ORIGINAL ARTICLE

Serum levels of anti-cyclic citrullinated peptide antibodies are associated with a beneficial response to traditional herbal medicine (Kampo) in rheumatoid arthritis

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Abstract This study investigated the usefulness of bio-markers indicating beneficial response to traditional herbal medicine (THM) among patients with rheumatoid arthritis (RA). We assessed 34 RA patients who received keishinieppiittokaryojutsubu (KER), one of the representative THM. The observational term was 12 months, and we calculated the disease activity score of 28 joints every 3 months and evaluated the response to KER using European League Against Rheumatism (EULAR) response criteria. Additionally, serum levels of anti-cyclic citrullinated peptide antibody (ACPA) were measured by enzyme-linked immunosorbent assay at the baseline and after 6 and 12 months of the treatment with KER. As a result, 14 (41.2%) of the 34 patients were defined as responders, 13 as non-responders and 7 as out of assessment after 6 months, respectively. Pretreatment levels of serum ACPA were lower in KER responders than in non-responders ($P = 0.042$), although other univariate analysis did not show any significant differences in baseline clinical measures between the two groups. Furthermore, responders to KER showed a significant decrease in the serum levels of ACPA. These findings suggest that pretreatment serum levels of ACPA are a useful predictor of a good response to treatment with KER. Furthermore, a decrease in serum levels of ACPA may be an adjunctive indicator in predicting the efficacy of this kind of treatment.

Keywords Traditional herbal medicine · Rheumatoid arthritis · Responder · Predictor · Anti-cyclic citrullinated peptide antibody

Introduction

Rheumatoid arthritis (RA) is a polyarticular chronic inflammatory disease characterized by cartilage destruction and bone erosion, and can lead to severe deformity of the joints and decrease daily activity. Recently, specific treatments, infliximab or etanercept, have targeted relevant proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-a). The therapeutic goal for RA has been changing from clinical remission to anatomical remission, or even cure based on a new strategy [1].

In Japan, RA treatment with traditional herbal medicines (THM: Kampo) has also been performed as adjunctive therapy for RA [2], and the clinical effects of THM have been shown by several investigators [3, 4]. However, there are distinct groups of responders and non-responders to THM. THM is administered according to traditional diagnostic system and it takes about 4–8 weeks to evaluate the effect of THM in RA, suggesting that joint damage progression has occurred in non-responders to THM before the application of specific treatments. For that reason, predictors of treatment response to THM need to be identified, to direct individual treatment decisions in RA.

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It has been shown that the presence and level of anti-cyclic citrullinated peptide antibodies (ACPA) are strongly associated with a worse disease course [5–9]. Therefore, we investigated the ability of ACPA levels in ACPA-positive patients to predict the response to THM treatment. Additionally, the effect of THM on the serum level of ACPA itself was assessed.

Patients and methods

Patients

Patients who fulfilled the American College of Rheumatology (ACR) criteria [10] for the classification of RA were enrolled in this assessment. All were outpatients attending our department of the Gunma University Hospital between 2005 and 2007, and were followed for 12 months. Patients who had previously been treated with biologics targeting TNF and tacrolimus (TAC) were excluded. This investigation was approved under the comprehensive agreement provided by Gunma University Hospital.

Study design

This study's design was a self-control trial. All patients were treated with keishinieppiittokaryojutsubu (KER; decoction) according to the traditional diagnostic system [11]. Some patients were also treated with non steroidal anti-inflammatory drugs, bucillamine, salazosulfapyridine, prednisolone (PSL) and methotrexate (MTX) at the start of treatment. These concomitant drugs were continued without changing the drugs or dosages during the 3 months before or during the observation period of this study. Every 3 months, joint symptoms were examined, and routine blood analysis and general serological tests were performed. Furthermore, we monitored the serum levels of ACPA every 6 months.

KER (THM) therapy

The herbs composed of KER are shown in Table 1. These herbs are covered by the national health insurance in Japan. Twelve herbs were mixed with 600 ml of water and boiled down to 300 ml, then the aqueous extract was filtered through a sieve. The extract, called a decoction, was administered twice a day before meals in the morning and evening.

