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ORIGINAL ARTICLE

Plasma trough levels of adalimumab and infliximab in terms of clinical efficacy during the treatment of psoriasis

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ABSTRACT

We examined the relation between adalimumab and infliximab plasma trough levels, anti-adalimumab and anti-infliximab antibody formation. We analyzed plasma from 32 adalimumab-treated and 20 infliximab-treated psoriasis patients for evaluating trough levels of each drug. The presence of anti-adalimumab and anti-infliximab antibodies was analyzed and the severity of psoriasis was evaluated. At week 28, 25 out of 32 and at week 48, 21 out of 30 adalimumab-treated patients maintained as more than PASI 75. At week 28, 12 out of 20 and at week 48, nine out of 18 infliximab-treated patients were evaluated as more than PASI 75. In patients treated with 40 mg adalimumab every other week, the mean trough level was 7.62 μg/mL (range, 0.05–10.6) at week 48. In patients treated with 80 mg adalimumab every other week, the mean trough level was 8.61 μg/mL (range, 0.08–13.5) at week 48. Mean trough level of infliximab-treated cases (4.1–5.2 mg/kg; mean, 4.6) was 4.64 μg/mL (range, 0.03–16.9) at week 48. Anti-adalimumab antibody was detected in five out of 32 cases and anti-infliximab antibody was detected in six out of 20 cases, respectively, at weeks 24 and 48. The optimal cut-off values of adalimumab and infliximab concentration for more than PASI 75 were more than 7.84 μg/mL and more than 0.92 μg/mL, respectively. The trough levels of adalimumab and infliximab in psoriasis patients were positively associated with clinical response and were significantly lower in cases having anti-adalimumab or anti-infliximab antibodies.

Key words: adalimumab, infliximab, Psoriasis Area and Severity Index, psoriasis, trough.

INTRODUCTION

Psoriasis is a complex chronic inflammatory skin disease characterized by inflammatory cell infiltration, epidermal hyperproliferation and dilated microvessels. Although the precise pathomechanism remains unknown, various cytokines and growth factors, such as tumor necrosis factor (TNF)-α, interleukin (IL)-23, IL-22 and IL-17 are involved.[1,2] Recently, anti-TNF-α antibodies, infliximab and adalimumab, and anti-IL-12 and IL-23 p40 antibody, ustekinumab, show remarkable clinical response.

Although infliximab and adalimumab are highly effective for psoriasis, not all patients respond to these modalities (primary failure) and some initial responders lose the effect over time (secondary failure).[3,4] Reasons for the secondary failure have been suggested to be the induction of anti-infliximab or anti-adalimumab antibodies as well as the alteration of pharmacokinetic and pharmacodynamic mechanisms in psoriasis.[5,6] In fact, low serum infliximab and adalimumab levels are associated with the failure of the clinical response in Crohn's disease, ulcerative colitis and rheumatoid arthritis.[7–10] In the treatment of psoriasis with adalimumab, correlation between clinical efficacy and anti-adalimumab antibody formation during 24 weeks of treatment has been described.[6] However, few studies exist to examine the optimal cut-off trough values of infliximab and adalimumab levels in terms of clinical efficacy. Therefore, we analyzed the relation between infliximab and adalimumab trough levels and clinical response up to 48 weeks treatment. Furthermore, we analyzed the effect of ant-infliximab and anti-adalimumab antibodies for the serum concentration levels of these molecules.

