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ORIGINAL RESEARCH

Efficacy and Safety of *Vitex agnus-castus* Extract for Treatment of Premenstrual Syndrome in Japanese Patients: A Prospective, Open-label Study

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ABSTRACT

Introduction: Herbal medicine containing *Vitex agnus-castus* (VAC) extract is widely used by women with premenstrual syndrome (PMS) in Europe, however, in Japan, clinical evidence remains to be determined. This study attempted to investigate the efficacy and safety profiles of VAC extract in Japanese patients with PMS.

Methods: A multi-center, prospective, open-label, single-arm, phase 3 study was performed in Japanese women with PMS and aged 18–44 years. The patients received Prefemin® (Max Zeller Söhne AG, Romanshorn, Switzerland), containing 20 mg of VAC extract, once daily for three menstrual cycles. The efficacy profile was examined based on the intensity of ten PMS symptoms—irritability, depressed mood, anger, headache, bloating, breast fullness, skin disorder, fatigue, drowsiness, and sleeplessness—recorded by patients via a visual analog scale (VAS). In addition, the responder rate was calculated based on the total VAS score defined by the sum of the VAS scores of the first six symptoms mentioned above. Furthermore, physician's global assessment (PGA) scores were recorded. Adverse events including vital signs and laboratory test values were monitored as safety evaluation.

Results: Sixty-nine patients received Prefemin®. After the first menstrual cycle, a statistically significant decrease in total VAS score was observed ($P < 0.001$), and the score continued to diminish for the following two cycles. Each of the ten symptom scores decreased significantly in this manner. In addition, the responder rate increased in a time-dependent manner; the rate at the third menstrual cycle was 91.0%, and almost all of

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the patients were without symptoms or exhibited only mild symptoms based on PGA. Eight patients exhibited non-serious adverse events, one of which was allergic dermatitis whose causal relationship with VAC was not ruled out.

Conclusion: VAC extract improved PMS symptoms in Japanese patients, with no substantial adverse events. This is the first study to report the effect of VAC extract in Japanese patients.

Keywords: Chaste tree; Clinical trial; Herbal medicine; Japanese patients; Phase 3; Prefemin®; Premenstrual syndrome; Reproduction; *Vitex agnus-castus*; Ze 440

INTRODUCTION

Premenstrual syndrome (PMS) is characterized by a complex combination of physical and psychological symptoms that occur during the luteal phase of the menstrual cycle [1]. According to the American College of Obstetricians and Gynecologists, diagnosis of PMS can be made if the patient has at least one of the affective symptoms, such as depression, angry outbursts, irritability, anxiety, confusion, and social withdrawal, or the somatic symptoms such as breast tenderness, abdominal bloating, headache, and swelling of extremities, during the 5 days before menses in each of the three prior menstrual cycles, and relief occurs within 4 days of the onset of menses [2]. PMS reportedly affects quality of life in 20–40% of women of reproductive age [1]. Since the pathogenic mechanisms of PMS are yet to be elucidated, no causal treatment for PMS has thus far been established; treatment has been symptomatic, employing such medications as antidepressants, analgesic drugs, oral contraceptives, and herbal medicine [3].

Herbal medicine derived from chaste tree fruit is commonly used for treating PMS in Europe [4]. In the German Commission E Monographs, chaste tree fruit is listed as an "approved herb" and its aqueous–alcoholic extract (50–70% v/v) is recognized for treating irregularities of the menstrual cycle, premenstrual complaints, and mastodynia [5]. Further, the Committee on Herbal Medicinal Products of the European Medicines Agency states in the community herbal monograph that Ze 440, an aqueous–alcoholic extract (60% m/m) with a drug-extract ratio (DER) of 6–12:1 from *Vitex agnus-castus* (VAC; synonym: chaste tree) fruit, is the only preparation that fulfills the requirements for "well-established use" status for PMS [6].

One possible mechanism of action of VAC extract could be the inhibition of prolactin secretion via activation of the dopamine D_2 receptor [7–9]. Prolactin is a pituitary-derived hormone, which may play an important role in reproduction and the development of mammary glands and lactation. An increase in prolactin levels may cause menstrual abnormality, anovulation, and PMS in non-lactating women [10].

