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The Efficacy and Safety of a Chinese Herbal Product (Xiao-Feng-San) for the Treatment of Refractory Atopic Dermatitis: A Randomized, Double-Blind, Placebo-Controlled Trial

Hui-Man Cheng[a, b] Leih-Chin Chiang[a] Ya-Min Jan[a] Guang-Wei Chen[b] Tsai-Chung Li[b]

[a]Department of Integration of Traditional Chinese and Western Medicine, China Medical University Hospital, and [b]School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan, ROC

Key Words
Atopic dermatitis · Traditional Chinese medicine · Randomized controlled trial

Abstract
Background: Severe and widespread atopic dermatitis often fails to respond adequately to topical steroids and oral antihistamines and requires immunomodulatory drugs which, although effective, have undesirable toxic effects. ***Methods:*** In this prospective, randomized, double-blind, placebo-controlled trial, 71 patients with severe intractable atopic dermatitis were given an 8-week treatment with oral Xiao-Feng-San (XFS; 47 patients) or placebo (24 patients). Total lesion score, erythema score, surface damage score, pruritus score and sleep score were measured at 4-week intervals. ***Results:*** Fifty-six patients completed both the treatment and follow-up periods. The decrease in the total lesion score in the treatment group at 8 weeks was significantly greater than that of the placebo group (79.7 ± 5.8% vs. 13.5 ± 7.64%; $p < 0.001$). There was also a statistically significant difference between the treatment and placebo groups with regard to erythema, surface damage, pruritus and sleep scores. The difference between the 2 groups was still significant for all outcome measures except the erythema score at the 12-week follow-up, 4 weeks after the 8-week treatment had ended. Patients reported no side effects from treatment, although some commented on the unpalatability of the medication. ***Conclusion:*** Our study results suggest that the traditional Chinese herbal medicine XFS may be an alternative choice of therapy for severe, refractory, extensive and nonexudative atopic dermatitis.

Introduction

Atopic dermatitis is a chronic, relapsing, inflammatory skin disease that affects 10–20% of children and 1–3% of adults in industrialized countries [1, 2]. Topical emollients, corticosteroid creams and oral antihistamines are effective in controlling mild to moderate disease with minimal side effects. However, current treatments for severe and widespread disease (e.g. systemic steroids, azathioprine, cyclosporine, PUVA), although beneficial, all have undesirable adverse effects. As a re-

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Correspondence to: Dr. Hui-Man Cheng
Department of Integration of Traditional Chinese and Western Medicine
China Medical University Hospital, 2 Yuh-Der Road, Taichung 40447, Taiwan (ROC)
Tel. +886 4 2205 2121, ext. 1689, Fax +886 4 2236 7789
E-Mail hm.cheng@msa.hinet.net

Table 1. Composition of XFS herbal medicine

Medicinal plants	Weight ratio, mg	Family	Species	Actions
Saposhnikovia divaricata	2.5	Umbelliferae	*Saposhnikovia divaricata* (Turcz.) Schischk	relieves itching, relieves pain
Schizonepeta tenuifolia	2.5	Labiatae	*Schizonepeta tenuifolia* (Benth.) Briq.	relieves pain, relieves itching, anti-inflammatory
Angelica sinensis	2.5	Umbelliferae	*Angelica sinensis* (Oliv.) Diels	promotes blood circulation
Rehmannia glutinosa	2.5	Scrophulariaceae	*Rehmannia glutinosa* Libosch.	antipyretic, anti-inflammatory
Sophora flavescens	2.5	Leguminosae	*Sophora flavescens* Ait.	anti-inflammatory, relieves itching
Atractylodes lancea	2.5	Compositae	*Atractylodes lancea* (Thunb.) DC.	harmonizes water metabolism
Cryptotympana pustulata	2.5	Cicadidae	*Cryptotympana pustulata* Fabricius	sedative, relieves itching
Linum usitatissimum	2.5	Pedaliaceae	*Sesamum indicum* L.	moistens
Anemarrhena asphodeloides	2.5	Liliaceae	*Anemarrhena asphodeloides* Bunge	sedative, anti-inflammatory
Gypsum fibrosum	2.5	Gypsum	*Gypsum fibrosum:* $CaSO_4$, $2H_2O$	anti-inflammatory
Clematis armandii	1.25	Ranunculaceae	*Clematis armandii* Franch.	harmonizes water metabolism
Glycyrrhiza uralensis	1.25	Leguminosae	*Glycyrrhiza uralensis* Fisch.	antitoxic, sedative, protects digestive system
Arctium lappa	2.5	Compositae	*Arctium lappa* L.	antibacterial, relieves itching

