Risk Factor Analysis for the Immunogenicity of Adalimumab Associated with Decreased Clinical Response in Chinese Patients with Psoriasis

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Although anti-drug antibodies against biologics have been associated with decreased clinical efficacy, the immunogenicity of biologics seems to vary between drugs, diseases and ethnicities. This study aims to investigate the predictors for the formation of anti-adalimumab antibodies (AAA) and the clinical consequences of AAA formation. In 53 Chinese psoriatic patients treated with adalimumab, AAA was detected in 50.9%. Differences in Psoriasis Area and Severity Index 75 (PASI75) response rates among patients with and without AAA were significant (44.4% vs. 88.5%; \( p = 0.001 \)). Patients with AAA had significantly lower trough concentrations of adalimumab than those without AAA. Risk factor analysis showed that treatment interruption, low trough adalimumab concentration, absence of concomitant methotrexate use and biologics switching were associated with a higher AAA titre. The treatment pattern of biologics influences the risk of AAA formation, thereby leading to reduced efficacy of adalimumab. Key words: immunogenicity; tumour necrosis factor-α inhibitor; psoriasis; adalimumab; etanercept; anti-drug antibody; methotrexate; anti-adalimumab antibody; anti-etanercept antibody.

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Biologics targeting tumour necrosis factor (TNF) and Th17/IL-17 are increasingly used for the treatment of moderate-to-severe psoriasis (1, 2). While the majority of patients respond well, primary or secondary treatment failure is common (3), and factors contributing to the heterogeneity of response to biologic treatment for psoriasis remain inconclusive. However, the presence of antibodies to TNF-α blockers has been reported to play a role in secondary treatment failure in rheumatoid arthritis (RA), Crohn’s disease and ankylosing spondylitis (3–6). Although adalimumab is a fully human monoclonal antibody, the incidence rate of anti-adalimumab antibody (AAA) has been reported to vary from 6% to 49% (7–12). Previous studies have further suggested that AAA is associated with lower serum adalimumab trough concentrations and with non-response or loss of response to adalimumab in patients with plaque psoriasis (7–9). However, studies designed to predict the development of AAA in patients with psoriasis are lacking. Moreover, few studies have dealt with the immunogenicity issue in Chinese patients with psoriasis. Considering the high cost of biologics and the unknown factors regarding long-term safety (13–16), this study aims to identify the risk factors for development of AAA in a Chinese population with psoriasis.

MATERIALS AND METHODS

Patients

We retrospectively enrolled 53 consecutive patients with psoriasis vulgaris who had been treated with adalimumab for at least 12 weeks in a tertiary referral centre in northern Taiwan between July 2007 and July 2013, after obtaining written informed consent and invited them to receive blood sampling for the measurement of AAA at their routine clinic visits. Most patients received a loading dose of subcutaneous adalimumab of 80 mg followed by 40 mg every 2 weeks. Based on the Bureau of National Health Insurance reimbursement policy in Taiwan, biologics are reimbursed for patients with psoriasis who have a Psoriasis Area and Severity Index (PASI) ≥ 10 after failure of conventional systemic agents and phototherapy (17). Pre-treatment authorization of biologics is needed for reimbursement after evaluation of the clinical picture. At minimum PASI50 response is needed for subsequent application, but treatment interruption is mandatory for psoriasis patients with remaining PASI <10 after 6 months of adalimumab therapy (17). The clinical parameters prior to AAA measurements, which were potential risk factors for the development of AAA, were also collected and included sex, age, age at onset of psoriasis, family history, psoriatic arthritis, previous and concomitant immunosuppressants, the number of previous biological treatment episodes and their efficacy, time interval between TNF-α blockers injections and PASI. The study was approved by the local investigational research bureau.

