Effects of Kampo medicines on atopic dermatitis and complement system

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Abstract

Kampo medicines have been shown to be effective treatment for AD at levels significant enough to justify substituting them for steroid agents. Furthermore, as no adverse side effects have been detected in patients treated with Kampo medicines, Kampo medicines stand, not only as a viable alternative to steroid agents, but as a great improvement on steroids in the treatment of AD. These results are particularly noteworthy given that no previous reports, to date, have demonstrated this dramatic recovery of serum CH50 titier count from less than normal to normal ranges in AD patients, through treatment with Kampo medicines. Sho-saiko-to, Sho-fu-san, Oren-gedoku-to, and Keishi-bukuryo-gan (applicable only to the oketsu group) were administered to 1531 subjects diagnosed with atopic dermatitis at various levels of severity. Results of the treatments were as follows; 52% of the subjects were assessed as showing "excellent" improvement (improvement within three months), while 41% were assessed "good" (showing improvement with six months), 4% were assessed "fair" (showing improvement within one year), and 2% were assessed "poor" (taking more than one year to show improvement). 0.2% of the subjects were assessed as showing an adverse response to the treatment (suffering from acute eczematization). Whereas the average serum CH50 titer count of all AD patients was lower than normal, 35% of the patients had a less than normal CH50 titier count before therapy began. Those patients in the less than normal group showed a continual increase in serum CH50 titer levels throughout the first six months of therapy with Kampo medicines, reaching the normal range around the six months point.

Key words Atopic dermatitis, complement system, Sho-saiko-to, Shofu-san, Oren-gedoku-to, Keishi-bukuryo-gan, Oketsu.

Abbreviations Ss, Sho-saiko-to; Sf, Shofu-san; Og, Oren-gedoku-to; Kb, Keishi-bukuryo-gan.

Introduction

We reported to have attained effective treatment for bronchial asthma with Kampo medicines, Sai-boku-to,[1,2)] and now our patients of bronchial asthma (approximately 500 patients per year) are quite well controlled without administration of steroid agents. On the other hand, reports of cases of protracted atopic dermatitis (AD) have been increasing in Japan. Under such a situation, we have been trying to control atopic dermatitis with Kampo medicines.

Currently, steroid treatment is generally given to AD patients without dietary control, but a long course of steroid therapy has been controversial because of severe adverse reactions such as bacterial, viral and fungal infections, vascular dilatation, thinning and discoloring of the skin and even cataracts. Therefore,as Kampo medicines have been shown to be effective in the treatment of bronchial asthma, an allergic disease, it

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would likely be an effective treatment for AD, as well. It would further be expected that side effects from Kampo medicines would be minimal.

In our previous report, we showed that Kampo medicines had been effective in the treatment of AD in both children and adults[3, 4] and also increased the serum complement titer count CH50.[5] The present report further investigates the effects of Kampo medicines on AD and complement titer with a larger number of subjects and for a longer term of therapy.

Materials and Methods

Patients: Infants, children, adolescents and adults with atopic dermatitis without any other complications were undertaken as subjects in this study. At the beginning of the therapy, the presence of "oketsu", Chinese pathological concept and diagnosis by craniocervical dark redness and lingual telangiectasia, was assessed according to craniocervical dark redness and lingual telangiectasia.

Medication: The combination of Sho-saiko-to (Ss), Shofu-san (Sf)and Oren-gedoku-to (Og), which are commercially available, was orally administered to children and adults without oketsu. Keishi-bukuryo-gan (Kb) was included only in the administration to adolescents and adults with oketsu. Adolescents and adults were given three doses a day. The dose for children was determined in proportion to body weight.

External treatment: In general, a non-steroid anti-inflammatory agent cream or ointment, and sometimes anti-fungal agent cream or purified vaseline was cutaneously applied to skin lesions instead of steroid agents.

Assay: Serum complement titer, CH50, was assayed by the Meyer method. C3 and C4 were assayed by the Leatherneferrometry (LN) method. Examinations were carried out on 456 patients with AD and 142 patients with cutaneous fungal infection at the beginning of therapy, and then, every three months for a year. Cutaneous fungal infection was diagnosed by ruling out AD on the base of Hanifin's criteria,[6] (e.g., IgE level and the count of eosinophils), and the positive RAST score of egg whites, cow milk, soy beans, rice, wheat, sesame, buck wheat, dog dandruff and cat skin. However, AD could not be ruled out on the basis of a positive RAST score for candida.