sult, there have been intensive efforts to develop better and safer treatment. One such treatment is the use of traditional Chinese medicine.

Although traditional Chinese medicine is widely used in many Asian countries, its beneficial effects in patients with atopic dermatitis have not been consistently demonstrated, and undesirable side effects have been noted [3, 4]. A recent Cochrane Review of Chinese herbal medicine for atopic dermatitis [5] found only 4 randomized controlled trials that met the Cochrane inclusion criteria, and these trials were all for a herbal mixture that is no longer being manufactured. Xiao-Feng-San (XFS) is a common Chinese herbal preparation, composed of 12 herbs, which is used to treat patients with atopic dermatitis in Asian clinical practice. The purpose of this study was to evaluate the efficacy and safety of XFS in atopic dermatitis, using a randomized, double-blind, placebo-controlled study design.

Methods

Patient Selection

Seventy-one Chinese patients with refractory atopic dermatitis, diagnosed by recognized clinical criteria [6], were recruited from the department of Integration of Traditional Chinese and Western Medicine, China Medical University Hospital, Taiwan. The study received approval from the Institutional Review Board of the China Medical University Hospital, and all patients gave written informed consent.

Inclusion criteria were the following: extensive (not limited to the skin folds and covering >20% of the body surface area) lichenified or erythematous papules or plaques of atopic dermatitis, no active exudation or infection and poor response to conventional treatment (topical steroids and oral antihistamines).

Patients were excluded if they had secondary bacterial infections or had received oral or intravenous steroid treatment, antibiotics, phototherapy or other immunosuppressive therapies (such as cyclosporine or azathioprine) in the previous 2 months. Other exclusion criteria were abnormal liver enzymes or kidney function tests (1.5 times higher than the upper normal limit), abnormal blood chemistry, concurrent systemic illness (except asthma or allergic rhinitis), current breastfeeding and pregnancy or the intention of becoming pregnant. In addition, all women of childbearing age agreed to take appropriate contraceptive precautions.

Patients were required to have normal full blood counts and renal and hepatic function tests before starting the study. They also answered questionnaires with regard to their age, sex, height, weight, disease progress, personal allergy, family allergy, past treatments and exacerbating factors, among others. Patients were asked to maintain their current diet and dermatological treatments (in particular, not to increase the potency or frequency of topical corticosteroid use) throughout the trial. Topical steroids were used with the same frequency and strength during the study and prior to the study in both groups.

Randomization and Blinding

Eligible patients were randomized at a ratio of 2:1 to receive XFS or placebo for an 8-week treatment period. The computer-generated randomization list was drawn up by an independent statistician and placed in an envelope until the study was completed. Eligible patients were assigned consecutive randomized numbers as they entered the study. Patients and the evaluating physicians were unaware during the study of whether the medication taken by the patients was placebo or the treatment drug.

