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ORIGINAL ARTICLE

Hiroshi Kajiyama · Hideto Akama · Hisashi Yamanaka
Akira Shoji · Yuko Matsuda · Eiichi Tanaka
Ayako Nakajima · Chihiro Terai · Masako Hara
Taisuke Tomatsu · Terunobu Saitoh · Naoyuki Kamatani

One third of Japanese patients with rheumatoid arthritis use complementary and alternative medicine

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Abstract We investigated the prevalence and predictors of complementary and alternative medicine (CAM) use by patients with rheumatoid arthritis (RA) in Japan. A cross-sectional descriptive study was performed using the database from a large observational cohort of RA patients in the Institute of Rheumatology, Tokyo Women's Medical University. Logistic regression analysis was carried out to reveal predictive factors for CAM use. Among 3815 RA patients, 1321 (34.6%; 174 males, 1147 females) used at least one type of CAM. Health foods, including dietary supplements, were the most commonly used. CAM was more frequently used by female patients (odds ratio: 0.578; 95% confidence interval [CI] = 0.451–0.740). A multiple logistic regression analysis revealed that sex (odds ratio: 0.489; 95% CI = 0.333–0.718) and degree of satisfaction with disease-modifying antirheumatic drugs (DMARDs) (odds ratio: 0.899; 95% CI = 0.852–0.948) were significant independent predictive factors for CAM use. The serum C-reactive protein level and erythrocyte sedimentation rate showed no significant associations with CAM use. Approximately 35% of RA patients used CAM in Japan. Female patients and patients dissatisfied with DMARDs used CAM more frequently, regardless of their disease activity.

Key words Complementary and alternative medicine (CAM) · Female predominance · Japanese patient · Patient satisfaction · Rheumatoid arthritis

H. Kajiyama (✉) · H. Akama · H. Yamanaka · Y. Matsuda · E. Tanaka · A. Nakajima · C. Terai · M. Hara · T. Tomatsu · T. Saitoh · N. Kamatani
Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan
Tel. +81-3-5269-1725; Fax +81-3-5269-1726
e-mail: hkajicongr@verizon.net

A. Shoji
Department of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Tokyo, Japan

Introduction

Complementary and alternative medicine (CAM) comprises medicines that are not considered to be part of conventional medicine practiced by medical doctors. Although most concrete evidence of their efficacy or mode of function is still lacking, many kinds of CAM are prevalent among patients with chronic conditions, since the uncomfortable symptoms cannot be completely controlled by conventional medicine. Therefore, many doctors have recognized the importance of CAM, and quite a few reports regarding CAM use have recently been published from many fields of medicine.[1–4] There have also been reports on CAM use by rheumatoid arthritis (RA) patients worldwide.[5–8] Furthermore, increasing interest in CAM led to the establishment of an office for alternative medicine in the United States in 1992, the status of which was subsequently elevated to the National Center for CAM (NCCAM) as an NIH center in 1998. The NCCAM supports clinical and basic research on CAM, and some clinical trials are in progress. However, information about CAM use by Japanese patients with RA is limited. Here, we report the prevalence, types, and predictive factors of CAM use by Japanese patients with RA.

Patients and methods

We established a large observational cohort of RA patients in the Institute of Rheumatology, Tokyo Women's Medical University (IORRA cohort) in 2000.[9] This database contains the information from the biannual data collection of the patients by patient's questionnaire, physician's assessment and laboratory data, and basically all patients with RA in our institute have been enrolled in this cohort. Written informed consent was obtained from all participants and a booklet containing questions about their health assessment and disease activity was handed to each RA patient in our outpatient clinic. We asked the patients to return the booklets to our institute within 2 weeks, and all postage was

covered by our institute. Telephone calls were made to confirm whether the booklets had been returned, if they were not received within 2 weeks. Over 95% of the booklets were collected in each phase. All of the patients who participated in this cohort satisfied the 1987 criteria for RA of the American College of Rheumatology.[10]

We used the data from phase 1 of the IORRA cohort in October 2000 to clarify the prevalence and types of CAM use in 3815 patients with RA (661 males, 3154 females). We made enquires about CAM use in the booklet for phase 1 of IORRA cohort as follows:

> Question 1. Have you ever experienced therapies for RA other than medical checkups in an outpatient clinic since you developed RA? Yes/No.
>
> Question 2. Please answer only if your answer to Question 1 is Yes. What kind of therapies have you ever experienced? (You can choose more than one therapy, if applicable). a) acupuncture and/or moxibustion; b) *seitai* and/or *sekkotsu* and/or chiropractic; c) folk remedies; d) Chinese herbal medicine (including over-the-counter drug products or products prescribed by physicians); e) dietary supplements: e-1: ginger extract, e-2: chlorella, e-3: propolis, e-4: immune milk, e-5: others.

We defined the therapies listed in question 2 as CAM in this study. Both *seitai* and *sekkotsu* are Japanese physical therapies. *Sekkotsu* originates from combative sports such as judo, and is provided by therapists with qualifications from the Japanese government. *Seitai* has a background of chiropractic/osteopathy and is provided by nonqualified therapists. Chiropracty is also provided by nonqualified therapists in Japan. If patients had experienced specific folk remedies, they were asked to write down the details. If patients had used dietary supplements, they were asked to choose one or more of the four dietary supplements listed above as e-1, e-2, e-3, and e-4. Patients who had experienced dietary supplements other than ginger extract, chlorella, propolis, and immune milk were asked to choose e-5 (others), and write down the name of the specific supplement.

Although NCCAM defined complementary medicine and alternative medicine separately, complementary medicine: used in addition with conventional medicine, and alternative medicine: used in place of conventional medicine (http://nccam.nih.gov/health/whatiscam/), the term CAM is widely used so far to describe the unconventional medicine not usually provided by physicians or hospitals. Complementary medicine or alternative medicine was also used in the previous reports to describe unconventional medicine,[8,11–13] regardless of being treated with conventional medicine. Therefore, we also used CAM to describe unconventional medicine as defined above in this report.

We used the data from phase 2 of the IORRA cohort in April 2001 to clarify the predictive factors for CAM use by 3121 patients with RA (542 males, 2579 females). We asked about CAM use from October 2000 to April 2001 in the booklet for phase 2 of the IORRA cohort, and analyzed the correlation between CAM use and potential factors. We selected sex (female 0, male 1), number of tender joints (0–64), serum level of C-reactive protein (CRP; mg/dl), erythrocyte sedimentation rate (ESR; mm/hour), patient's Visual Analog Scale (VAS) for pain and general status, doctor's VAS for RA severity, and degrees of satisfaction with nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and corticosteroids as potential factors. The degrees of satisfaction with NSAIDs, DMARDs, and corticosteroids were originally developed with scores of 0–10. If the participants in the IORRA cohort were satisfied with each drug, they were asked to score 10 as the maximum. If they were dissatisfied, they were asked to score 0 as the minimum. A Mann–Whitney analysis was performed to compare the ages and male-to-female ratios between the phase 1 and phase 2 populations in the IORRA cohort. A Mann–Whitney analysis and chi-square analysis were used to compare the characteristics of the patients between phases 1 and 2 of the IORRA cohort. A logistic regression analysis was carried out to reveal statistically significant predictive factors of CAM use. In this logistic regression analysis, we regarded the male sex as 1 and the female sex as 0. Stat-View was used for the statistical calculations. A P value of less than 0.05 was regarded as significant.

Results

Patient characteristics

Table 1 shows the characteristics of the patients who participated in phases 1 and 2 of the IORRA cohort. The values in phase 1 all differed significantly from those in phase 2, with the exception of HAQ, but the differences were not large. The reasons for using two different phases were to study the prevalence of CAM and its incidence separately, and to correlate the incidence with the background information of the RA patients.

