CLINICAL REPORT

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 adalimumab injection in each patient. AAAs were detected 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 titres of AAA (22).

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 χ^2 test for discrete variables. The Kolmogorov-Smirnov test was applied to test the normal distribution of all continuous variables. For the missing values, the analysis 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 SI[1]) (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,

Table I. *Clinical characteristics of responder and non-responder for adalimumab*

	Non-responder (*n*=18)	Responder (*n*=35)	*p*-value
Clinical features at baseline			
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)	22/25 (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 antibotics			
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.

intermediate and non-detectable titres. Serum mean trough concentrations of adalimumab in patients with AAA were significantly lower than in patients without AAA (0.84 vs. 4.79 mg/l; $p<0.001$). Good responders had significantly higher serum mean adalimumab concentrations than non-responders (3.55 vs. 1.27 mg/l; $p=0.02$; 95% CI$=0.0001–0.002$) (Table I). Of the 14 patients with intermediate AAA titre, 11 patients achieved a clinical response when AAA was checked. However, of these 11 patients, 6 (55%) patients lost clinical response during a 3-month follow-up period. The percentage of concomitant methotrexate use (5/5 patients maintained response (100%) vs. 3/6 patients who lost response (50%); OR$=2.0$; $p=0.06$) and the mean dose of methotrexate (3.3 vs. 10.5 mg weekly; $p=0.015$) were higher in patients maintaining the response than patients who subsequently lost clinical response.

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 ($3.17±3.90$

Table II. *Clinical characteristics of patients with a higher titre antiadalimumab antibody (AAA) and non-detectable to intermediate titre AAA*

Antibody titre	Non-detectable to intermediate ($n=40$)	High ($n=13$)	p-value
Clinical features			
Age, years, mean$±$SD	$47.7±12.8$	$43.6±13.6$	0.48
Gender (male/female)	25/15	9/4	0.66
Body weight, kg, mean$±$SD	$73.8±15.9$	$76.3±17.2$	0.56
Body length, cm, mean$±$SD	$164.8±7.9$	$168.6±10.2$	0.21
Duration of psoriasis, years, mean$±$SD	$14.2±8.7$	$6.9±3.74$	**0.003**
Baseline PASI, mean$±$SD	$16.3±9.1$	$16.3±9.8$	0.94
Arthritis, n (%)	21/40 (52.5)	4/13 (30.8)	0.17
Previous biologics used, n, mean$±$SD	$0.48±0.75$	$0.62±0.65$	0.32
Previous traditional antipsoriatic therapy used, n, mean$±$SD	$2.08±1.32$	$2.08±1.26$	0.85
Erythroderma, n (%)	8/40 (20)	3/13 (23.1)	0.81
Treatment pattern and response			
Biologics switching, n (%)	18/40 (45)	10/13 (76.9)	**0.045**
Concomitant methotrexate, n (%)	25/40 (62.5)	4/13 (30.8)	**0.046**
Dose reduction, n (%)	13/40 (32.5)	2/13 (15.4)	0.234
Treatment interruption, n (%)	13/40 (32.5)	9/13 (69.2)	**0.020**
Duration of biologics treatment, months, mean$±$SD	$21.8±17.1$	$19.5±19.2$	0.62
Responder, n (%)	34/40 (85)	1/13 (7.7)	**<0.001**
Adalimumab trough concentration, mg/l, mean$±$SD	$3.58±3.96$	$0.29±1.00$	**<0.001**

$p<0.05$ is shown in **bold**. PASI: Psoriasis Area and Severity Index.

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 naive 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, biologics 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.