XFS and Placebo Preparation and Dosage

XFS, the active treatment, consisted of a standardized formulation of plant materials in widespread use in China (table 1). The powder was manufactured, packaged and labeled by the Sheng Chang Pharmaceutical Company (Taiwan), using good manufacturing practice standards. The optimal composition of each herb included was standardized prior to manufacturing. The powder

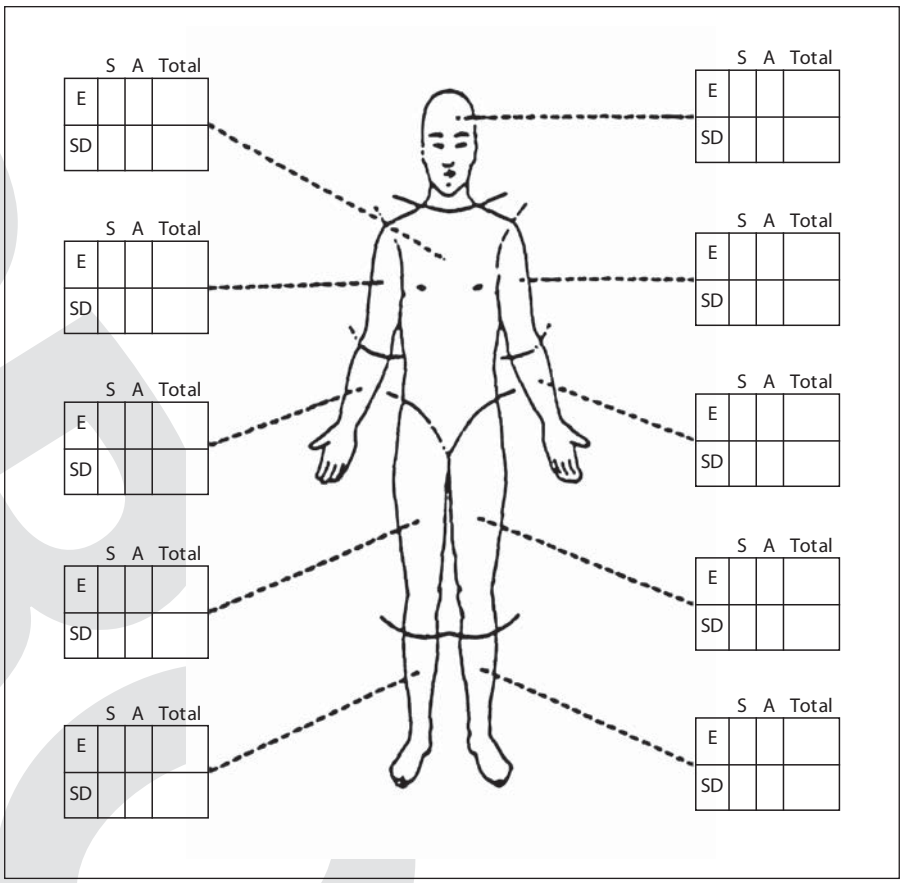

Fig. 1. Standardized disease scoring system used. E = Erythema; SD = surface damage; S = severity; A = area.

was formulated into uniform dose packets under the supervision of the Clinical Trials Section, China Medical University Hospital, according to established procedures. All materials were checked before use for heavy metal content and for possible microbial contaminants. Thin-layer chromatography was used to 'fingerprint' each batch of every constituent, and batches were rejected (about 10%) if they differed substantially from the reference material.

Patients took the medicine 3 times a day, and the number of packs taken differed according to the enrollee's age. Those 3–7 years of age took 1 pack, those 8–12 years of age took 2 packs and those aged 13 and over took 3 packs at each dosing point. There were 3 g of XFS concentrated particles or placebo in each pack. Placebo was made of caramel, lactose and starch at a ratio of 2:1:1 and put into identical-appearing 3-gram packs. The placebo mixture has no known benefit in atopic dermatitis but has a similar appearance and taste to the active treatment.

Patients were instructed to take the medicine by mixing it in a cup with 120 ml of warm drinking water and then drinking the mixture.

Assessment

Patients were randomly assigned to the treatment or control group. They took the herbal treatment or placebo daily for 8 weeks and were assessed at the beginning of the study and after 4, 8 and 12 weeks. The following investigations were performed during each assessment: full blood count, serum bilirubin, aspartate aminotransferase, alkaline phosphatase, albumin, urea and electrolytes, creatinine, calcium, phosphate, glucose, creatine phosphokinase and immunologic markers (IgE, eosinophil count, eosinophil cationic protein, IL-5, IL-13). Blood pressure and weight were also measured and side effects were monitored.