Prevalence of CAM use by RA patients in Japan

In this study, 1321 patients (34.6%; 174 males, 1147 females) had used CAM after they developed RA, compared

Table 1. Characteristics of rheumatoid arthritis (RA) patients in phases 1 and 2 of the IORRA cohort

	Phase 1	Phase 2
Males (*n*/age)	661/60.5 ± 11.9	542/60.7 ± 11.7
Females (*n*/age)	3154/57.2 ± 12.4	2579/57.6 ± 12.1
Total (*n*/age)	3815/57.8 ± 12.4	3121/58.2 ± 12.1*
Disease duration (years)	10.2 ± 8.5	10.6 ± 8.57*
HAQ	0.76 ± 0.73	0.78 ± 0.73
Doctor's VAS	26.6 ± 20.8	24.9 ± 19.8*
Patient's VAS	35.1 ± 24.5	37.2 ± 25.7*
Pain VAS	33.4 ± 25.6	35.8 ± 27.1*
CRP (mg/dl)	1.44 ± 1.94	1.61 ± 2.05*

Values are shown as mean ± standard deviation
HAQ, Stanford Health Assessment Questionnaire; VAS, Visual Analog Scale; CRP, C-reactive protein
* $P < 0.05$, significant difference between phases 1 and 2 by the Mann–Whitney test

with 2244 patients (58.8%; 439 males, 1805 females) who had not. However, 250 patients (6.6%; 48 males, 202 females) did not answer, even though they participated in phase 1 of IORRA cohort (Fig. 1).

Types of CAM use by RA patients in Japan

Table 2 shows the types of CAM used by Japanese patients with RA. Dietary supplements were the most frequently used (886 patients; 23.2% of all patients), followed by acupuncture and/or moxibustion (355 patients; 9.3%), Chinese herbal medicine (284 patients; 7.4%), *seitai* and/or *sekkotsu* and/or chiropractic (272 patients; 7.1%) and folk remedies (148 patients; 3.8%). More specifically among the dietary supplements, ginger extract was the most popular (252 patients; 6.6%) (Table 3), followed by propolis (214 patients; 5.6%), chlorella (155 patients; 4.1%) and immune milk (139 patients; 3.6%). Other dietary supplements were also used, but to much lower extents as follows: chondroitin (29 patients; 0.76%), royal jelly (25 patients; 0.65%), shark cartilage (24 patients; 0.62%), glucosamine (22 patients; 0.58%), cat's claw (21 patients; 0.55%), prunes (20 patients; 0.52%), aloe extract (19 patients; 0.50%), agaricus (16 patients; 0.42%), as well as others.

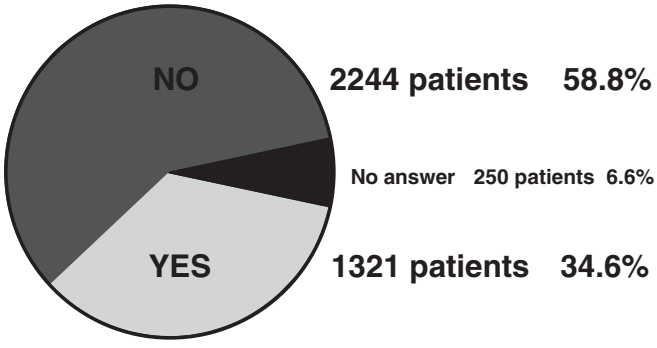

Fig. 1. Prevalence of complementary and alternative medicine (CAM) use by rheumatoid arthritis (RA) patients in Japan. One third of Japanese patients with RA use at least one CAM

Table 2. Types of complementary and alternative medicine (CAM) used by RA patients in Japan

CAM	*n*	% of RA patients
Dietary supplements	886	23.2
Acupuncture and/or moxibustion	355	9.3
Chinese herbal medicine	284	7.4
Seitai and/or *sekkotsu* and/or chiropractic	272	7.1
Folk remedies	148	3.8

Table 3. Kinds of dietary supplements used

Dietary supplements	*n*	% of RA patients
Ginger extract	252	6.6
Propolis	214	5.6
Chlorella	155	4.1
Immune milk	139	3.6
Others	417	10.9

Predictive factors for CAM use by RA patients in Japan

A simple logistic regression analysis revealed significant predictive factors for CAM use (Fig. 2). However, a multiple logistic regression analysis clarified female sex and a low degree of satisfaction with DMARDs as independent factors that facilitated CAM use (Fig. 3).