In an epidemiological study, approximately 95% of a sample of Japanese women ($N = 1,152$) reported having had an experience of general malaise during the weeks before each of the menses within the last 3 months, and 5.3% of them reported moderate to severe PMS [11]. Another study reported that approximately 52.0% of a sample of Japanese women ($N = 285$) suffered from physical and psychological abnormalities late in the menstrual cycle, 20% stated that the abnormalities hindered their daily activities, and 8% wanted to treat their symptoms [12].

The percentage of 8% was similar to the proportion of patients with PMS who require treatment in Western countries [12].

Many products containing a VAC extract Ze 440 have already been on the market as an over-the-counter drug for PMS in European countries for more than 10 years [4]. Several studies have suggested that Ze 440 could be effective for treating certain PMS symptoms in the European population [4, 13–15]; however, evidence has not been reported in the Japanese population. Therefore, a prospective, multicenter, open-label, phase 3 study was conducted in an attempt to confirm the efficacy and safety profiles of Ze 440 in Japanese patients with PMS. The authors hypothesized that the VAC extract Ze 440 would be effective and tolerable in Japanese patients, as it is in European patients.

METHODS

Ethics

This study was approved by the institutional review board of Yoshii Chuo Shinryojo, Gunma, Japan. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008, and Good Clinical Practice guidelines. Informed consent was obtained from all patients for being included in the study.

Subjects

Female patients who were aged 18–44 years at the time of the study and who provided informed consent were investigated based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) [16]. Patients were excluded if they had disorders such as depression, anxiety, dysthymia, or panic attacks; chronic anorexia or bulimia; serious chronic disorders; alcohol or drug abuse/dependence; dysmenorrhea; endometriosis; pituitary insufficiency; chronic febrile disorders; malignancy; thyroid dysfunction; personality disorder; menopause or abnormal menstrual cycles; Parkinson's disease; hypersensitivity to preparations from chaste tree or to the excipients of the study drug; a plan to breast-feed or become pregnant during this study; any serious concomitant cardiopathy, hematological, renal, liver, or pulmonary disease, or a previous history of the diseases mentioned above. Participation in any other clinical study within 3 months prior to the informed consent, or the use of prohibited drugs or therapy during the run-in period also resulted in exclusion.

Study Drug

The study drug Prefemin® (Max Zeller Söhne AG, Romanshorn, Switzerland), containing 20 mg of VAC extract as an active ingredient, was manufactured and provided by Max Zeller Söhne AG, Romanshorn, Switzerland. VAC extract is a 60% m/m aqueous–ethanolic extract from the fruit of the chaste tree, with a DER of 6–12:1. Patients received one tablet daily for three menstrual cycles after confirmation of their eligibility on the last visit in the run-in period. Drug compliance was assessed by counting the returned unused medication and by questioning the patients.

Study Design

This prospective, multicenter, open-label, phase 3 study was conducted at four obstetrics and

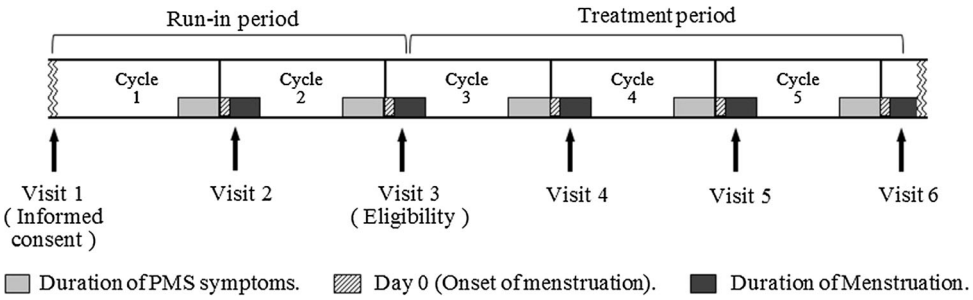

Fig. 1 Timeline of the study based on the menstrual cycle. *PMS* premenstrual syndrome

gynecology clinics in Japan from May 2009 to November 2009. The timeline of the study is shown in Fig. 1. Patients were asked to record the severity of the ten symptoms listed in the DSM-III-R, body temperature, and presence or absence of menstrual bleeding in a patient diary during the first and the second menstrual cycles in the run-in period. The investigator then assessed whether the patients met the DSM-III-R criteria by means of their patient diary and an interview, taking into account considerations such as the number of symptoms reported, and eligible patients were given the study drug.