Assessment of symptomatic severity and improvement: Symptomatic severity was assessed mainly by distribution and pruritus of skin lesions at the beginning of therapy. Patients were assessed "severe" when they had facial and extensor skin lesions with eczematous or lichenoid morphology and had such severe pruritus that sleep was disturbed. Patients whose sleep was not disturbed were assessed "moderate". Patients who had only the flexural skin area affected were assessed "mild". Improvement was judged as "excellent" When skin lesions disappeared within three months, "good" within six months,"fair" within one year, and "poor" when it took more than a year for lesions to disappear and "adverse" when lesions eczematized.

Results

1. Efficacy of Kampo medicine: Effectiveness of Kampo medicines on AD with three degrees of severity is shown in Table I. 565 patients (37%) were assessed severe, 661 patients (43%) were assessed moderate, and 305 patients (20%) were

Table I Effectiveness of Kampo medicines on atopic dermatitis.

	excellent	good	fair	poor	adverse	total
severe	311(55%)	219(39%)	25(4%)	9(2%)	1(0%)	565
moderate	299(45)	323(49)	23(3)	15(2)	1(0)	661
mild	185(61)	92(30)	18(6)	9(3)	1(0)	305
total	795(52)	634(41)	66(4)	33(2)	3(0)	1531

assessed mild. The total number of patients was 1531. Excellent improvement was observed in 795 patients (52%), moderate, in 634 patients (41%), fair, in 66 patients (4%), poor, in 33 patients (2%), and adverse, in 3 patients (negligible). There was a higher percentage of excellent improvement in the severe group than in the moderate group, perhaps because of the difference in physical constitution, namely the presence or absence of oketsu, and the difference of medication. Two thirds of the severe group had oketsu and oketsu patients were given the additive medication of Kb, which was reported to have anti-telangiectatic effects.

2. Serum complement : CH50 titer was assayed in 456 patients (52 infants, 89 children, 152 adolescents, and 163 adults) at the beginning of therapy. The results are shown in Table II. For patients categorized as having a less than normal serum titer count (<29 units), there was no remarkable difference in serum titer count between age groups. The average percentage of less than normal titer in total 456 patients was 35%.

3. The correlation of CH50 titer count and severity is shown in Fig. 1. No remarkable difference of titer level was observed between groups based on different levels of severity or on age.

4. Values of CH50, C3 and C4 in AD and fungal infection are shown in Table IIIa and IIIb. One hundred fifty eight patients out of 456 AD

Table II Serum CH50 titer levels in atopic dermatitis patients by age group.

		normal	less than normal
A	Infants (n=52)	37(71%)	15(29%)
B	Children (n=89)	59(66)	30(34)
C	Adolescents (n=152)	96(63)	56(37)
D	Adults (n=163)	106(65)	57(35)
E	C+D (n=315)	202(64)	113(36)
Total	A+B+C+D (n=456)	298(65)	158(35)

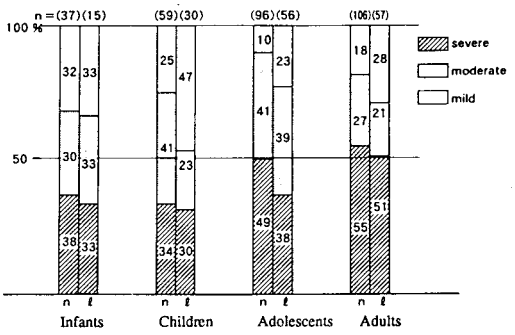

Fig. 1 Comparison of serum CH50 titer levels of each age group.
n : normal group
l : less than normal group

Teble IIIa The average of CH50 titer, C3 and C4 levels in atopic dermatitis patients.