Clinical response to TNF-α blockers

PASI and Physician’s Global Assessment (PGA) scores were recorded at baseline; after 4, 12 and 24 weeks of treatment; and at the most recent visit. Dynamic PGA was scored as 0–5 (0, no change or worse; 1, <25%; 2, 25–49%; 3, 50–74%; 4, 75–99%; 5, 100% improvement) compared with baseline pictures. In patients
with moderate-to-severe psoriasis, responders were defined as having a 75% reduction in PASI (PASI75) compared with baseline within 6 months of treatment, or PGA score of ≥3. Non-responders were further defined as either primary or secondary failure. Primary failure was defined as failure to achieve PASI75 or PGA ≥3 within 6 months. Secondary failure was defined as a loss of PASI50 response after initially achieving PASI75 or a decrease of at least 2 points in PGA after achieving a score of ≥3.

To analyse factors that influence the development of AAA and subsequent clinical response, we defined the treatment parameters as follows: “dose reduction” includes both lengthening of the dosing interval and dose reduction; “interrupted therapy” refers to a withdrawal period for more than one month, followed by a retreatment. Dose reduction and interrupted therapy occurred due to patient treatment dissatisfaction, loss of health insurance coverage, financial constraint or preparation for surgery. Biologics switching was due to unsatisfactory or poor response. We collected only the above-mentioned treatment parameters, which predated the AAA measurement.

Measurement of anti-adalimumab antibodies

After receiving at least 3 months of adalimumab, blood samples were collected at a single time-point just prior to the end of adalimumab injection in each patient. AAA's were determined by radioimmunoassay (RIA) as described previously (3, 18–21). Adalimumab levels were determined by enzyme-linked immunosorbent assay (ELISA) as described elsewhere (3, 20, 21). RIA and ELISA were both performed at Sanquin Research, Amsterdam, The Netherlands. The detection limit of the assay is approximately 0.004 mg/l. The antibody test was considered positive when the concentration of AAA exceeded 12 arbitrary units (AU)/ml. A concentration between 12 and 100 AU/ml or above 100 AU/ml were, respectively, considered as an intermediate and high titre of antibodies to adalimumab.

Statistical analyses

To detect differences between groups, analyses were conducted using the t-test or Wilcoxon rank-sum test for continuous variables and the Fisher’s exact or χ² test for discrete variables. The Kolmogorov-Smirnov test was applied to assess the normal distribution of all continuous variables. For the missing values, the listwise deletion approach was performed using the last-observation-carried-forward approach. Logistic regression analysis was performed to analyse predictors for AAA development. All the confounding factors adjusted in the multivariable regression models are described in the text.

RESULTS

Clinical efficacy of adalimumab and antibodies against adalimumab

A total of 53 adalimumab-treated patients were enrolled in the study, 25 (47.2%) of whom had psoriatic arthritis. Of the 53 adalimumab-treated patients, 35 (66%) achieved a clinical response within 6 months of treatment, which is compatible with previous results (Table S1) (17, 23, 24). Among the 18 non-responders, 11 (61%) and 7 (39%) patients were classified as primary and secondary failures, respectively. There was no significant difference between responders and non-responders in age, gender, body weight, baseline PASI, the number of previous biologics or traditional antipsoriatic therapies used. However, the duration of psoriasis was longer in responders than in non-responders (14.5 vs. 8.2 years; p = 0.02; 95% confidence interval (CI) = 0.016–0.022) (Table I).

The measurement of AAA was performed after 21 ± 17 months (mean ± standard deviation (SD); range 3–60) of adalimumab treatment and AAAs were detected in 27 of 53 patients (50.9%). Among these 27 patients, 13 (24.5%) and 14 (26.4%) patients, respectively, developed an intermediate and high titre of antibodies to adalimumab. There were no significant differences in the background characteristics between patients with and without AAA.

Association between clinical response and anti-adalimumab antibodies and adalimumab trough concentration

Of the patients with high, intermediate and non-detectable AAA titres, 1 (7.7%), 11 (78.6%) and 23 (88.5%) patients were responders, respectively (p < 0.001). There were significant differences in adalimumab responders between AAA-positive and -negative subjects (44.4% vs. 88.5%, odds ratio (OR) = 0.104; p = 0.001; 95% CI = 0.03–0.43).

