be eligible for dose reduction [5]. Pouw et al. [6] identified the therapeutic range of adalimumab (ADA) trough levels at 5–8 μg/ml for maximal clinical response, which can be useful for down-titration of ADA dosage. However, the exact effects of dose reduction of TNF-α inhibitors on anti-ADA antibody titre and drug level in RA patients remain unclear.

Therefore this prospective study aimed to evaluate the impact of ADA dose-halving on therapeutic responses by assessing the change in the 28-joint DAS (DAS28) at baseline and at week 24 of dose-halving therapy, the effect of dose-halving therapy on anti-ADA antibody and serum drug trough levels and the differences in drug trough levels among patients with different therapeutic responses. Subsequently we determined the baseline cut-off ADA levels for predicting persistent remission or LDA at week 24 of dose-halving therapy using receiver operating characteristic (ROC) curve analysis.

**Methods**

**Patients**

We enrolled 64 initially biologic-naive patients who fulfilled the 1987 ACR criteria for RA [7] and had already achieved remission or LDA after receiving ADA full-dose therapy according to the guidelines [8]. Based on the Taiwan Health Insurance Bureau’s regulations, their treatment should be switched to ADA dose-halving at a dose of 40 mg monthly and a concomitant stable dose of MTX. Disease activity was assessed using DAS28-ESR. Remission was defined as a DAS28 <2.6 and LDA as DAS28 <3.2 [9]. Persistent remission and persistent LDA were defined as the maintenance of remission or LDA assessed at week 24 of ADA dose-halving, respectively, and disease flare as a DAS28 ≥3.2 at week 24 of dose-halving. Blood samples were obtained immediately before ADA injection. The Ethics Committee of Taichung Veterans General Hospital approved the study (CE12205-2) and written consent from each participant was obtained according to the Declaration of Helsinki.

**Assessments of anti-ADA antibodies**

Detection for anti-ADA antibodies were performed at baseline and at week 24 of dose-halving therapy using bridging ELISA (Progenika Biopharma, Derio, Spain) as described in our previous study [10]. Test results were converted into arbitrary units per millilitre (AU/ml) by comparison with dilutions of a reference serum. Positive results were defined as titres >3.5 AU/ml in combination with ADA levels <5.0 μg/ml. The intra-assay and interassay coefficients of variation were both 6.6%.

**Determination of serum trough levels of ADA**

Serum ADA trough levels were determined at baseline and at week 24 of dose-halving therapy using sandwich ELISA (Progenika Biopharma) as described in our previous study [10]. The minimal detectable ADA levels were 0.002 μg/ml and the intra-assay and interassay coefficients of variation were 6.1% and 5.1%, respectively.

**Determination of the cut-off trough levels for persistent remission or LDA**

Because ADA trough levels are positively associated with therapeutic response [10], we identified the optimal baseline cut-off level of ADA for predicting persistent remission or LDA at 24 weeks of dose-halving therapy using ROC curve analysis.

**Statistical analysis**

Results are presented as the mean (±S.D.) or median [interquartile range (IQR)]. The chi-square test was used to compare binary variables and the Kruskall–Wallis test to compare ADA trough levels among patients with different therapeutic responses. The correlation between ADA level and the decrement of DAS28 or MTX dosage was determined by the non-parametric Spearman’s rank test. The diagnostic sensitivity, specificity and area under the ROC curve (AUC) were determined using MedCalc statistical software version 9.3 (MedCalc Software, Ostend, Belgium). A P-value <0.05 was considered significant.