The extent and severity of the dermatitis was assessed by quantitative measurement of erythema and surface damage (i.e. papulation, vesiculation, scaling, excoriation and lichenification) using a standardized scoring system [7, 8]. The body surface was divided into 20 roughly equal areas, and within each area, a score of 0 (none) to 3 (severe) for the degree of erythema and surface damage was given (fig. 1). For each of these clinical features, an estimate of the percentage of the area within each zone affected by that particular feature was measured; a score of 1 was given where the area affected was <33%, 2 where the area was between 34 and 66%, and 3 where the area was >67%. The sum of the severity scores multiplied by the area scores provided a total body score for each feature, the maximum score being 180.

Patients were asked to keep a daily diary during the study to record their compliance with treatment and any side effects. At each monthly visit, patients were asked to record the severity of itching (0 = no itching at all; 1 = slight itching; 2 = moderate itching; 3 = severe itching; 4 = very severe itching) and sleep disturbance (0 = no sleep interruptions; 1 = sleep interrupted 1 or 2

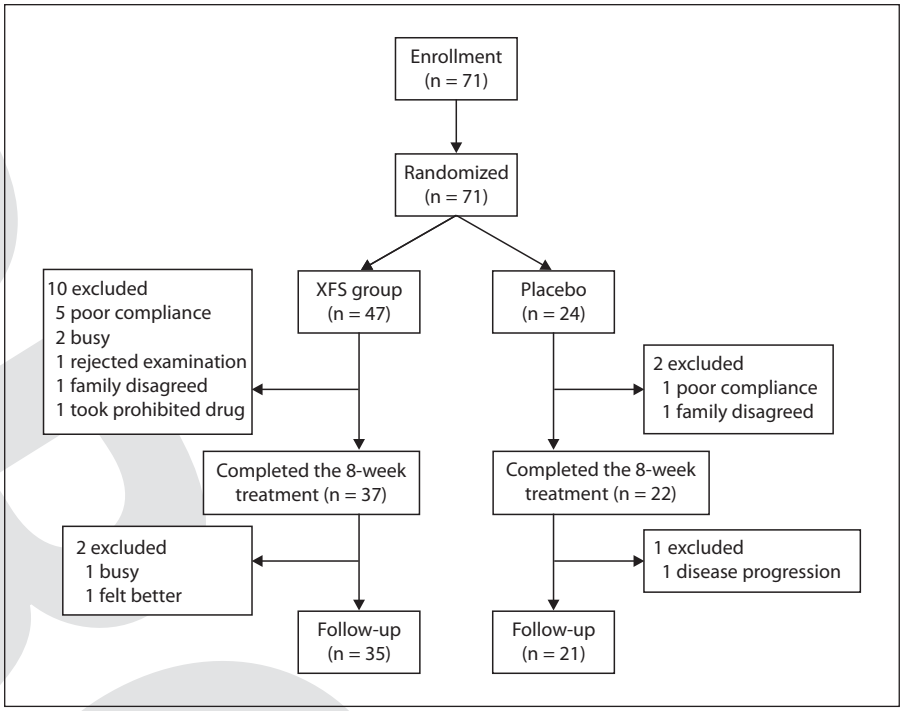

Fig. 2. Enrollment, randomization and treatment flowchart.

times; 2 = sleep interrupted 3 or 4 times; 3 = sleep interrupted more than 5 times; 4 = unable to sleep) and whether they had fewer episodes or less severe asthma than usual during that phase of the trial.

The protocol specified that patients who showed a persistent abnormality in blood chemistry, including increases in serum total bilirubin or liver enzymes >1.5 times the normal range, diastolic blood pressure persistently above 95 mm Hg or other complications believed to be due to treatment should be withdrawn from the study. Furthermore, patients who failed to comply with the protocol (a failure to take the treatment on more than 5 days in any 4-week period) or who were given systemic antibiotics or corticosteroids for any reason during the study were withdrawn.