Prohibited Concomitant Drugs and Therapy

Concomitant use of the following drugs or therapies was prohibited during this study: contraceptive drugs (oral contraceptives, levonorgestrel-releasing intrauterine system), psychotropic drugs (including selective serotonin reuptake inhibitors), anxiolytic drugs, diuretic drugs (including hypotensive drugs with diuretic effects), non-steroidal anti-inflammatory drugs, Chinese herbal medicines, gonadotropin, gonadotropin-releasing hormones, corticosteroids (excluding external preparations), thyroid hormones, sex hormones, anti-thyroid drugs, ovulation-inducing drugs, prostaglandin, vitamin B_6, dopamine agonists or antagonists, psychotherapy, and supplements used for treating PMS. Use of non-steroidal anti-inflammatory drugs was permitted as a concomitant drug during menstruation.

Efficacy Assessment

VAS Score

Patients assessed the intensity of the following ten symptoms daily throughout the study using the validated visual analog scale (VAS) [17], ranging from 0 (no symptom) to 100 (as severe as possible), measured in millimeters on a linear scale; irritability, depressed mood, anger, headache, bloating, breast fullness, skin disorder, fatigue, drowsiness, and sleeplessness, where the first six symptoms comprised the total VAS score. These six symptoms were selected because previous European studies reported that these were the main complaints of patients suffering from PMS, and designated their sum as the total VAS score [13, 14]. The other four symptoms were investigated as they are alluded to in the Prefemin® package insert [18]. The VAS score was defined as the mean of the scores of the 3 days from Day −3 to Day −1 before the onset of menstruation (Day 0), and was determined for cycle 2 (baseline), and for the subsequent three cycles after the commencement of intervention (cycles 3, 4, and 5).

Physician's Global Assessment Score

Physician's global assessment (PGA) scores were determined based on the definition in Table 1. Investigators scored the symptoms of PMS from 0 (no symptom) to 4 (very severe) for each patient based on the symptoms during the three consecutive days (from Day −3 to Day −1) before the onset of menstruation (Day 0), and the scores were determined in cycle 2 (baseline) and in the subsequent three cycles after the commencement of study medicine (cycle 3, 4, and 5).

Safety Assessment

The following vital signs and laboratory test values were determined during the run-in period, and on visit 4 and visit 6 (or at the time of discontinuation): body temperature, blood pressure, pulse rate, white blood cell count, leukocyte fractions, red blood cell count, hemoglobin, hematocrit, platelet count, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, γ-glutamyl transpeptidase, total bilirubin, creatinine, uric acid, urea nitrogen, Ca^{2+}, Na^{+}, K^{+}, Cl^{-}, and qualitative urinalysis for glucose and urobilinogen. Physicians determined whether any adverse events had occurred by asking a non-leading question on each visit throughout the study.

Statistics and Analysis

Variations in VAS score were calculated based on the difference between the baseline score and the score at each menstrual cycle during the treatment period. Variations in total VAS score and PGA score were similarly determined. With regard to responder rate, responders were defined as patients with a reduction in total VAS score of 50% or more from the baseline. Responder rate was calculated as the ratio of responders for a population of efficacy analysis, at each of the menstrual cycles.

With regard to efficacy, the full analysis population comprised patients with any efficacy data after the administration of the study drug and with no deviation from the inclusion criteria. The descriptive statistics for continuous variables consisted of mean, median, standard deviation, minimum, maximum, and the number of cases. Discrete variables were summarized by frequency and proportion, and 95% confidence interval (95% CI) as appropriate. The safety analysis population was defined as patients with any safety data after the intervention. Adverse events reported during the treatment period were coded based on MedDRA/J terminology (MedDRA/J ver.13.0) and aggregated in preferred terms. Paired *t* tests were conducted for both VAS score and total VAS score, and the Wilcoxon signed-rank test was employed for categorical variables and the PGA

Table 1 Physician's global assessment of premenstrual syndrome: score definition

Score	Intensity
0	No symptom
1	The symptom is mild (symptom present but not disturbing)
2	The symptom is moderate (symptom disturbing but not interfering with sleep or daily activity)
3	The symptom is severe (symptom interfering with sleep or daily activity)
4	The symptom is very severe (immediate consultation with physicians necessary because of disturbing symptom)