	CH50 (37.4±4.0 unit/ml)	C3 (70.0±10.0 mg/dl)	C4 (25.0±5.0 mg/dl)
A. Infants (n=52)	30.6±2.4*	68.9±5.2	24.2±2.0
B. Children (n=89)	30.6±2.1*	70.7±4.6	23.4±1.8
C. Adolescents (n=152)	30.5±1.7**	67.3±3.7	23.1±1.5
D. Adults (n=162)	30.6±1.6**	65.2±3.5	23.9±1.4
E. C+D (n=315)	30.6±1.2**	66.1±2.5	23.5±1.0
F. A+B+C+D (n=456)	30.6±0.9**	67.5±2.0	23.6±0.8

*represents $p<0.01$, **represents $p<0.001$

Table IIIb Serum CH50 titer, C3 and C4 levels in atopic dermatitis and cutaneous fungal infection patients.

	CH50*		C3**		C4**	
	normal	less than normal	normal	less than normal	normal	less than normal
Atopic dermatitis	298(65%)	158(35%)	442(97%)	14(3%)	431(95%)	25(5%)
Oketsu(+)	147(68)	70(32)	209(96)	8(4)	210(97)	7(3)
Oketsu(−)	71(56)	55(44)	119(96)	5(4)	113(91)	11(9)
Fungal infection	80(55)	62(45)	132(94)	9(6)	122(87)	19(13)

* CH50 was represented by units/ml.

** C3 and C4 were represented by mg/dl

patients had a less than normal titer of CH50. Of the total number of AD patients, there was no remarkable difference between the less than normal groups based on the presence or absence of oketsu. There was similarly no difference between the AD and cutaneous fungal infection groups. Both serum C3 and C4 levels were not significantly lower in AD.

5. CH50 titer change in AD through therapy is shown in Fig. 2. At the beginning of therapy, the mean value of 231 patients with a normal serum titer count was 33.5 units and that of 129 patients with less than normal serum titer count was 25.8 units. While the normal group showed no significant change for 12 months, the less than normal group showed a significant (evaluated by paired t-test) increase in serum titer count approximating that of the normal range, in six months.

On the other hand, as shown in Fig. 3, there was no remarkable change in the oketsu group (217 patients), or in the non-oketsu group (126 patients). The antioketsu agent, Kb, may not

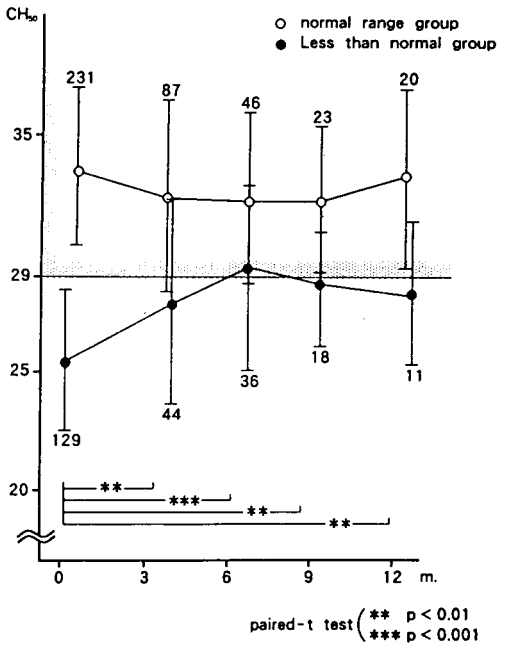

Fig. 2 Profiles of serum CH50 titer levels in atopic dermatitis patients comparing normal and less than normal groups throughout treatment with Kampo medicines.

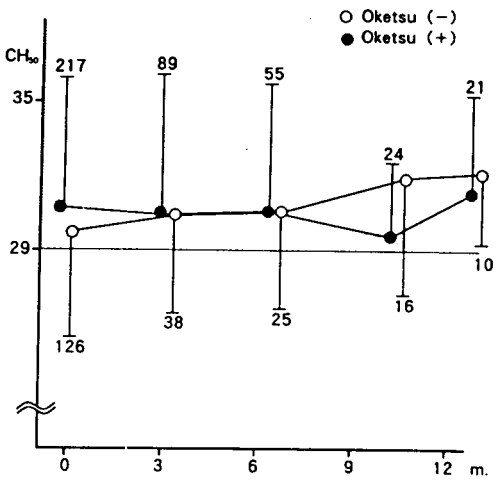

Fig. 3 Profiles of serum CH50 titer levels in atopic dermatitis patients comparing with and without Oketsu throughout treatment with Kampo medicines.