The median trough level was 1.86 mg/l (interquartile range (IQR) 0.024–3.63) in patients treated with adalimumab. The mean trough concentrations of adalimumab were 0.29 (range 0.004–3.66), 1.34 (range 0.004–4.1) and 4.79 mg/l (range 0.004–12) in patients with high, intermediate and non-detected AAA, respectively.

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| Table I. Clinical characteristics of responder and non-responder for adalimumab |
|---------------------------------|-----------------|-----------------|-----------------|
| **Clinical features at baseline** | **Non-responder** | **Responder** | **p-value** |
| Age, years, mean ± SD | 45.1 ± 11.5 | 47.6 ± 13.8 | 0.55 |
| Gender (male/female) | 11/7 | 23/12 | 0.74 |
| Body weight, kg, mean ± SD | 73.5 ± 15.3 | 74.8 ± 16.7 | 0.88 |
| Body length, cm, mean ± SD | 166.2 ± 10.5 | 166.5 ± 7.7 | 0.66 |
| Duration of psoriasis, years, mean ± SD | 8.22 ± 4.06 | 14.5 ± 9.20 | 0.02* |
| PASI at baseline | 15.6 ± 9.1 | 16.6 ± 9.4 | 0.77 |
| Arthritis, n (%) | 7/18 (38.9) | 18/35 (51.4) | 0.39 |
| Previous biologics used, n, mean ± SD | 0.61 ± 0.70 | 0.46 ± 0.74 | 0.309 |
| Previous traditional antipsoriatic therapy used, n, mean ± SD | 2.44 ± 1.04 | 1.89 ± 1.39 | 0.08 |
| Erythroderma, n (%) | 4/18 (22.2) | 7/35 (20) | 0.85 |
| **Treatment parameters of biologics** | | | |
| Biologics switching, n (%) | 12/18 (66.7) | 16/35 (45.7) | 0.148 |
| Concomitant methotrexate, n (%) | 7/18 (38.9) | 22/35 (62.9) | 0.097 |
| Dose reduction, n (%) | 6/18 (33.3) | 9/35 (25.7) | 0.56 |
| Treatment interruption, n (%) | 12/18 (66.7) | 10/35 (28.6) | 0.008* |
| Duration of biologics treatment prior to AAA measurement, months, mean ± SD | 18.5 ± 16.7 | 22.60 ± 17.9 | 0.402 |
| Drug concentration and anti-drug antibiotics | | | |
| Adalimumab trough concentration, mg/l, mean ± SD | 1.27 ± 2.96 | 3.55 ± 3.9 | 0.002* |
| AAA, n (%) | 15/18 (83.3) | 12/35 (34.3) | 0.001* |
| High-titre AAA, n (%) | 12/18 (66.7) | 1/35 (2.9) | <0.001* |

*p < 0.05. AAA: anti-adalimumab antibody; PASI: Psoriasis Area and Severity Index.
Risk factors affecting the immunogenicity of adalimumab

Concomitant methotrexate. Concomitant methotrexate use was observed in 54.7% in adalimumab-treated patients. Sixteen (55%) patients started concomitant methotrexate at the beginning of adalimumab therapy, and the remaining 13 (45%) patients received methotrexate 5 ± 9.2 months (median ± SD) after the start of adalimumab treatment. The median ± SD of dose and duration of methotrexate were 10 ± 3.2 mg weekly (range 5–15 mg weekly) and 7 ± 16.5 months (range 2–60 months), respectively. Because the Spearman’s rank correlation coefficient showed that a high titre AAA has a stronger association with clinical treatment response than a low or intermediate titre AAA, we investigated the difference in treatment associated factors between patients with high titre and non-detectable to intermediate titre of AAA. Patients receiving concomitant methotrexate had a lower rate of high titre AAA than patients receiving adalimumab monotherapy (14% vs. 38%, OR = 0.30; p = 0.046; 95% CI = 0.07–1.02). However, the percentage of concomitant methotrexate use between patients with and without AAA was not significantly different. Moreover, the rate of AAA formation and mean trough concentrations of adalimumab were not significantly different between patients receiving high-dose (> 7.5 mg weekly) and low-dose methotrexate (≤ 7.5 mg weekly). Nevertheless, patients without AAA had a significantly shorter time lapse between the start of methotrexate use and adalimumab therapy than patients with AAA (mean ± SD: 0.78 ± 1.7 vs. 6.4 ± 9.5 months; p = 0.034).