Table 2 Characteristics of patients involved in efficacy analyses ($N = 67$)

Items		%
Age (years)		
Mean	30.9	
SD	6.5	
Maximum	44	
Median	31.0	
Minimum	18	
18–20	3	4.5
21–25	14	20.9
26–30	14	20.9
31–35	18	26.9
36–40	13	19.4
41–44	5	7.5
Weight (kg)		
Mean	54.00	
SD	9.95	
Maximum	98.4	
Median	52.30	
Minimum	38.1	
<40.0	1	1.5
40.0–49.9	22	32.8
50.0–59.9	32	47.8
60.0–69.9	8	11.9
≥70.0	4	6.0
Age at menarche (years)		
≤9	2	3.0
10–14	63	94.0
≥15	2	3.0
History of pregnancy		
No	35	52.2
Yes	32	47.8
History of parturition		
No	38	56.7
Yes	29	43.3
Cycle length (days)		
≤24	8	11.9
25–35	54	80.6
≥36	5	7.5
Menses duration (days)		
Mean	5.7	
SD	1.1	
Maximum	8	
Median	6.0	
Minimum	3	

SD standard deviation

score. *P* values of less than 0.05 were considered to indicate statistical significance. All statistical calculations were performed with SAS Release 9.1.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Subjects

Eighty-three patients entered the run-in period, and 14 were withdrawn; nine failed to meet the DSM-III-R criteria, one had an abnormal menstrual cycle, two did not return to the clinic, and two were judged as inadequate for enrollment by the investigator. The remaining 69 patients were enrolled in the study and received the study drug. Two patients were withdrawn during the treatment period: one due to an adverse event (allergic dermatitis) and the other due to use of a prohibited drug during

Table 3 Variation of each item in the VAS score ($N = 67$)

Symptoms	Time	Variation in VAS score[a]					95% CI of mean	*P* value[b]
		Mean	SD	Minimum	Median	Maximum		
Irritability	1st cycle	−28.6	29.7	−97	−27.0	42	−35.7, −21.4	<0.001
	2nd cycle	−34.9	26.2	−86	−33.0	36	−41.3, −28.6	<0.001
	3rd cycle	−41.0	24.9	−96	−39.0	18	−47.0, −34.9	<0.001
Depressed mood	1st cycle	−23.5	27.0	−96	−18.0	20	−30.0, −16.9	<0.001
	2nd cycle	−25.3	30.3	−83	−21.0	64	−32.6, −17.9	<0.001
	3rd cycle	−28.0	27.5	−96	−26.0	24	−34.7, −21.3	<0.001
Anger	1st cycle	−26.0	31.2	−96	−22.0	83	−33.6, −18.5	<0.001
	2nd cycle	−33.2	29.5	−90	−33.0	66	−40.3, −26.0	<0.001
	3rd cycle	−35.8	30.0	−94	−36.0	59	−43.1, −28.5	<0.001
Headache	1st cycle	−9.7	22.0	−81	0.0	53	−15.0, −4.4	<0.001
	2nd cycle	−11.5	25.4	−82	−2.0	52	−17.7, −5.4	<0.001
	3rd cycle	−15.3	21.8	−85	−3.0	7	−20.6, −10.0	<0.001
Bloating	1st cycle	−15.6	19.8	−74	−10.0	43	−20.4, −10.9	<0.001
	2nd cycle	−19.7	26.7	−91	−14.0	48	−26.2, −13.2	<0.001
	3rd cycle	−20.2	22.5	−78	−13.0	7	−25.6, −14.7	<0.001
Breast fullness	1st cycle	−17.2	24.2	−82	−10.0	56	−23.1, −11.4	<0.001
	2nd cycle	−20.9	32.4	−89	−20.0	70	−28.8, −13.0	<0.001
	3rd cycle	−26.3	26.8	−100	−21.0	18	−32.7, −19.8	<0.001
Skin disorder	1st cycle	−17.2	25.8	−92	−13.0	60	−23.4, −10.9	<0.001
	2nd cycle	−21.4	27.5	−97	−17.0	51	−28.1, −14.8	<0.001
	3rd cycle	−24.8	26.3	−92	−24.0	29	−31.2, −18.4	<0.001
Fatigue	1st cycle	−31.9	30.7	−100	−31.0	72	−39.3, −24.4	<0.001
	2nd cycle	−40.9	30.7	−100	−42.0	50	−48.3, −33.4	<0.001
	3rd cycle	−43.8	31.4	−100	−41.0	75	−51.4, −36.2	<0.001
Drowsiness	1st cycle	−33.0	27.7	−100	−29.0	25	−39.7, −26.3	<0.001
	2nd cycle	−38.0	29.1	−100	−39.0	25	−45.1, −31.0	<0.001
	3rd cycle	−42.1	30.0	−100	−39.0	20	−49.4, −34.8	<0.001
Sleeplessness	1st cycle	−8.2	20.9	−100	0.0	13	−13.2, −3.1	0.002
	2nd cycle	−8.5	20.7	−97	0.0	22	−13.5, −3.5	0.001
	3rd cycle	−9.7	22.6	−100	0.0	9	−15.2, −4.2	<0.001