Sample Size Determination

For the primary outcome, the clinical lesion score, a sample size of 67 subjects (45 for the XFS group and 22 for the placebo group) would provide a statistical power of 80% to detect a mean difference of 40.

Statistical Analysis

Continuous data are presented as means ± SD, and the two-sample t test was used for comparisons. When the hypothesis of normal distribution was violated, the Mann-Whitney U test was adopted. Categorical data are presented as numbers of patients (percentages) and were compared with Fisher's exact test.

The primary outcome, clinical lesion score, was the total of the erythema score plus the surface damage score. There were 4 secondary outcomes: erythema score, surface damage score, pruritus score and sleep score. All efficacy endpoints were defined as the mean improvement from baseline. Because the sleep score at baseline showed a borderline nonsignificant difference between the 2 treatment groups, analysis of covariance was used to adjust the baseline sleep score for efficacy analysis. The mean score improvement is presented as the least-squares mean ± SE. Statistical assessments were two-sided, and the 0.05 level was considered statistically significant. Statistical analyses were performed using SPSS 15.0 statistics software (SPSS Inc., Chicago, Ill., USA).

Results

Patients

Seventy-one patients were enrolled in this study, and 47 and 24 patients were randomly divided into the XFS group and placebo group, respectively. Two patients (1 in the XFS group, 1 in the control group) who were not treated with any investigational drugs were dropped from the study at baseline (week 0), so that a total of 69 patients (46 in the XFS group, 23 in the placebo group) were included in the intention-to-treat population.

During the 8-week treatment period, 10 patients (9 in the XFS group and 1 in the placebo group) were excluded from the per-protocol population due to poor compliance (5 in the XFS group and 1 in the placebo group), refusal to continue treatment (in the XFS group, 2 were too busy, 1 was afraid to have blood drawn) and use of a prohibited drug (1 in the XFS group).

Table 2. Demographic and baseline characteristics for the intention-to-treat population

Variable	Total (n = 69)	XFS (n = 46)	Placebo (n = 23)	p value
Age[a], years	13.1 (8.4, 22.6)	12.2 (8.1, 23.2)	13.6 (10.8, 19.5)	0.706
Gender[b], male	37 (52.1)	25 (53.2)	12 (50.0)	1.000
Height[a], cm	154.3 (127.0, 168.0)	149.5 (126.0, 168.0)	158.0 (144.5, 166.5)	0.415
Weight[a], kg	45.5 (26.0, 58.0)	40.0 (25.0, 57.0)	50.0 (35.5, 64.0)	0.172
BMI[a]	18.9 (16.5, 22.1)	17.5 (16.3, 21.0)	20.1 (17.3, 23.5)	0.077
Age at onset[a], years	4.0 (1.0, 12.0)	3.0 (1.0, 8.0)	7.0 (0.0, 12.5)	0.809
Duration of illness[a], years	7.1 (4.4, 12.7)	8.4 (4.4, 15.5)	6.7 (2.4, 11.6)	0.263
Clinical lesion score[a]	129.0 (90.0, 160.0)	142.0 (90.0, 166.0)	120.0 (90.0, 158.0)	0.461
Erythema score[a]	42.0 (28.0, 60.0)	42.0 (28.0, 64.0)	44.0 (24.0, 60.0)	0.730
Surface damage score[c]	88.4 ± 36.5	90.5 ± 36.1	84.0 ± 37.7	0.487
Pruritus score[a]	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 4.0)	0.808
Sleep score[a]	1.0 (1.0, 2.0)	1.5 (1.0, 3.0)	1.0 (0.0, 2.0)	0.050[d]

[a] Data presented as median (interquartile range); the Mann-Whitney U test was used to compare the difference between the 2 treatment groups.
[b] Data presented as number of patients (percentage); Pearson's χ^2 test was used to compare the difference between the 2 treatment groups.
[c] Data presented as mean ± SD; the two-sample t test was used to compare the difference between the 2 treatment groups.
[d] There was a borderline nonsignificant difference in sleep scores between the XFS and placebo groups.