Discussion

We have clarified the prevalence and predictive factors of CAM use by Japanese patients with RA. In our study, approximately 35% of patients with RA used CAM. However, in other reports, 40%–60% patients with rheumatic diseases used CAM.[8,11–13] Therefore, the prevalence of CAM use by Japanese patients with RA seemed to be slightly lower than those in the other studies. This discrepancy could be due to differences in the way in which the patients were asked and in the population, as well as differences in the definition of CAM. As shown in Fig. 1, there were 250 patients (6.6%) who did not answer the question about CAM use, and we did not follow these patients up. Therefore, we may have underestimated the prevalence. Previous studies have revealed that patients do not always disclose CAM use.[14,15] For example, Rao et al. reported that the most common reasons for not disclosing CAM use were that the physician did not ask about it and that the patient forgot to tell the physician.[8] Direct interviews with patients on the phone or at our outpatient clinic would reduce this type of error.

Meanwhile, this study was conducted before biological agents began to be prescribed, and the disease activity of RA could not be sufficiently controlled despite the high percentage of patients prescribed DMARDs in Japan. If this kind of study had been performed several years later, the prevalence of CAM use would probably decrease further.

In the current study, we revealed dietary supplements as the most popular type of CAM, and that ginger extract was the most frequently used among the dietary supplements. Ginger extract was recently reported to reduce pain in osteoarthritis,[16] which may partly explain the high frequency. In contrast, only a very small proportion of patients used glucosamine, which has also been reported to be effective in osteoarthritis.[17] This might partly be affected by the way in which the answers were collected from the patients.

As previously reported,[7] our data revealed that female RA patients used CAM more frequently than male patients. We therefore need to interview patients about CAM use more carefully than ever, especially when they are female.

Many people tend to believe that CAM is safe. Besides, any adverse effects may be overlooked if doctors are un-

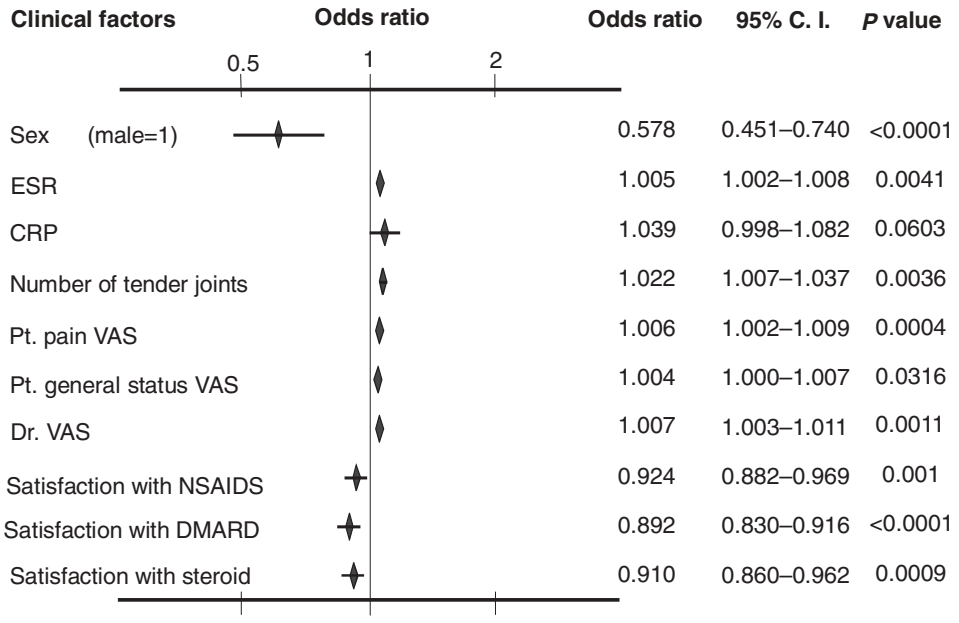

Fig. 2. Predictive factors for CAM use by RA patients in Japan, as evaluated by a simple logistic regression analysis. Almost all of the clinical factors, except for CRP, have some association with CAM use. Satisfaction with drugs is negatively correlated with CAM use, whereas the VAS scores and number of tender joints are positively correlated with CAM use. *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *Pt*, patient; *VAS*, Visual Analog Scale; *Dr*, doctor; *NSAID*, nonsteroidal anti-inflammatory drug; *DMARD*, disease-modifying antirheumatic drug; *C.I.*, confidence interval