CI confidence interval, *SD* standard deviation, *VAS* visual analog scale
[a] Variation = Score at each menstrual cycle − Score at baseline
[b] Paired *t* test

the run-in period. For these two patients, only their safety data were incorporated, because no efficacy data (VAS and PGA scores) were obtained. All 69 patients exhibited drug compliance of 75% or more. The characteristics of 67 patients involved in the efficacy analyses are summarized in Table 2.

VAS Score

The mean VAS scores (95% CI) at baseline for each of the ten symptoms were as follows: irritability, 49.4 (43.0–55.7); depressed mood, 33.1 (26.0–40.1); anger, 39.7 (32.5–46.9); headache, 17.0 (11.3–22.7); bloating, 27.3

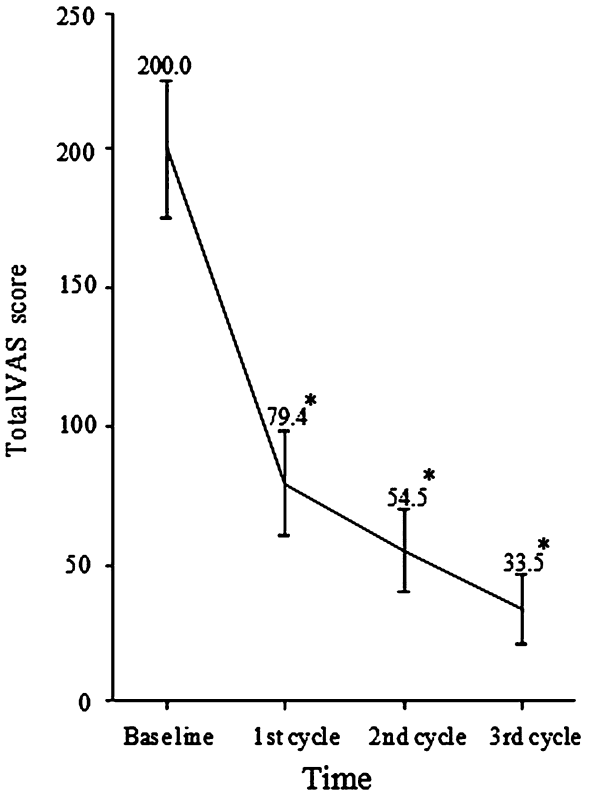

Fig. 2 Variations in total visual analog scale (VAS) score. Calculated from the sum of VAS scores of six symptoms (irritability, depressed mood, anger, headache, bloating, breast fullness). *Statistically significant difference from baseline ($P < 0.05$). *Error bars* represent the 95% confidence interval

(20.5–34.2); breast fullness, 33.5 (25.9–41.1); skin disorder, 30.2 (24.0–36.4); fatigue, 49.5 (43.1–55.9); drowsiness, 50.5 (44.1–57.0); and sleeplessness, 10.7 (4.9–16.5). The scores of all ten of the symptoms decreased remarkably at the first menstrual cycle, and thereafter decreased sequentially, and by the third period they all differed statistically significantly from the corresponding baseline score ($P < 0.01$, paired t test; Table 3). In addition, the mean baseline total VAS score (95% CI) was 200.0 (175.4–224.7), and at the menstrual cycles following the commencement of the intervention it was 79.4 (60.6–98.1), then 54.5 (39.4–69.6), and then 33.5 (20.6–46.4) (Fig. 2). The total VAS score differed significantly from baseline at all of the assessment points ($P < 0.001$).