After the treatment period (week 8), 1 patient in the XFS group felt better and refused to continue the trial and a second patient in the XFS group was too busy to continue the trial. One patient in the placebo group was discontinued due to disease progression. Fifty-nine of the patients (83%) completed the treatment period, and 56 (79%) completed the entire study period. This information is summarized in the flowchart shown in figure 2.

Table 2 shows the baseline characteristics for the intention-to-treat population of the 2 treatment groups. There was no significant difference between the 2 treatment groups with regard to baseline characteristics. However, there was a borderline nonsignificant difference in the sleep scores [median (interquartile range): 1.5 (1.0, 3.0) for XFS vs. 1.0 (0.0, 2.0) for placebo].

Efficacy

Efficacy outcomes are shown in table 3 and figure 3. At the end of the 8-week treatment period, the primary endpoint, mean improvement in the total clinical lesion score, was significantly higher in the XFS group than in the placebo group (least-squares mean ± SE with adjustment for baseline sleep scores: 79.10 ± 5.70 vs. 13.50 ± 7.56; $p < 0.001$). The 4 secondary endpoints (erythema score, surface damage score, pruritus score and sleep score) all also showed significantly greater improvement in the XFS group than the placebo group ($p < 0.001$ for all comparisons; table 3). In addition, 4 weeks after termination of the treatment, the mean improvement in the clinical lesion score in the XFS group was still significantly higher than that of the placebo group ($p < 0.05$). Significantly better scores in the XFS group were also

Table 3. Improvement in scores between baseline and week 8

Index	XFS (n = 46)	Placebo (n = 23)	p value
Improvement in clinical lesion score	79.10 ± 5.70	13.50 ± 7.56	<0.001*
Improvement in erythema score	25.70 ± 3.33	4.10 ± 4.41	<0.001*
Improvement in surface damage score	53.40 ± 3.96	10.30 ± 5.25	<0.001*
Improvement in pruritus score	1.30 ± 0.15	0.20 ± 0.20	<0.001*
Improvement in sleep score	0.80 ± 0.10	0.00 ± 0.13	<0.001*

Data are presented as least-squares means ± SE. Analysis of covariance was used to compare the difference between the 2 treatment groups, with baseline sleep score adjustment. There were 5 missing values in the XFS group and 1 missing value in the placebo group. * $p < 0.05$: significant difference between the XFS and placebo groups.