Treatment interruption. Interrupted treatment of adalimumab was noted in 22 of the 53 (41.5%) patients and the median ± SD length of interruption was 4 ± 3.6 months (range: 1.5–12 months). The median ± SD time of re-treatment of adalimumab before AAA measurement was 4 ± 8.7 months (range: 2–42). Interrupted treatment was significantly associated with decreased clinical response rate compared with continuous therapy (45% vs. 81%, OR = 0.20; p = 0.008; 95% CI = 0.06–0.68). More treatment interruptions were also observed in patients with high AAA titre than in patients with non-detectable to intermediate AAA titres (Table II).

Logistic regression analysis. In the univariate analysis, interrupted therapy, adalimumab trough concentration and duration of psoriasis were significantly associated with the development of high AAA titre. Of these variables, interrupted therapy had the highest OR of developing high titre AAA (OR = 4.67; p = 0.025). However, the influence of the dose and duration of concomitant methotrexate and biologics switching on the AAA development did not reach statistically significant levels. In the multivariate model, only variables reaching statistical significance at the 0.05 level in univariate analyses were included. Multivariate analysis revealed that adalimumab trough concentration (OR = 0.40; p = 0.040; 95% CI = 0.16–0.96) and duration of psoriasis (OR = 0.75; p = 0.02; 95% CI = 0.59–0.96) retained the association with high AAA titre formation.

In this study, 22 patients had neither interrupted adalimumab therapy nor dose alteration. These 22 patients when compared with the remaining 31 patients, had a higher rate of concomitant methotrexate use (73.0% vs. 42.0%; p = 0.026), higher mean dose of methotrexate (8.2 ± 5.4 vs. 4.0 ± 5.3 mg weekly; p = 0.008), higher mean trough concentrations of adalimumab (3.17 ± 3.90 mg weekly).
vs. 2.49 ± 3.65 mg/l; p = 0.53), higher rate of good responder (81.8% vs. 54.8%; p = 0.04) and lower rate of AAA formation (40.9% vs. 58.1%; p = 0.22).

DISCUSSION

AAA was associated with secondary treatment failure by either directly neutralizing the activity of the biologics or by forming an immune complex with subsequent accelerated drug clearance (25). Although biologics are usually used continuously for responsive patients, the unique health insurance policy in Taiwan provides us with the unique opportunity to investigate the effect of treatment-related factors, such as interrupted treatment, on the development of AAA. In this study, we have identified the risks for the development of AAA and have suggested that a concomitant medication, methotrexate, can help to minimize AAA formation. In this study, AAA was detected in 50.9% of patients, which is similar to some studies (7, 8), but higher than others (9–12). The use of the RIA method to detect anti-drug antibodies (ADA), ethnic differences, longer follow-up period (mean 21.2 months) and different clinical practice setting may all account for the difference in AAA detection in our cohort. RIA is a more sensitive detection method than ELISA, and has been the main method used in pivotal trials (3, 18, 26). Furthermore, ethnic differences may also affect the immunogenicity of biologics, although many unknown factors remain (27–29). For example, recent studies have shown a higher percentage of AAA (22) and anti-efalizumab antibody development (30, 31) among Taiwanese patients respectively treated with adalimumab and efalizumab, compared with Caucasians.