The responder rates at the three menstrual cycles after the commencement of intervention were 64.2% (43/67), 80.6% (54/67), and 91.0% (61/67); the rate increased with the duration of treatment.

PGA Scores

All of the patients had an initial PGA score of either 3 or 4 (severe or very severe, respectively); however, the number of patients with those scores dropped at the first cycle after the commencement of intervention and kept decreasing during the treatment period, with statistical significance from baseline at all the assessment points ($P < 0.001$, Wilcoxon signed-rank test; Fig. 3). No worsening of PGA scores was detected.

Safety

Eight adverse events were reported (11.6%, 8/69 patients), but none were serious or related to the laboratory test values. Three events were judged as moderate: infective dermatitis, asthma, and allergic dermatitis (1 event each). The rest, that were all judged as mild, included cystitis (1 event), nasopharyngitis (2 events), back pain (1 event), and polymenorrhea (1 event). One adverse drug reaction (allergic dermatitis) with a causal relationship to the study drug was reported (1.4%, 1/69 patients). This event occurred on Day 1 after administration of the study drug and resulted in withdrawal of that subject from further participation. The patient had fully recovered by Day 7, without any treatment.

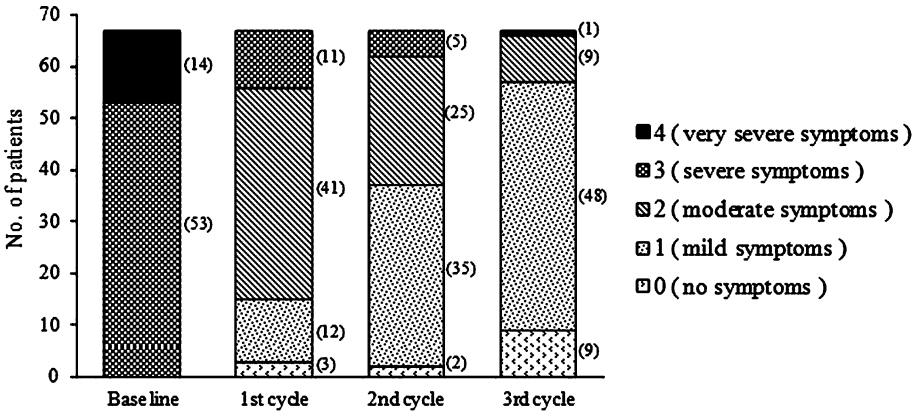

Fig. 3 Variations in physician's global assessment scores. Physicians assessed the symptoms of premenstrual syndrome using a categorical scale of "score 0: no symptom" to "score 4: the symptom is very severe", based on the impression from Day −3 to Day −1 at baseline and at each menstrual cycle during the treatment period

DISCUSSION

This is the first study reporting the efficacy and safety of VAC extract in Japanese patients with PMS. We put primary emphasis on confirmation of the similarity of the findings obtained in a European study [13, 14] and in the Japanese population.

In the present study, the administration of VAC extract resulted in a dramatic and statistically significant decrease in the total VAS score. Further, the VAC extract successfully improved each of the ten individual symptoms investigated. These results are similar to the previous trials that VAC extract showed superior decrease of six individual symptoms (irritability, mood alteration, anger, headache, bloating, breast fullness) [13] and five symptoms as irritability, mood alteration, anger, headache and breast fullness [14], compared to placebo, respectively.

The mean PGA score had diminished at the first menstrual cycle after the commencement of intervention, and decreased further as the treatment period progressed. In addition, the responder rate among the Japanese patients was 91.0% after treatment for three menstrual cycles. The results were consistent with those of a European study (81%), where a statistically significant difference was observed between the VAC-treated and placebo groups [13]. Hence patient self-assessment VAS determination and physician's own evaluation were improved simultaneously in the current study; the reliability of the subjective symptoms was corroborated by objective assessment by physician.