METHODS

Patients

A total of 32 (18 male, 14 female) adalimumab-treated psoriasis cases and 20 (12 male, eight female) infliximab-treated cases were enrolled in the study. Among all psoriasis patients treated with adalimumab, seven patients were diagnosed as having psoriatic arthritis and the others (25 patients) had plaque type psoriasis. Patients treated with infliximab included four with pustular psoriasis, two with psoriatic arthritis and 14 with plaque type psoriasis. These patients were aged 47–72 years (mean, 57.5), with Psoriasis Area and Severity Index (PASI) scores of 7.9–32.3 (mean, 15.7) and body surface area of 8–45 (mean, 14.6). The patients were treated with adalimumab (40 or 80 mg) every other week after the initial dose of 80 mg. The patients treated with infliximab received the mean dose of

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4.6 mg/kg (4.1–5.2 mg/kg) i.v. at weeks 0, 2, 6 and 14, and every 8 weeks thereafter. The study was approved by Asahikawa Medical University Ethics Committee and signed informed consent was taken from all the patients according to the guideline of Asahikawa Medical University Ethics Committee.

Measurement of clinical severity, adalimumab or infliximab trough concentration, and anti-adalimumab or anti-infliximab antibodies

Disease severity was assessed at baseline, at week 24 and at week 48 using PASI scores. Blood samples (1–2 mL) were taken in vacutainer tubes under sterile conditions from psoriasis patients just before administration of adalimumab or infliximab at week 48 after the initiation of the treatment. Plasma was obtained fresh and centrifuged and was immediately frozen at −70°C and stored until use. Adalimumab and infliximab trough levels were measured by using enzyme-linked immunosorbent assay (ELISA) kits (Matriks Biotek Laboratories, Ankara, Turkey). The minimal detectable concentrations were 0.001 μg/mL for adalimumab and 0.05 μg/mL for infliximab, respectively. Anti-adalimumab and anti-infliximab antibodies were detected by using ELISA kits (Matriks Biotek Laboratories).

Statistical analysis

A Mann–Whitney *U*-test was used to compare the mean values. Identification of optimal cut-off levels for adalimumab and infliximab trough were determined using receiver–operator curve (ROC) analysis, and cut-off levels providing minimal difference between sensitivity and specificity were determined.

RESULTS

Clinical efficacy of adalimumab and infliximab

Among 32 patients treated by adalimumab, 25 cases (78%) showed more than PASI 75, five (16%) showed PASI 75–50 and two (6%) showed less than PASI 50 at week 28 (Table 1). At week 48, 21 out of 30 (70%) cases were evaluated as more than PASI 75, eight (27%) as PASI 75–50 and one (3%) as less than PASI 50 (Table 1). Among 20 patients treated by infliximab, 12 (60%) cases showed more than PASI 75, six (30%) showed PASI 75–50 and two (10%) showed less than PASI 50 at week 28 (Table 1). At week 48, nine out of 18 cases (50%) showed more than PASI 75, seven (39%) showed PASI 75–50 and two (11%) showed less than PASI 50 in the treatment of infliximab (Table 1).

Table 1. Clinical efficacy of adalimumab and infliximab

	Adalimumab, *n* (%)		Infliximab, *n* (%)	
	28 W	48 W	28 W	48 W
>PASI 75	25 (78)	21 (70)	12 (60)	9 (50)
PASI 50–75	5 (16)	8 (27)	6 (30)	7 (39)
<PASI 50	2 (6)	1 (3)	2 (10)	2 (11)

PASI, Psoriasis Area and Severity Index; W, weeks.

Measurement of adalimumab and infliximab plasma trough concentrations

Plasma trough levels of adalimumab ranged 0.05–13.5 μg/mL at week 48. In patients treated with 40 mg every other week, the mean trough level was 7.62 μg/mL (range, 0.05–10.6) at week 48 (Fig. 1a). In patients treated with 80 mg every other week, the mean trough level was 8.61 μg/mL (range, 0.08–13.5) at week 48 and was significantly higher than that of patients treated with 40 mg. Infliximab trough level was 4.64 μg/mL (range, 0.03–16.9) at week 48 (Fig. 1b).

Detection of anti-adalimumab and anti-infliximab antibody

Anti-adalimumab antibody was detected in five out of 32 (15.6%) cases at week 48 (Fig.1a). Anti-infliximab antibody was detected in six out of 20 (30%) cases at week 48 (Fig. 1b). Trough levels of patients with anti-adalimumab or anti-infliximab antibodies were significantly lower than those without the antibodies (Fig. 2).