Clinical evaluation

Disease activity was assessed by the disease activity score, including a 28-joint count (DAS28)–C-reactive protein (CRP) that was calculated according to the authorized

Table 1 The herb composed of keishinieppiittokaryojutsubu

Component (herb)	Weight (g)
Atractylodis lanceae rhizoma	10.0
Hoelen	5.0
Gypsum fibrosum	5.0
Zizyphi fructus	4.0
Cinnamomi cortex	3.0
Ephedrae herba	3.0
Paeoniae radix	3.0
Glycyrrhizae radix	3.0
Zingiberis rhizoma	1.0
Aconiti tuber	1.5
Sinomeni Caulis et Rhizoma	5.0
Astragali radix	5.0

Twelve herbs were mixed with 600 ml of water and boiled down to 300 ml, then the aqueous extract was filtered through a sieve. The extract, called a decoction, was administered twice a day at the morning and evening

formula (http://www.das-score.nl/). The value of DAS28–CRP is reported to be less than the original DAS28 using the erythrocyte sedimentation rate (ESR), and we used a threshold of 4.1 instead of the original 5.1 as the cut-off for high activity and 2.7 instead of 3.2 as the cut-off for low activity. Thus, we defined a value of DAS28–CRP > 4.1 as high activity, 2.7–4.1 as moderate activity, <2.7 as low activity, with <2.3 being defined as remission [12]. The response to KER therapy every 3 months was evaluated by the European League Against Rheumatism (EULAR) response criteria using 4.1 and 2.7 as the thresholds for high and low disease activities, respectively. Consequently, the patients who showed low activity (DAS28–CRP < 2.7) after treatment with KER, and whose DAS28 decreased to >1.2 were defined as showing a good response. We recognized patients showing a good or moderate response as responders to KER, and patients showing no response as non-responders. In addition, patients showing low activity (DAS28 < 2.7) from the start of treatment with KER until 12 months after treatment was started, were excluded from analysis.

Patients receiving additional drug treatments

None of the patients discontinued KER treatment during the observation period. Increase in the dosage of MTX (one patient), additional administration of MTX (one patient) or TAC (four patients), or the introduction of anti-TNF drugs (two patients) was carried out since these patients (eight patients) showed high or moderate activity without a decrease >0.6 in DAS28–CRP 3 or 6 months after treatment with KER was initiated. These patients were defined

as non-responders to KER. Although their baseline serum levels of ACPA were assessed, the titers at 6 or 12 months were not used in the assessment of change in titers, because the contribution of these additional drugs to the overall efficacy could not be distinguished.

Measurement of serum levels of ACPA

Serum IgG ACPA was measured using enzyme-linked immunosorbent assay kits (Axis-Shield, UK), according to the manufacturer's instructions. Each assay was carried out in duplicate. Antibody titers of over five arbitrary unit per milliliter were considered positive.

Statistical analysis

Data are expressed as mean (SD) values. All data were collected in a computer database. Mann–Whitney test or repeated measures ANOVA was used to analyze each set of data for baseline and changes in ACPA titers. For all statistical tests, differences were regarded as significant at $P < 0.05$.

Results

Baseline demographic and clinical characteristics

Baseline demographic and clinical characteristics of 34 patients receiving KER therapy are summarized in Table 2. Fourteen patients were classified in the responder group, and 13 patients were classified in the non-responder group based on DAS28–CRP findings. Patients with low activity (DAS28 < 2.7) from the start of KER treatment until 12 months after treatment was started were excluded; these patients were described as the out of assessment group. On comparison of the responder group and non-responder group, there was no significant difference with regard to age
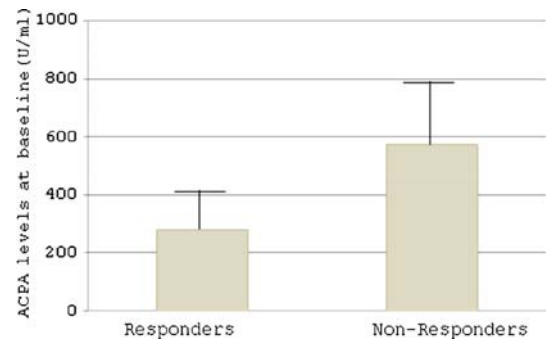
Fig. 1 Anti-cyclic citrullinated peptide antibodies (*ACPA*) levels at baseline in keishinieppiittokaryojutsubu (KFR) responders and non-responders within the RA patients. KER responders had lower levels of ACPA at baseline than non-responders ($P = 0.042$, Mann–Whitney test)

or disease duration. Furthermore, the dosages of concomitant PSL at baseline did not vary between two groups.