ACKNOWLEDGEMENTS

REFERENCES

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009; 361: 496–509.
2. Chiu HY, Cheng YP, Tsai TF. T helper type 17 in psoriasis: from basic immunology to clinical practice. Dermatologica Sinica 2012; 30: 136–141.
3. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA 2011; 305: 1460–1468.
4. Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003; 348: 601–608.
5. de Vries MK, Wolbink GJ, Stapel SO, de Vrieze H, van Denderen JC, Dijkmans BA, et al. Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation. Ann Rheum Dis 2007; 66: 1252–1254.
6. de Vries MK, Brouwer E, van der Horst-Bruinsma IE, Spoorenberg A, van Denderen JC, Jamnitski A, et al. Decreased clinical response to adalimumab in ankylosing spondylitis is associated with antibody formation. Ann Rheum Dis 2009; 68: 1787–1788.
7. Menting SP, van Lumig PP, de Vries AC, van den Reek JM, van der Kleij D, de Jong EM, et al. Extent and consequences of antibody formation against adalimumab in patients with psoriasis: one-year follow-up. JAMA Dermatol 2013; 150: 130–136.
8. Lecluse LL, Driessen RJ, Spuls PI, de Jong EM, Stapel SO, van Doorn MB, et al. Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. Arch Dermatol 2010; 146: 127–132.
9. Hsu L, Snodgrass BT, Armstrong AW. Anti-drug antibodies in psoriasis: a systematic review. Br J Dermatol 2013; 170: 261–273.
10. Asahina A, Nakagawa H, Etoh T, Ohtsuki M. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study. J Dermatol 2010; 37: 299–310.
11. Takahashi H, Tsuji H, Ishida-Yamamoto A, Iizuka H. Plasma trough levels of adalimumab and infliximab in terms of clinical efficacy during the treatment of psoriasis. J Dermatol 2013; 40: 39–42.
12. Mahil SK, Arkir Z, Richards G, Lewis CM, Barker JN, Smith CH. Predicting treatment response in psoriasis using serum levels of adalimumab and etanercept: a single-centre, cohort study. Br J Dermatol 2013; 169: 306–313.
13. Chiu HY, Hsueh PR, Tsai TF. Clinical experience of QuantiFERON((R)) -TB Gold testing in patients with psoriasis treated with tumour necrosis factor blockers in Taiwan. Br J Dermatol 2011; 164: 553–559.
14. Cho YT, Chen CH, Chiu HY, Tsai TF. Use of anti-tumor necrosis factor-alpha therapy in hepatitis B virus carriers with psoriasis or psoriatic arthritis: a case series in Taiwan. J Dermatol 2012; 39: 269–373.
15. Chiu HY, Chen CH, Wu MS, Cheng YP, Tsai TF. The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. Br J Dermatol 2013; 169: 1295–1303.
16. He GY, Tsai TF. Concomitant occurrence of acneiform eruption, alopecia areata, and urticaria during adalimumab treatment in a patient with pustulosis palmoplantaris: case report and literature review. Dermatologica Sinica 2012; 30: 51–56.
17. Chiu HY, Wang TS, Chang CY, Tsai TF. The effectiveness and safety of adalimumab in the treatment of non-reimbursed patients with mild-to-moderate psoriasis. J Eur Acad Dermatol Venereol 2012; 26: 991–998.
18. Hart MH, de Vrieze H, Wouters D, Wolbink GJ, Killestein J, de Groot ER, et al. Differential effect of drug interference in immunogenicity assays. J Immunol Methods 2011; 372: 196–203.
19. Rispens T, de Vrieze H, de Groot E, Wouters D, Stapel S, Wolbink GJ, et al. Antibodies to constant domains of therapeutic monoclonal antibodies: anti-hinge antibodies in immunogenicity testing. J Immunol Methods 2012; 375: 93–99.
20. van Schouwenburg PA, Bartelds GM, Hart MH, Aarden L, Wolbink GJ, Wouters D. A novel method for the detection of antibodies to adalimumab in the presence of drug reveals "hidden" immunogenicity in rheumatoid arthritis patients. J Immunol Methods 2010; 362: 82–88.
21. Jamnitski A, Krieckaert CL, Nurmohamed MT, Hart MH, Dijkmans BA, Aarden L, et al. Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients. Ann Rheum Dis 2012; 71: 88–91.
22. Kneepkens EL, Wei JC, Nurmohamed MT, Yeo KJ, Chen CY, van der Horst-Bruinsma IE, et al. Immunogenicity, adalimumab levels and clinical response in ankylosing spondylitis patients during 24 weeks of follow-up. Ann Rheum Dis 2015; 74: 396–401.

23. Wang TS, Tsai TF. Safety and effectiveness of adalimumab in patients with moderate-to-severe psoriasis who had inadequate therapeutic response to prior etanercept. Dermatologica Sinica 2013; 31: 11–18.

24. Strober BE, Poulin Y, Kerdel FA, Langley RG, Gu Y, Gupta SR, et al. Switching to adalimumab for psoriasis patients with a suboptimal response to etanercept, methotrexate, or phototherapy: efficacy and safety results from an open-label study. J Am Acad Dermatol 2011; 64: 671–681.

25. van der Laken CJ, Voskuyl AE, Roos JC, Stigter van Walsum M, de Groot ER, Wolbink G, et al. Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. Ann Rheum Dis 2007; 66: 253–266.

26. Krieckaert CL, Bartelds GM, Lems WF, Wolbink GJ. The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review. Arthritis Res Ther 2010; 12: 217.