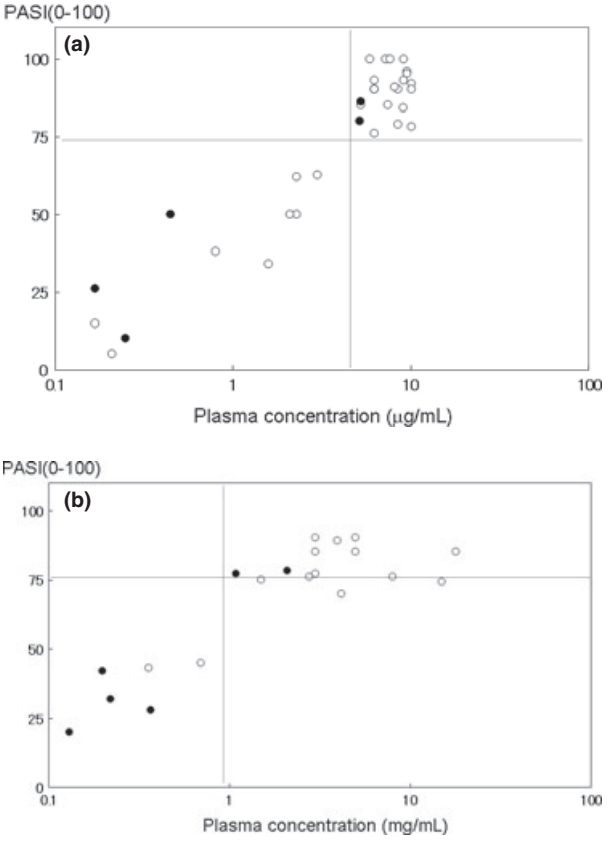

Figure 1. Association between Psoriasis Area and Severity Index (PASI) score and trough levels of adalimumab and infliximab. The PASI score and trough levels of adalimumab (a) and infliximab (b) at 48 weeks are shown. Bold and white circles indicate patients with or without anti-adalimumab (a) or anti-infliximab antibodies (b), respectively.

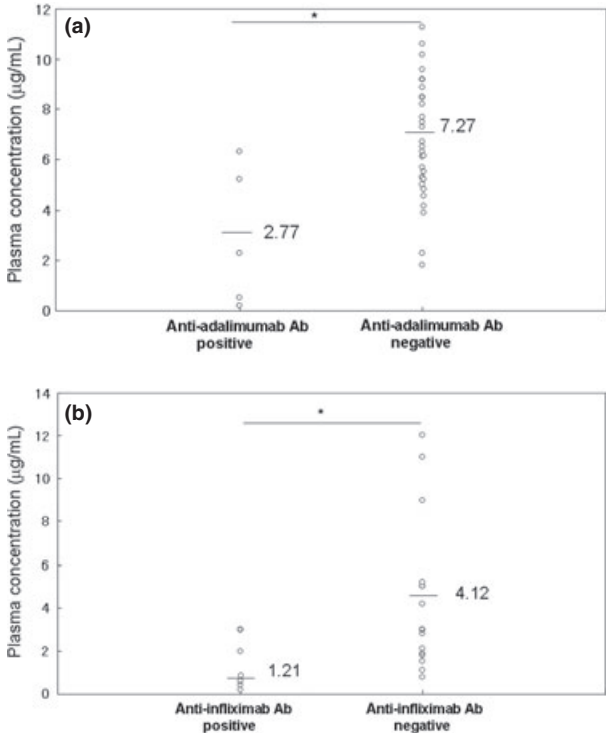

Figure 2. Trough levels of adalimumab and infliximab are lower in patients having anti-adalimumab or anti-infliximab antibodies. Trough levels of adalimumab (a) and infliximab (b) at 48 weeks. Comparison was made between antibodies positive and negative patients. *$P < 0.01$.

