gaki Island, which is located to the south of the Japanese mainland. Since symptoms are known to become apparent during the first 5 years of life in 85% of children having AD [12], it is worthwhile determining the associated factors as well as the prevalence of AD in nursery school children.

Compared with other allergic disorders [13-17], the prevalence of rhinitis (3.3%) in Ishigaki Island was remarkably lower than in other reports (19.9-29.8%) [13, 14]. This is partially because in Ishigaki there is no Japanese cedar pollen which is one of the major aeroallergens for rhinitis in Japan; none of the children in Ishigaki had a specific IgE antibody for this antigen [9]. These data suggest that cedar pollen might be an important antigen not only in adults but also in nursery school children.

Both genetic factors [2] and environmental factors [6] are known to be involved in the etiology of AD. Contrary to previous reports [8, 18], parental history of AD was not related to AD among nursery school children in Ishigaki Island, and siblings' AD and maternal rhinitis were the only familial associated factors for AD. Environmental factors rather than genetic factors might have a critical effect on the occurrence of AD in Ishigaki Island. The lifestyle in Ishigaki Island is changing very rapidly; houses are increasingly made of concrete and steel instead of the traditional wooden houses, and more roads have been paved.

Past history of asthma and FA were significantly associated with AD in both univariate and multivariate studies. Although the prevalence of asthma and FA in students with AD varies among reports, a relatively high prevalence has been observed (asthma; 22.9-46.3% and FA; 9.5-51%) [14, 15, 19-22]. Similar levels of prevalence were also found in the present study. However, it was difficult to confirm this association due to the low prevalence of rhinitis in Ishigaki Island.

Previous studies showed that total IgE and some specific IgEs were associated with AD in univariate analysis [8, 9, 20]. However, in this study only the elevation of total IgE remained a significant associated factor in multivariate analysis. In addition, another report revealed that children having either long-term AD or newly developed AD had a higher serum total IgE level than normal children [10]. These results suggest that a high value for total IgE is an important associated factor as well as an indicator of continuous morbidity of AD. It should also be noted that elevated total IgE was not related to asthma, rhinitis or FA, although this trend is not consistent with findings from other studies [23, 24].

In conclusion, siblings' AD, personal history of asthma and FA, maternal rhinitis, and the elevation of total IgE were significantly related to AD in pupils on Ishigaki Island. A high total IgE level might be an AD-specific associated factor in this population. ■

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Excellent Clinical Results with a New Preparation for Chemical Peeling in Acne: 30% Salicylic Acid in Polyethylene Glycol Vehicle

TERUKI DAINICHI, MD, PHD,* SETSUKO UEDA, MD, PHD,† SHUHEI IMAYAMA, MD, PHD,‡ AND MASUTAKA FURUE, MD, PHD*

BACKGROUND Chemical peeling by salicylic acid in ethanol or another vehicle may be accompanied by stinging and burning followed by postinflammatory hyperpigmentation in the treated area, or salicylism. We have developed a new formulation: 30% salicylic acid in polyethylene glycol (SA-PEG). A topical application of SA-PEG remodels photodamaged skin in mice and humans, without systemic absorption.

OBJECTIVE The objective was to evaluate the safety and efficacy of SA-PEG for clinical use in the treatment of acne.

MATERIALS AND METHODS We evaluated the effects of the preparation histologically in mice and its safety and efficacy in 44 volunteers with normally aged skin and in 436 patients with acne.

RESULTS Histologic studies in animals showed no inflammatory changes in the skin following topical application of SA-PEG. Volunteers noted an improved skin texture. In the acne patients, the comedones and papules disappeared, resulting in an excellent outcome. There was a notable absence of stinging and burning, edema, bleeding, or crusting in the treated area.

CONCLUSION The SA-PEG preparation appeared to be safe and effective, with minimal associated inflammation or adverse effects, even in Asian patients who tend to develop hyperpigmentation or keloids. This preparation is thus ideal for chemical peeling.

The authors have indicated no significant interest with commercial supporters.