27. Ordas I, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther 2012; 91: 635–646.

28. Chiu HY, Huang PY, Jee SH, Hu CY, Chou CT, Chang YT, et al. HLA polymorphism among Chinese patients with chronic plaque psoriasis: Subgroup analysis. Br J Dermatol 2012; 166: 288–297.

29. van den Reek JM, Tummers M, Zweegers J, Seyger MM, van Lumig PP, Driessen RJ, et al. Predictors of adalimumab drug survival in psoriasis differ by reason for discontinuation: long-term results from the Bio-CAPTURE registry. J Eur Acad Dermatol Venereol 2015; 29: 560–565.

30. Tsai TF, Liu MT, Liao YH, Licu D. Clinical effectiveness and safety experience with efalizumab in the treatment of patients with moderate-to-severe plaque psoriasis in Taiwan: results of an open-label, single-arm pilot study. J Eur Acad Dermatol Venereol 2008; 22: 345–352.

31. Leonardi CL, Papp KA, Gordon KB, Menter A, Feldman SR, Caro I, et al. Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. J Am Acad Dermatol 2005; 52: 425–433.

32. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis 2012; 71: 1914–1915.

33. Garman RD, Munroe K, Richards SM. Methotrexate reduces antibody responses to recombinant human alpha-galactosidase A therapy in a mouse model of Fabry disease. Clin Exp Immunol 2004; 137: 496–502.

34. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007; 56: 31 e1–15.

35. Moore A, Gordon KB, Kang S, Gottlieb A, Freundlich B, Xia HA, et al. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. J Am Acad Dermatol 2007; 56: 598–603.

36. Brezinski EA, Armstrong AW. Off-label biologic regimens in psoriasis: a systematic review of efficacy and safety of dose escalation, reduction, and interrupted biologic therapy. PLoS One 2012; 7: e33486.

37. Papp K, Crowley J, Ortonne JP, Leu J, Okun M, Gupta SR, et al. Adalimumab for moderate to severe chronic plaque psoriasis: efficacy and safety of retreatment and disease recurrence following withdrawal from therapy. Br J Dermatol 2011; 164: 434–441.

38. Chiu HY, Wang TS, Cho YT, Tsai TF. Etanercept use for psoriasis in Taiwan: a case series study. Int J Dermatol 2013; 52: 673–680.

39. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003; 349: 2014–2022.

40. Ortonne JP. Clinical response to alefacept: results of a phase 3 study of intramuscular administration of alefacept in patients with chronic plaque psoriasis. J Eur Acad Dermatol Venereol 2003; 17 Suppl 2: 12–16.

41. Lebwohl M, Christophers E, Langley R, Ortonne JP, Roberts J, Griffiths CE. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. Arch Dermatol 2003; 139: 719–727.

42. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41: 1552–1563.

43. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. 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. Ann Rheum Dis 2010; 69: 817–821.

44. Wolbink GJ, Vis M, Lems W, Voskuyl AE, de Groot E, Nurmohamed MT, et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum 2006; 54: 711–715.

45. Leonardi C, Sobell JM, Crowley JJ, Mrowietz U, Bao Y, Mulani PM, et al. Efficacy, safety and medication cost implications of adalimumab 40 mg weekly dosing in patients with psoriasis with suboptimal response to 40 mg every other week dosing: results from an open-label study. Br J Dermatol 2012; 167: 658–667.

46. Martyn-Simmons CL, Green L, Ash G, Groves RW, Smith CH, Barker JN. Adalimumab for psoriasis patients who are non-responders to etanercept: open-label prospective evaluation. J Eur Acad Dermatol Venereol 2009; 23: 1394–1397.

47. Woolf RT, Smith CH, Robertson K, Barker JN. Switching to adalimumab in patients with moderate to severe psoriasis who have failed on etanercept: a retrospective case cohort study. Br J Dermatol 2010; 163: 889–892.

48. West RL, Zelinkova Z, Wolbink GJ, Kuipers EJ, Stokkers PC, van der Woude CJ. Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease. Aliment Pharmacol Ther 2008; 28: 1122–1126.

49. Jamnitski A, Bartelds GM, Nurmohamed MT, van Schouwenburg PA, van Schaardenburg D, Stapel SO, et al. The presence or absence of antibodies to infliximab or adalimumab determines the outcome of switching to etanercept. Ann Rheum Dis 2011; 70: 284–288.

50. Armstrong AW, Robertson AD, Wu J, Schupp C, Lebwohl MG. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003–2011. JAMA Dermatol 2013; 149: 1180–1185.

51. Menter A, Gordon KB, Leonardi CL, Gu Y, Goldblum OM. Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis. J Am Acad Dermatol 2010; 63: 448–456.