The titers in serum ACPA at baseline

We have investigated the titers of serum levels of ACPA between the responder group and non-responder group. The result is shown in Fig. 1. KER responders had lower levels of ACPA at baseline than non-responders (mean ± SD 281.0 ± 113.3 U/ml vs 573.3 ± 235.7 U/ml, respectively) ($P = 0.042$, Mann–Whitney test). Other univariate analysis did not show any significant differences in baseline clinical measures of anatomical stage [13], functional class [14], DAS28–CRP, or rheumatoid factor (RF) levels, between the two groups.

KER effect on ACPA levels

We are interested in ACPA changes during KER treatment, because there have been recent reports focusing on ACPA changes induced by biologics targeting TNF or MTX and other DMARDs [15]. There was no significant difference in

Table 2 Baseline demographic and clinical characteristics of 34 patients receiving KER therapy

Male/female	All	Responder	Non-responder	Out of assessment
	3/31	1/13	2/11	0/7
Age	57.5 ± 10.3	59.7 ± 7.5	53.1 ± 12.2	59.6 ± 10.2
Duration (year)	7.3 ± 6.1	7.5 ± 6.7	5.5 ± 4.6	10.0 ± 7.1
Stage	2.4 ± 0.8	2.4 ± 0.8	2.5 ± 0.7	2.2 ± 1.3
Class	2.0 ± 0.4	1.9 ± 0.3	2.2 ± 0.4	2.0 ± 0.8
PSL dosage (mg/day)	1.5 ± 2.6	1.7 ± 3.1	1.9 ± 2.5	1.1 ± 0.5
RF	174.1 ± 154.7	169.2 ± 156.8	189.3 ± 181.6	158.2 ± 83.1
DAS28–CRP	3.60 ± 0.98	3.84 ± 0.49	3.89 ± 0.45	2.51 ± 0.21

Stage: anatomical stage (adapted from Ref. [22]), Class: functional class (adapted from Ref. [23])
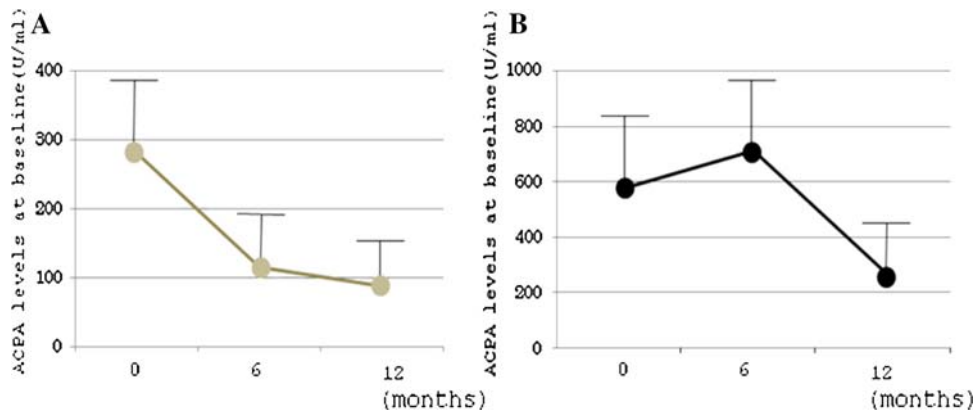
PSL prednisolone, *RF* rheumatoid factor, *DAS28–CRP* disease activity score including a 28-joint count–C-reactive protein
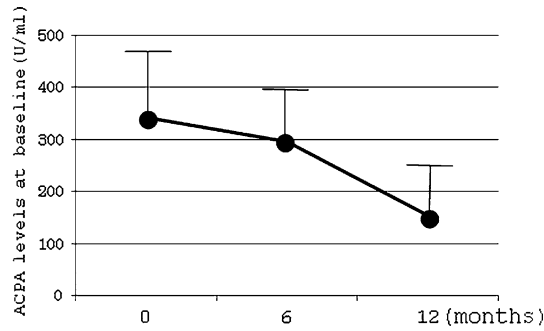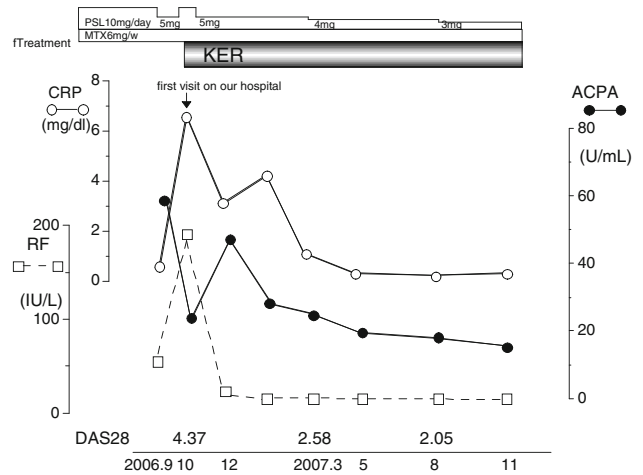
Fig. 2 Changes in ACPA levels in all patients. There was no significant difference in ACPA levels between the baseline and 6 months although ACPA titers showed a tendency to decrease. Between 6 and 12 months, the ACPA levels decreased, however, other drugs were added after 6 months in some non-responders, it was considered that the changes were not derived from KER treatment