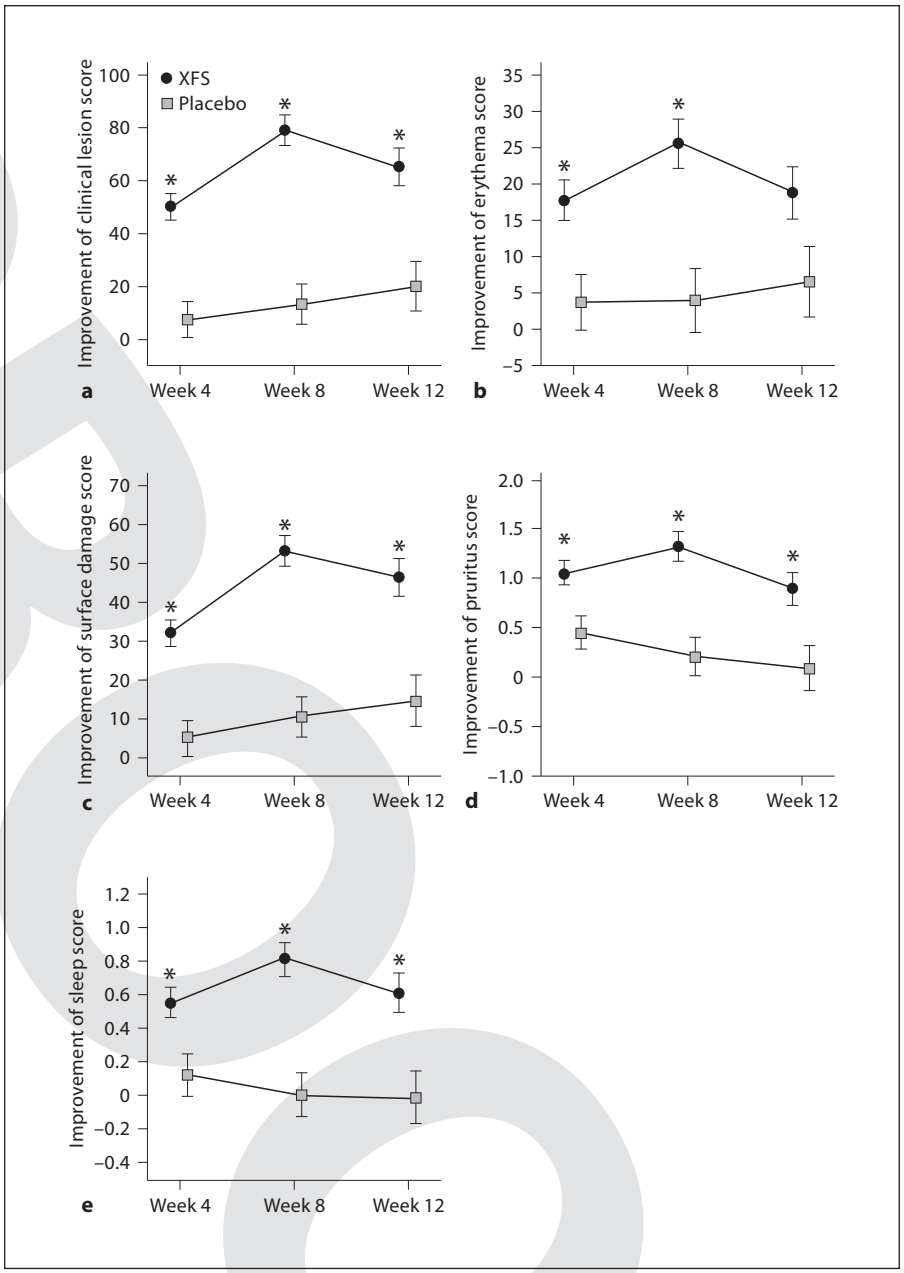

Fig. 3. Score improvement from baseline to weeks 4, 8 and 12. **a** Clinical lesion score. **b** Erythema score. **c** Surface damage score. **d** Pruritus score. **e** Sleep score. * $p < 0.05$.

seen at 12 weeks for surface damage, pruritus and sleep scores (fig. 3).

The immunologic markers, IgE, eosinophil count, eosinophil cationic protein, IL-5 and IL-13, were above the normal range at baseline. Eleven patients had intrinsic atopic dermatitis (serum IgE <165 IU/ml). However, there were no statistical differences in immunologic markers between the active treatment and placebo groups during the 8-week treatment period (table 4).

Safety Profile

No abnormalities were detected in the patients' blood chemistry or renal function tests at any time. Transient elevation of aspartate aminotransferase was noted in 1 patient, but this was reversed within 8 weeks of stopping treatment. Two patients in the active group complained of gastrointestinal upsets, including abdominal colic and dyspepsia, in the first week. This side effect was transient. There was no change in blood pressure or weight.