Methotrexate was reported to reduce ADA formation in a dose-dependent manner in patients with RA (32). However, studies determining the effect of methotrexate on immunogenicity in adalimumab-treated patients with psoriasis are scarce and have yielded controversial results (7–9). One study showed that, while methotrexate did not reduce ADA formation in patients with psoriasis, only 8 of 80 (10%) study subjects actually used methotrexate (7). Conversely, Lecluse et al. (8) found none of their 3 psoriasis patients receiving concomitant methotrexate, but 50% of patients (13/26) not receiving methotrexate developed AAA. Our study also showed that concomitant methotrexate can diminish the appearance of a higher AAA titre, although only a marginally significant association was found. Early initiation of methotrexate use may decrease the risk of AAA formation, which is consistent with the results from a previous murine model (32, 33). The explanation for the insignificant association between the dose and duration of methotrexate use and AAA formation may be that the small sample number and higher dose of concomitant methotrexate administration is less common in patients with psoriasis than in those with other inflammatory diseases.

Previous research has only evaluated the influence of treatment interruption on the therapeutic response of biologics, and no study has investigated the impact of treatment interruption on the immunogenicity of biologics in patients with psoriasis (34–37). Continuous infliximab and etanercept therapy was associated with greater longer-term efficacy than intermittent as-needed therapy (34–36). Papp et al. (37) also showed an association between the presence of AAA and a reduced response following treatment discontinuation and relapse in patients with psoriasis. Our study demonstrated that interrupted therapy was associated with a higher chance of developing a high titre AAA. The main reason for the high level of treatment interruptions in our study cohort is that reimbursed patients with a good response to biologics are required to discontinue the drug until relapse with PASI ≥ 10 according to the national health insurance policy in Taiwan (17, 28, 38).

With regard to dose reduction, studies have found that decreased doses of biologics resulted in worse outcomes compared with standard biologic treatment (36, 39–41). Moreover, previous investigations showed that a low dosage could lead to immunogenicity (42, 43). A reduced ADA formation was also found by dose escalation of infliximab and adalimumab in patients with RA (3, 42, 44, 45). In our analysis, dose reduction did not exert a significant effect on AAA development, probably because few patients adopted dose reduction in this study. A further large cohort with stratification of dose reduction is needed to confirm these results. On the other hand, our results demonstrate that biologics switching is associated with higher titre AAA, similar to previous studies (23, 46, 47). In RA, switchers with ADA against their first TNF-α blocker more often develop antibodies to the subsequent TNF-α blocker, even though they have similar clinical responses to the second anti-TNF treatment compared with anti-TNF naïve patients (43, 48, 49).

One interesting finding of our study is the longer disease duration in adalimumab responders and longer duration of psoriasis was associated with a lower probability of a higher titre ADA. One explanation is that a high proportion of patients do not receive treatment irrespective of disease severity, mainly because of treatment dissatisfaction (50). Thus, it is likely that patients with a longer disease duration who continuously received treatment might be those patients who had at least partial treatment response to prior treatment. However, a pivotal study suggested that psoriasis duration did not significantly affect adalimumab efficacy (51). The reasons for the different results are unknown, but differences in entry criteria, comorbidities, concomitant medication, cultural or even racial factors may all be possible explanations.

The main limitations of this study are its retrospective study design, the limited number of included patients, AAA measured at different time-points, and measurement of drug level and AAA at a single time-point.
Nevertheless, given that a prior study showed that most AAA developed before week 24 of treatment (7), a single measurement of AAA after a mean of 21 months of adalimumab therapy should be sufficient to detect most cases of AAA.

In conclusion, the current study demonstrated that AAA was detected in 50.9% of the psoriasis patients treated with adalimumab, and that the development of ADA was linked to decreased treatment efficacy and decreased trough drug level with adalimumab. Treatment interruption, absence of concomitant methotrexate use, biologies switching, trough adalimumab concentration and duration of psoriasis were strongly correlated with the formation of a higher AAA titre. Early initiation of concomitant methotrexate at the start of adalimumab therapy may decrease the development of AAA. The findings of this study will help clinicians to identify the clinical parameters predicting the risks for the development of AAA and to develop strategy for the prevention of ADA formation in order to improve and maintain the therapeutic efficacy of biologics.

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REFERENCES