**Results**

**The impact of 24 weeks of dose-halving therapy on therapeutic responses**

Before starting ADA dose-halving therapy (at baseline), 25 (39.1%) and 39 (60.9%) patients had achieved remission and LDA, respectively. After 24 weeks of dose-halving, persistent remission was observed in 23 patients, remission turned LDA in 2, persistent LDA in 24 and disease flare (DAS28 ≥3.2) in 15 (23.5%) (Fig. 1A). Patients with persistent remission or LDA had received significantly longer periods of ADA full-dose therapy with lower baseline DAS28 and CRP levels when compared with those with disease flare (Table 1).
Fig. 1 Association of adalimumab (ADA) levels with therapeutic responses in RA patients before and after dose-halving therapy

(A) The proportion of achieved clinical remission, low disease activity (LDA) and moderate to high disease activity (DAS28 ≥3.2) in RA patients at baseline and at week 24 of ADA dose-halving therapy. (B) The correlation between serum ADA trough levels and therapeutic response (ΔDAS28: the change in 28-joint DAS after full-dose ADA therapy) assessed at baseline was obtained by the Spearman rank correlation test. (C) Comparison of ADA levels at baseline and at week 24 of dose-halving therapy among patients with different therapeutic response status (persistent remission, persistent LDA and disease flare) was determined by the Kruskal–Wallis test. The data are presented as box plot diagrams, with the box encompassing the 25th percentile (lower bar) to the 75th percentile (upper bar). The horizontal line within the box indicates the median value for each group. *P < 0.001 vs those with disease flare after ADA dose-halving therapy; #P < 0.001 vs those with persistent LDA after ADA dose-halving therapy. Receiver operating characteristic (ROC) curves analysis for identifying the optimal drug cut-off level for predicting (D) persistent remission and (E) persistent LDA at week 24 of ADA dose-halving therapy. AUC: area under ROC curve; sen.: sensitivity; spe.: specificity. P-value was determined by the chi-square test with Yate’s correction of contingency.
TABLE 1 Baseline demographic and laboratory data in RA patients with different therapeutic responses after adalimumab dose-halving

<table>
<thead>
<tr>
<th></th>
<th>Persistent remission (n = 23)</th>
<th>Persistent LDA(a) (n = 26)</th>
<th>Disease flare(b) (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>57.1 (14.7)</td>
<td>53.5 (14.4)</td>
<td>56.3 (14.4)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>21 (91.3)</td>
<td>24 (92.3)</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>Disease duration, mean (s.d.), years</td>
<td>9.1 (2.5)</td>
<td>9.0 (3.8)</td>
<td>9.3 (2.6)</td>
</tr>
<tr>
<td>ADA duration, mean (s.d.), years</td>
<td>3.2 (0.4)**</td>
<td>2.9 (0.6)*</td>
<td>2.4 (0.4)</td>
</tr>
<tr>
<td>RF positivity, n (%)</td>
<td>18 (78.3)</td>
<td>18 (69.2)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Anti-CCP positivity, n (%)</td>
<td>19 (82.6)</td>
<td>22 (84.6)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>ESR at baseline, mean (s.d.), mm/1 h</td>
<td>10.1 (9.7)</td>
<td>12.7 (9.3)</td>
<td>12.7 (9.7)</td>
</tr>
<tr>
<td>CRP at baseline, mean (s.d.), mg/dl</td>
<td>0.24 (0.27)**</td>
<td>0.33 (0.23)**</td>
<td>0.88 (0.58)</td>
</tr>
<tr>
<td>DAS28 at baseline, mean (s.d.)</td>
<td>2.21 (0.13)**</td>
<td>2.86 (0.14)*</td>
<td>3.15 (0.05)</td>
</tr>
<tr>
<td>ADA at baseline, median (IQR)</td>
<td>10.5 (8.1–11.8)**</td>
<td>4.5 (2.9–5.9)**</td>
<td>0.9 (0.7–1.0)</td>
</tr>
<tr>
<td>ADA at dose-halving, median (IQR)</td>
<td>5.2 (3.6–6.6)**</td>
<td>2.0 (1.1–2.8)**</td>
<td>0.1 (0.0–0.3)</td>
</tr>
<tr>
<td>Steroid at baseline, mean (s.d.), mg/day</td>
<td>2.3 (2.1)</td>
<td>1.9 (1.9)</td>
<td>2.9 (2.3)</td>
</tr>
<tr>
<td>MTX</td>
<td>21 (91.3)</td>
<td>24 (92.3)</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>SSZ</td>
<td>7 (30.4)</td>
<td>8 (30.8)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>HCQ</td>
<td>6 (26.1)</td>
<td>6 (23.1)</td>
<td>2 (16.7)</td>
</tr>
</tbody>
</table>