Treatment with VAC extract for the relief of PMS symptoms was well tolerated in Japanese patients. All adverse events were deemed either mild or moderate. Allergic dermatitis was the only adverse event of which a causal relationship with the study drug was not ruled out. It was probably caused by drug hypersensitivity, as the event occurred shortly after administration. Hypersensitivity with VAC extract is documented in the community herbal monograph [6], thus this adverse drug reaction is not specific to Japanese patients. Given the above-mentioned considerations, there appears to be no obvious discrepancies in the safety profile of VAC extract in terms of severity and frequency of adverse events between the Japanese and the European populations.

With regard to study design, the present study employed the DSM-III-R criteria for diagnosis of PMS, because one aim of the study was to compare its results with those of previous studies [13–15]. With regard to the duration of intervention, we selected a period of three menstrual cycles based on the findings that administration of VAC markedly alleviated PMS symptoms during a treatment period of three menstrual cycles, and the effect remained for the following three menstrual cycles after cessation of treatment [15]. The treatment period was sufficient to demonstrate the efficacy of VAC extract in Japanese patients.

With regard to the mechanisms of action, the pharmacological mechanism by which VAC extract relieves the symptoms of PMS remains unclear. VAC extract may activate the dopamine D_2 receptor [7–9], resulting in the inhibition of prolactin secretion, which may be related to menstrual abnormality, anovulation, and PMS in non-lactating women [10]. Although the present study did not measure prolactin levels, Berger et al. [15] reported that VAC did not affect the level of prolactin in patients with PMS. In contrast, it has been reported that VAC significantly reduced prolactin levels in patients with latent hyperprolactinemia [19]. We suggest that it is important to elucidate the effect of VAC on prolactin levels in PMS patients. Other possible mechanisms of action include an increase in melatonin secretion, and binding activity of flavonoids contained in VAC to the beta estrogen receptor [20].

Several limitations should be considered when interpreting the results of the present study. One is that patient bias could have contributed to the improvements reported, in part because the present study was conducted in an open-label manner without any control group, and in part because the study targeted patients with a psychosomatic medical disease, i.e., PMS. However, we predict that VAC extract will prove superior to placebo in Japanese patients with PMS, for a number of reasons. Firstly, two previous placebo-controlled trials have reported that the responder rates for placebo and VAC were 11% versus 81% [13] and 24% versus 52% [14], respectively, after treatment periods of three menstrual cycles. In addition, the responder rate for VAC in the present study was 91.0% at the third menstrual cycle after the commencement of intervention. Taking these results into consideration, the responder rate in the present study was similar to that of the above-mentioned studies; VAC demonstrated robust effectiveness. Secondly, in the afore-mentioned placebo-controlled trials, the changes in the total VAS scores of placebo and VAC groups were −32.5 versus −211.1 [13] and −78.1 versus −128.5 [14] after treatment for three cycles. In the present study, the total VAS score had diminished by 166.5 after the third menstrual cycle. Although we did not examine the effect of placebo in the present study, we consider that these results are supportive of the effectiveness of VAC extract for the alleviation of PMS symptoms.

Another limitation of the study is that the sample size was small, which can lead to a failure to detect infrequent adverse events. Studies with larger groups of patients are needed to enable more meaningful conclusions with regard to the clinical benefit of VAC extract in Japanese PMS patients.

CONCLUSION

The present study established evidence that in the Japanese population, treatment with Prefemin® containing 20 mg of VAC extract for three menstrual cycles was effective and well

tolerated in patients with PMS, as has been reported in European studies.

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Conflict of interest. Mikio Momoeda has received consulting fees from Zeria Pharmaceutical Co., Ltd. Kazunori Ochiai has received consulting fees from Zeria Pharmaceutical Co., Ltd. Hidetaka Sasaki is an employee of Zeria Pharmaceutical Co., Ltd. Eiko Tagashira is an employee of Zeria Pharmaceutical Co., Ltd. Masayuki Ogishima is an employee of Zeria Pharmaceutical Co., Ltd. Yuichi Takano is an employee of Zeria Pharmaceutical Co., Ltd.

Compliance with ethics guidelines. This study was approved by the institutional review board of Yoshii Chuo Shinryojo, Gunma, Japan. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 and 2008, and Good Clinical Practice guidelines. Informed consent was obtained from all patients for being included in the study.

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