Detection of optimal trough levels in terms of clinical response

In order to determine the optimal trough levels to maintain the clinical response, ROC analysis was performed in adalimumab- and infliximab-treated psoriasis patients. A plasma adalimumab trough level of more than 7.84 μg/mL provided the optimal cut-off value for more than PASI 75. Sensitivity and specificity were 76% (43–96%) and 100% (52–100%), respectively. A plasma infliximab trough level of more than 0.92 μg/mL provided the optimal cut-off value for more than PASI 75. Sensitivity and specificity were 78% (48–98%) and 100% (51–100%), respectively.

DISCUSSION

Although adalimumab and infliximab are highly effective for psoriasis, cases with primary and secondary failure exist. In order to identify the factors that maximize the clinical response, the present study was undertaken. Our results indicate that well-controlled patients represented as more than PASI 75 are strongly associated with the higher trough plasma concentrations of each drug.

Lecluse *et al.*[6] reported that the minimal trough level of adalimumab in good responders (>PASI 75) during 24 weeks of the treatment was 9.7 μg/mL. In our study, the cut-off level of more than PASI 75 was 7.84 μg/mL. In Crohn's disease, the average trough level was 5.9 μg/mL, showing a similar trough level with that of psoriasis.[11] In contrast, the average trough level in rheumatoid arthritis (RA) responders was 12 μg/mL,[12] indicating disease-specific difference in the minimal trough levels for the clinical efficacy.

Our study for the first time indicated that the minimal trough level of infliximab in good responders (>PASI 75) was 0.92 μg/mL, compatible with that in RA (>1.0 μg/mL).[13] In Crohn's disease, the trough level of more than 0.33 μg/mL infliximab was the critical concentration to control the disease.[11] Steenholdt *et al.* showed that a trough level below 0.5 μg/mL was associated with the loss of infliximab response.[14] In contrast to adalimumab in the treatment of Crohn's disease, lower concentration of infliximab was sufficient to reduce the disease severity compared with psoriasis and RA, again suggesting the different optimal trough levels among each disease.

Autoantibody against infliximab has been detected in 22.4–41% in RA, Crohn's disease and ulcerative colitis patients.[9,15,16] Immunogenicity of biologics is not restricted to the chimeric antibody, infliximab, and in a cohort study of adalimumab-treated RA patients, 28% of patients developed anti-adalimumab antibodies after 3 years of treatment.[12] In adalimumab-treated psoriasis patients, 45% of cases had anti-adalimumab antibodies.[12] In our study, 15.6% of adalimumab-treated and 30% of infliximab-treated psoriasis patients were antibody-positive, indicating the immunogenicity even in the fully humanized antibody, adalimumab. The different incidence of antibodies might reflect the disease, methods of antibody detection, ethnicity and duration of the treatment. Recent study revealed that IL-10 gene polymorphism is associated with the incidence of anti-adalimumab antibody.[17] Among RA patients, concomitant use of methotrexate significantly decreased the induction of anti-adalimumab and anti-infliximab antibodies.[18–21]

Previous studies revealed that the development of antibodies correlated with decreased trough levels and low clinical efficacy.[6,12,22] In contrast, the development of antibodies and trough levels did not correlate with the loss of responder cases and prediction of treatment response.[8,16,23] In our study, trough levels of patients with anti-adalimumab or anti-infliximab antibodies were significantly lower than those without the antibodies. However, some responders exist even in the presence of antibodies, suggesting that the titer of antibodies is critical for neutralizing the effect of adalimumab or infliximab.

In conclusion, our study demonstrated the association between the clinical efficacy and trough levels of adalimumab and infliximab during the long-term treatment of psoriasis. The presence of antibodies against adalimumab and infliximab contribute to the loss of response of these biologics. Thus, detection of antibodies to these molecules and the measurement of the trough levels would be useful to evaluate the clinical efficacy of adalimumab and infliximab therapy in psoriasis.

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