\(a\)Two patients who had remission turned LDA after drug dose-halving were included. \(b\)Three patients with anti-ADA antibody after drug dose-halving were included. *P < 0.01 and **P < 0.001 vs RA patients who had disease flare at week 24 after ADA dose-halving therapy as determined by Mann-Whitney U test. ADA: adalimumab.

The effect of dose-halving therapy on anti-ADA antibody and drug trough levels

In three patients (4.7%), anti-ADA antibody was not detected at baseline, but turned positive at week 24 of dose-halving (77.5, 134 and 309.0 AU/ml). Poor adherence to MTX therapy after ADA dose-halving was observed in these patients: two patients discontinued MTX and one received low-dose MTX (7.5 mg/week). In anti-ADA antibody-positive patients, ADA trough levels markedly declined to very low levels (2.28, 1.92 and 2.21 μg/ml at baseline to 0.024, 0.024 and 0.004 μg/ml at week 24 of dose-halving, respectively), with disease flare in all of them.

Among the other 61 persistently anti-ADA antibody-negative patients, ADA trough levels declined in half after 24 weeks of dose-halving [median 5.5 μg/ml (IQR 2.2–9.0) vs 2.6 μg/ml (IQR 0.9–4.0)], with disease flare in 12 (19.7%) patients. In addition, the dosage of MTX used was positively correlated with ADA levels at baseline (r = 0.469, P < 0.001).

The differences in drug trough levels among patients with therapeutic response status

Before dose-halving, ADA levels were significantly higher in patients who had achieved remission [median 9.9 μg/ml (IQR 7.8–11.7)] than in those who had achieved LDA [2.9 μg/ml (IQR 1.0–5.0), P < 0.001]. There was a positive correlation between ADA levels and the change in DAS28 (ΔDAS28) (Fig. 1B). Likewise, ADA levels assessed at baseline and at week 24 of dose-halving therapy were significantly higher in patients with persistent remission or LDA compared with those with disease flare (Fig. 1C and Table 1).

The optimal cut-off ADA level and MTX dosage for predicting persistent remission or LDA

The optimal cut-off ADA trough level at baseline for predicting persistent remission after dose-halving was 6.4 μg/ml (AUC 0.998, P < 0.001) and that for predicting persistent LDA was 1.9 μg/ml (AUC 0.995, P < 0.001) (Fig. 1D and E). The cut-off MTX dosage at baseline for predicting persistent remission or LDA was 10 mg/week (AUC 0.717, P < 0.005 and AUC 0.672, P < 0.05, respectively).

Discussion

This study evaluated the impact of ADA dose-halving on therapeutic response and drug levels. Similar to previous findings that dose reduction of TNF-α inhibitors after achieving remission could maintain good outcome [4], we observed that ADA dose-halving after achieving remission or LDA was feasible for 76.5% of RA patients. Interestingly, while undetectable anti-ADA antibody was observed, the average ADA trough levels nevertheless declined by half after 24 week dose-halving among the 61 persistently anti-ADA antibody-negative patients, with disease flare in 12 patients. Also, ADA trough levels assessed at baseline and at week 24 of dose-halving were significantly higher in patients who sustained remission or LDA than in those with disease flare.