Table 4. Immunologic markers before and after treatment

		XFS (n = 46)	Placebo (n = 23)	p value
IgE, [redacted]	baseline	1,764.7 (348.8, 4,127.5)	1,522.4 (295.8, 4,796.0)	0.728
	week 8	2,090.0 (444.0, 4,945.0)	1,735.0 (334.0, 4,004.0)	0.548
Eosinophil count [redacted]	baseline	5.9 (4.1, 10.4)	8.0 (3.4, 10.6)	0.731
	week 8	6.7 (5.1, 11.5)	6.0 (4.6, 8.4)	0.358
ECP, [redacted]	baseline	21.6 (10.6, 45.0)	19.7 (14.0, 31.0)	0.791
	week 8	19.3 (11.7, 25.8)	17.9 (10.5, 22.8)	0.760
IL-5, [redacted]	baseline	53.0 (48.0, 65.5)	57.0 (47.0, 58.0)	0.783
	week 8	54.0 (50.5, 62.5)	51.0 (45.0, 58.0)	0.086
IL-13, [redacted]	baseline	1,925.5 (1,242.5, 2,720.0)	2,157.0 (1,133.0, 3,377.0)	0.625
	week 8	1,733.0 (1,054.0, 3,441.0)	2,261.0 (1,681.5, 2,866.0)	0.430

Data are presented as medians (interquartile range); the Mann-Whiney U test was used to compare the difference between the 2 treatment groups. ECP = Eosinophil cationic protein.

Concomitant Medications

There were 21 patients (45.7%) in the XFS group and 7 (30.4%) in the placebo group who took concomitant medications during the study period (p = 0.301); 12 patients (26.1%) in the XFS group and 4 (17.4%) in the placebo group took antihistamines (p = 0.550), and 12 patients (26.1%) in the XFS group and 5 (21.7%) in the placebo group had taken medications for colds (p = 0.774). No significant difference was found in concomitant medication usage between the 2 treatment groups.

Discussion

In this prospective, randomized, double-blind, placebo-controlled trial, XFS formula significantly lessened disease severity in patients with atopic dermatitis as well as the distressing symptoms of itch and sleep loss. These therapeutic effects persisted for 4 weeks after treatment was stopped.

Chronic atopic dermatitis, such as was seen in our patients, is thought to be a disorder involving cell-mediated immunity [9]. Although it is unclear by what mechanisms Chinese herbal preparations, which contain mixtures of herbal ingredients, act, a number of reports have been published showing the anti-inflammatory actions of single species. Some reports have demonstrated that the species *Schizonepeta tenuifolia* Briq. and *Saposhnikovia divaricata* (Turcz.) Schischk have significant anti-inflammatory effects [10, 11]. An aqueous extract of the steamed root of *Rehmannia glutinosa* dose-dependently inhibited the skin allergic reaction activated by anti-DNP IgE [12]. Polysaccharide isolated from *Angelica sinensis* has immunomodulatory activity by regulating the expression of Th1- and Th2-related cytokines [13]. Another study reports that polysaccharides isolated from *Glycyrrhiza uralensis* Fisch. have macrophage immunomodulatory activity [14].

Modulation of some part of the immune system is a likely explanation of the action of XFS, but it must be noted that in our study, serum levels of inflammatory markers were not changed by XFS administration. The exact mechanism of action of XFS formula is not known. Further investigations are needed to delineate the exact biological mechanisms of XFS formula.

It has been reported that the use of some Chinese herbal preparations has resulted in serious adverse systemic effects such as liver toxicity and dilated cardiomyopathy [15–17]. However, XFS, as used in this study, was found to be quite safe. Transient elevation of aspartate aminotransferase was noted in 1 patient, but this was reversed within 8 weeks of stopping treatment. We did not detect any hematologic or biochemical abnormalities in our patients. Complete blood chemistry and renal function were all normal throughout the entire treatment period.

The lack of pharmacokinetic and pharmacodynamic data for the XFS formula is a limitation in understanding the mechanism of action of the drug.

Although the mechanism of action of XFS formula in the treatment of atopic dermatitis still needs to be explored, our studies showed that XFS formula was able to effectively improve lesion scores, pruritus symptoms and

sleep conditions. There were no obvious adverse events noted during the intervention period. The results of this study suggest that XFS formula can be a useful treatment for patients with recalcitrant atopic dermatitis. However, additional randomized, controlled trials with adequate sample sizes need to be conducted to corroborate our findings.

Acknowledgements

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