Fig. 4 Clinical course in a representative responder. The patient with RA receiving concomitant methotrexate was successfully treated with KER. KER treatment resulted in a decrease in ACPA levels, as well as DAS28–CRP. *KER* keishinieppiittokaryojutsubu (decoction), *ACPA* anti-cyclic citrullinated peptide antibodies, *CRP* C-reactive protein, *RF* Rheumatoid factor (class IgM)

the levels of ACPA between the baseline and after 6 months of treatment in all patients receiving KER although ACPA titers showed a tendency to decrease (Fig. 2). Between 6 and 12 months, the ACPA titers decreased, however, other drugs had been added after 6 months in some non-responders (see patients and methods) and we considered that these changes were not attributable to KER treatment.

The changes in ACPA titers were separately assessed in the responder group and non-responder group (Fig. 3). First, in responders to KER, the serum levels of ACPA significantly decreased at 6 months compared with those at baseline. Subsequently, ACPA levels gradually decreased to 12 months although there was no significant difference between findings at 6 and 12 months in responders. Additionally, the serum levels of RF were also decreased significantly in responders (data not shown). In contrast,

non-responders did not show a decrease of ACPA levels at 6 months (Fig. 3). Additionally, there was a significant difference in the change in levels of ACPA between the responder group and non-responder group. After 6 months, the serum levels of ACPA decreased in non-responders due to additional medications except for KER as described above.

Representative case among responders to KER

A representative patient, who was categorized in the responder group based on DAS28–CRP findings, is discussed (Fig. 4).

Fig. 3 Changes in ACPA levels were assessed in each group. **a** Responder group: The levels of ACPA were significantly decreased after 6 months of treatment compared with the baseline values. **b** Non-responder group: There was no significant decrease in ACPA levels at 6 months. It was thought that the decrease in ACPA levels after

6 months was due to additional medications other than KER. Importantly, there was a significant difference in the change in ACPA levels between the responder group and non-responder group when baseline values were compared with those after 6 months ($P < 0.048$: repeated measures ANOVA)

A 57-year-old female developed a low fever, and bilateral wrist joint pain in May 2006. She consulted a local hospital and was diagnosed as having RA since RF was positive. PSL 10 mg/day and MTX 6 mg/week were initiated in July and symptoms improved. However, when the PSL dosage was reduced, the condition worsened again. She refused the increase in the dosage of MTX due to the worry about its advised effects. Thereafter, she consulted our hospital with a request for herbal medicine in October 2006. At the first medical examination, she had severe polyarthralgia in the bilateral MCP and wrists, knees and right shoulder joints. There were no significant findings on physical examination of the neck, chest and abdomen. Laboratory data were as follows: Hb 9.5 g/dl, ESR 124 mm/h, CRP 6.5 mg/dl, RF 185 IU/ml, Antinuclear antibody: negative. Hepatic, renal and thyroid functions were normal. We reduced PSL dosage from 10 to 5 mg/day, and continued the administration of MTX. Additionally, we prescribed KER. After 2 months her symptoms decreased, and 6 months later, the serum levels of a series of serological markers containing ACPA was decreased. PSL dosage was reduced to 3 mg/day in August 2007. This patient was categorized as showing a good response (4.37 to 2.05) based on DAS28–CRP findings.

Discussion

Traditional herbal medicine (Kampo), which is covered by national health insurance in Japan, is often prescribed in the primary care field, and is also applied as an alternative remedy for serious diseases such as RA. In RA, the clinical effects of THM were reported by several investigators and its immunomodulatory effects were demonstrated in several mouse models of arthritis [2–4]. The components of KER, which is a crude drug, are shown in Table 1. Some of the twelve herbs composing KER are: pseudoephedrine (Ephedrae herba), paeoniflorin (Paeoniae radix) and tetrandrine (Sinomeni Caulis et Rhizoma). These components have anti-inflammatory or immunomodulatory effects. The clinical effects of KER on RA are thought to be at least partially due to the effects of each of these herbs. In addition, there are probably some interactions between one ingredient and others. We have previously demonstrated that this kind of treatment decreased the serum level of RF, as well as disease activity using self-controlled trial [4]. Furthermore, it has been demonstrated that THM is effective for inflammatory arthritis in responders to THM [2]. In this study, we have also demonstrated the clinical efficacy of THM for RA using a self-controlled trial, but not a placebo-controlled trial. Therefore, it is considered that this is a pilot study and that further randomized controlled trials should be carried out.