Among 25 patients achieving remission at baseline, 23 (92%) could sustain remission after 24 weeks of...
dose-halving therapy, which supports the 2013 EULAR recommendations that clinicians may consider tapering biologics after first reducing the dosage of glucocorticoids for patients in remission [11]. Moreover, our patients with persistent remission had significantly lower baseline DAS28s compared with those with disease flare after dose-halving, compatible with previous findings that lower baseline disease activity increases the likelihood of persistent remission after withdrawal of biologics [12]. Besides, our patients with persistent remission had a longer period (>3 years in 95.7%) of full-dose therapy before baseline compared with those with disease flare, similar to previous findings that those who have achieved a long-term remission could sustain a good outcome after discontinuation of TNF-α inhibitors [13]. Our results suggest that sustained remission after dose-halving could be more readily achieved if patients received full-dose therapy with remission for at least 3 years at baseline.

Although anti-ADA antibody often develops within the first 6 months of biologic therapy [14], three (4.7%) patients developed anti-ADA antibody after 24 weeks of dose-halving therapy. As was found in other studies [10, 14], the emergence of anti-ADA antibody in our three patients was linked to reduced drug levels and disease flare. The detectable anti-ADA antibody in our patients receiving dose-halving therapy may be related to the poor adherence to MTX therapy, which is supported by the findings that concomitant use of MTX could significantly reduce anti-ADA antibody development [14]; the effect of dose reduction on the emergence of anti-ADA antibody, which is supported by the observation that a low dose of infliximab may increase immunogenicity [15]; or drug interference in assays that detect free anti-ADA antibody only [16], such as bridging ELISA used in our study. It would be interesting to measure anti-ADA antibody using a more sensitive assay such as the pH-shift anti-idiotype antigen binding test, which can detect both free anti-ADA antibody and complexed anti-ADA antibody [17–19], to determine whether ADA dose reduction indeed triggers the immunogenicity.

In our anti-ADA antibody-negative patients, ADA levels declined in half after 24 weeks of dose-halving, with disease flare in 12 (19.7%) patients. Moreover, ADA levels assessed at baseline and at week 24 of dose-halving were significantly higher in patients with persistent remission or LDA than in those with disease flare, indicating that ADA levels were associated with therapeutic responses. It is clinically important to determine the optimal drug level that identifies patients who may maintain good outcome under dose reduction of biologics. Our results showed that RA patients whose baseline ADA trough level was >6.4 μg/ml could sustain remission at week 24 of dose-halving with high sensitivity of 100% and specificity of 93.4%, a finding similar to the observation that ADA levels within a range of 5–8 μg/ml are sufficient to achieve adequate therapeutic response [6]. Based on this cut-off value, we found that all of the 23 patients who had high baseline drug levels (>6.4 μg/ml) could sustain remission at week 24 of dose-halving therapy. This agrees with previous findings that dose reduction of biologics may be a feasible strategy without aggravating disease activity for patients who have baseline drug levels above the therapeutic range and can sustain adequate drug levels after de-escalation [5, 6]. Similar to a previous study [20], our patients whose baseline MTX dosage was >10 mg/week could more likely sustain remission/LDA after dose-halving. However, the cut-off value of 6.4 μg/ml may not be extrapolated to other studies using different assays.

In contrast, all 12 anti-ADA antibody-negative patients with disease flare after dose-halving had low baseline drug levels [median 0.9 μg/ml (IQR 0.7–1.0)]. In these patients, drug levels after ADA dose-halving fell [median 0.1 μg/ml (IQR 0.0–0.3)] below the minimal effective level for sustaining therapeutic response. These observations indicate that the monitoring of drug levels is valuable in predicting therapeutic responses to dose reduction.

There were some limitations in this study. The sample size may be too small to draw a definitive conclusion regarding the optimal baseline cut-off drug level for predicting therapeutic response after dose reduction, and our preliminary results await further confirmation by controlled and larger-scale studies.

In conclusion, we demonstrated that dose reduction is feasible for RA patients who have achieved remission and sufficient drug levels under ADA therapy. The monitoring of drug trough levels is a valuable guide for clinicians to optimize dosing regimens using a personalized treatment algorithm [2] and avoid overtreatment for RA patients receiving anti-TNF-α therapy.

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