Oketsu (−) indicates treatment with Ss, Sf and Og.
Oketsu (+) indicates treatment with Ss, Sf,Og and Kb.

contribute to increase CH50 titer count in AD.

Discussion

As previously reported, there have been several projects aiming to control bronchial asthma with the Kampo medicines, Sai-boku-to. Results of these projects have shown the medicines to have high efficacy. Therefore, in our clinic we are less troubled by the problem of controlling bronchial asthma than by the lack of symptoms severe enough (e.g., status asthmaticus) to warrant admitting a patient into the hospital. A related concern regards extremely adverse side-effects suffered by patients during and following treatment with steroid agents.

The high incidence of AD reported in Japan suggests a long-term prevalence of the disease in this country. Due to the large number of AD cases, many research projects have been carried out in recent years focusing on the control of AD. Currently, the most commonly employed treatment of AD is steroid agent administration, except in cases when AD can be treated solely with dietary control. Adverse reactions to steroid agents (e.g., various kinds of cutaneous infections and vascular dilatation) leave important problems which remain to be resolved.

Kampo medicines, on the other hand, have been shown to be effective treatment for AD at levels significant enough to justify substituting them for steroid agents. Furthermore, as no adverse side-effects have been detected in patients treated with Kampo medicines, Kampo medicines stand, not only as a viable alternative to steroid agents, but as a great improvement on steroids in the treatment of AD.

Kapp reported in 1985 that serum C3 and C4 levels in AD increased.[7] On the other hand, Chiarelli reported in 1987 that C3 levels decreased, but C4 levels were not significantly altered.[8] We obtained different results from our previous reports that serum CH50 titer count, C3 and C4 levels tend to decrease together.[5] The present report establishes that the average serum CH50 titer count of all AD patients was lower than the normal range and was at less than normal levels in at least one third of all patients treated. However, a significant change was not observed in C3 and C4 levels.

These results are particularly noteworthy given that no previous reports, to date, have demonstrated this dramatic recovery of serum CH50 titer count from less than normal to normal ranges in AD patients, through treatment with Kampo medicines. Because C3 and C4 are constituents of serum CH50 titer, it may be inferred that either, or both, C3 and C4 would also increase through treatment with Kampo medicines. We hope to obtain precise data confirming this hypothesis in near future.

Conclusions

1. The Kampo medicines Sho-saiko-to, Sho-fu-san, Oren-gedoku-to and Keishi-bukuryo-gan (applicapable only to the oketsu group) were administered to 1531 subjects diagnosed with atopic dermatitis at various levels of severity. Results of the treatments were as follows: 52% of the subjects were assesed as showing "excellent" improvement (improvement within three months), while 41% were assessed "good" (showing improvement within six months), 4% were assessed "fair" (showing improvement within one year), and 2% were assessed "poor" (taking more than one year to show improvement), 0.2% of the subjects were assessed as showing an adverse response to the treatment (suffering from acute eczematization).

2. Whereas the average serum CH50 titer count of all AD patients was lower than normal, 35% of the patients had a less than normal CH50 titer count before therapy began. Those patients in the less than normal group showed a continual increase in serum CH50 titer levels throughout the first six months of therapy with Kampo medicines, reaching the normal range around the six month point.

和文抄録

漢方療法がステロイド療法に代るアトピー性皮膚炎に有効な治療法であるだけでなく，副作用も認め

られずより一層秀れた療法であることを報告する。また補体価低値群が漢方療法により正常値域に回復するという報告は未だない。小柴胡湯，消風散，黄連解毒湯それに瘀血患者には桂枝茯苓丸を追加する合方を種々の重症度の乳幼児，学童，思春期および成人の患者1531名に行ない，3ヶ月以内に改善された著効は52％，6ヶ月以内のそれを良好41％，1年以内をやや有効4％，1年以上要したのは2％，湿疹化などで中止したのは0.2％であった。補体価の平均値は低く，治療前に正常値域下の低値をとった患者は追跡調査し得たうちの35％に認められ，これらは6ヶ月後に正常値域内に回復することが認められた。

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