We cannot predict the response to THM in patients with RA before such a remedy is prescribed, because THM is administered according to the traditional diagnostic system. Its diagnosis is usually determined, based on observations of pulse, tongue and abdomen [11], differing from the approach used in Western Medicine. Thus, predictors of treatment response to THM need to be identified. It was recently reported that haptoglobin alpha 1 chain might be a candidate for a predictive biomarker for the response to keishibukuryogan (KBG), another THM [16]. However, the main targets of KBG are the microcirculation system such as increased arterial stiffness and indication of endothelial dysfunction in long-standing RA, and it has not been demonstrated that KBG alone is able to control joint inflammation in human subjects with RA. It has been shown, however, that both the presence and level of ACPA are strongly associated with a worse disease course [5–9]. Recently, it has been demonstrated that serum levels of ACPA may be a useful predictor of the response to MTX: an anchor drug for RA treatment [17]. Therefore, we investigated the potential for the levels of ACPA in RA patients to predict responses to KER treatment. Data from this study suggest that low pretreatment levels of serum ACPA are associated with a more favorable response to KER treatment for RA, whereas high levels are associated with an insufficient response, despite the limited number of patients. Quantitative evaluation of ACPA levels might be an additional tool to determine which patients will most likely benefit from KER treatment. Two hundred and fifty units per milliliter as the cut-off for the serum level of ACPA may indicate that responses can be expected. Because, RA patients with serum levels of ACPA < 250 U/ml showed good or moderate responses to KER. In contrast, there were no differences on univariate analysis for other variables such as anatomical stage, functional class, DAS28–CRP and RF levels, between the two groups.

Recent reports have demonstrated that effects on the levels of serum ACPA vary with each drug. It has been reported that MTX did not influence the production of ACPA [18]. According to TNF-a blocking agents (infliximab or etanercept), several diverse results in patients showing clinical improvement have been reported. First, the levels of serum ACPA are unchanged by anti-TNF-α treatment [19, 20], second, treatment results in a decrease in ACPA titers [21] and third, serum ACPA decreased after 6–7 months but then returned to the baseline [22]. Although the differences among these findings have not yet been explained, many investigators have highlighted significant variations in ACPA titers among patients treated with anti-TNF-a drugs, and other DMARDs. Therefore, we further investigated changes in the levels of serum ACPA during treatment with KER. The levels of serum ACPA showed a tendency to decrease in all patients 6 months after KER

treatment. In the responder group, these levels decreased significantly. In contrast, the levels of ACPA did not show a decrease at 6 months. Additionally, there was a significant difference in the change in ACPA levels between the responder and non-responder groups. These findings suggest that decrease in serum ACPA levels after treatment, as well as low pretreatment ACPA levels, are associated with a better response to KER treatment in RA. Thus, monitoring the levels of ACPA may provide predictive guidelines for treatment with KER.

Our data demonstrated that responders to KER showed a significant decrease in serum levels of ACPA. This observation is also attractive from the perspective of controlling joint damage in RA. Recently, the clinical significance of the serial determination of ACPA has been discussed. It has been reported that serial determination of ACPA over a 3-year follow-up period is more useful than baseline determination for predicting the radiographic progression in RA [23]. We have also demonstrated that RA patients in whom the serum level of ACPA did not decrease demonstrated severe progression of joint damage while mild progression of the erosive lesion was observed in RA patients with a decrease in ACPA [6]. These findings suggest that radiographic progression may be suppressed in responders to KER who show a decrease in their serum levels of ACPA. However, this suggestion should be considered tentative until a further long-term study is carried out, since the association between ACPA titer and RA severity remains controversial [10].

In conclusion, this is the first report to demonstrate that pretreatment serum levels of ACPA are a useful predictor of a good response to treatment with KER, and that a decrease in serum levels of ACPA may be an adjunctive indicator predicting the efficacy of this kind of treatment. These findings may promote the establishment of evidence-based complementary and alternative medicine.

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