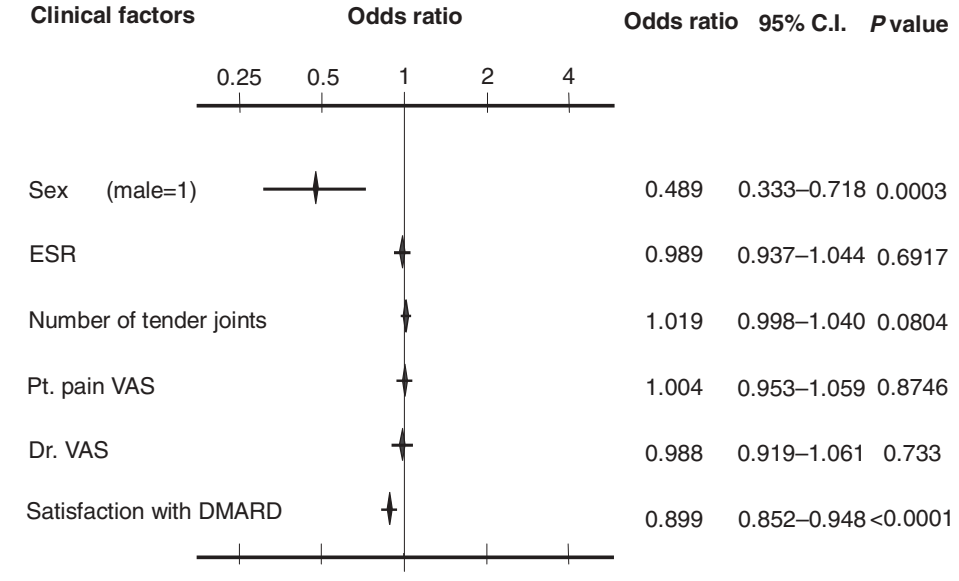

Fig. 3. Predictive factors for CAM use by RA patients in Japan, as evaluated by a multiple logistic regression analysis. Female sex and dissatisfaction with DMARDs are significant predictive factors for CAM use

aware of CAM use by RA patients. Therefore, it is very important to elucidate the frequency of adverse effects in CAM use. Through a systematic review of case reports, a considerable number of adverse effects, including fatalities, caused by acupuncture have been reported in Japan.[18] Adverse effects of herbal products, including possible interactions with synthetic drugs, were also reported in a recent review.[19] An analysis of the IORRA cohort data did not detect any significant deterioration in the serum levels of aspartate aminotransferase, alanine aminotransferase and creatinine, or proteinuria in RA patients using CAM for at least 1 year (data not shown). A similar analysis of Chinese herb users in our institute also showed no deterioration in the clinical data (data not shown). On the other hand, we experienced renal failure in a patient with systemic scleroderma, which was subsequently proved to be caused by Chinese herbs containing aristolochic acid.[20] Therefore we need to be more aware, in order to avoid overlooking cases with potential adverse effects due to CAM use, which may be the tip of the iceberg.

The NCCAM initiated many clinical trials of CAM in the late 1990s and strives to provide useful information about CAM to U.S. citizens, thereby facilitating CAM use by patients. Recently, a chair of CAM was established at a university in Japan, and this may be expected to accelerate research in Japan as well as in Western societies to delineate the prevalence of CAM and its precise merits and demerits, including cost performance, in Japan.

Although there are already some reports regarding CAM use by RA patients in Japan, the populations involved were not large, and no reports have been published in English. The population in the current study is the largest

investigated in Japan to date. This is also the first report written in English, and sufficiently reliable to introduce recent CAM use by RA patients in Japan to Western society. A multicenter study is necessary to make CAM use in Japan much clearer. Finally, all medical staff, including doctors, nurses, physical therapists, and occupational therapists need to pay more attention to CAM use by RA patients.

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