Because of its keratolytic and anti-inflammatory effects, salicylic acid (*ortho*-hydroxybenzoic acid) has been used at low concentrations for chemical peeling of the facial skin. There has been an increased interest and demand for this procedure, because patients with such conditions as acne, freckles, and wrinkles have obtained a satisfactorily rejuvenated or improved cosmetic appearance. However, salicylic acid and various other chemical peeling agents may cause stinging and burning in patients with acne. Recently, salicylic acid has been used to obtain a superficial wounding of the skin at the relatively high concentrations of 20% to 30% formulated in 95% ethyl alcohol,[1] utilizing its corrosive action on the skin. While cosmetically very effective, such high concentrations of salicylic acid in ethyl alcohol may cause stinging, burning, redness, and frosting (Figure 1) followed by crusting and pigmentation of the treated area.[1–3] Another problem, especially in Asian patients, is the residual hyperpigmentation that frequently develops after inflammation of the skin, which can adversely affect the clinical outcome.[3] Furthermore, application of salicylic acid to large areas of the skin, or repeated applications, can lead to absorption, which might cause salicylate intoxication.[4]

We previously developed a new formulation consisting of 30% salicylic acid in polyethylene glycol vehicle (SA-PEG).[5–7] The ability of SA-PEG to

*Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka; †Ueda-Setsuko Clinic, Fukuoka; ‡Department of Dermatology, Kyushu Medical Center, Fukuoka, Japan

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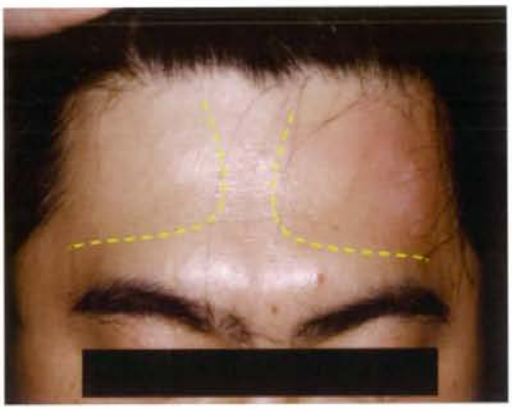

Figure 1. Cutaneous adverse effect of salicylic acid in ethanol vehicle. A 33-year-old healthy man received chemical peeling for 5 minutes with 30% salicylic acid in ethanol vehicle on his left forehead and with 30% SA-PEG on the right side in standard protocol. Within 1 minute he had pain, redness, and frosting only on the left side.

exfoliate the cornified cells in hairless mice is comparable to that of salicylic acid in ethanol vehicle.[5] Polyethylene glycol (PEG) is a vehicle with a fairly strong affinity for phenol compounds including salicylic acid, which is itself capable of retaining the agent. Thus, a topical preparation of SA-PEG would not release salicylic acid onto the skin.[8,9] We have confirmed that there is only minimal absorption of 30% SA-PEG through the intact skin of hairless mice in experiments using ^{14}C-labeled 30% SA-PEG.[7]

In ultraviolet (UV)B-irradiated skin of hairless mice, which served as a model for sun-damaged skin, the structural atypia and expression of p53 protein in keratinocytes induced by UVB irradiation were intensely suppressed in the SA-PEG–treated mice when compared to that in the control UVB-irradiated mice.[10] Incomplete expression of filaggrin and loricrin in keratinocytes from the UV-irradiated control mice was also improved in keratinocytes from the SA-PEG–treated mice.[10] In photoexposed human facial skin, immature cornified envelopes (CEs) were replaced with mature CEs 4 weeks after treatment with SA-PEG.[10] Moreover, skin specimens treated with SA-PEG exhibited a unique connective tissue layer composed of fine collagen fibers beneath the epidermis without evidence of inflammatory infiltrates.[6] These results indicate that chemical peeling with SA-PEG leads to reorganization of the epidermis and a rebuilding of the superficial dermal connective tissue.

This study evaluated the safety and efficacy of the SA-PEG in hairless mice, studying the histologic changes in cornified cells on the surface of the skin and in the hair follicles. We then evaluated the safety and efficacy of this new preparation in 44 volunteers with normally aged skin and in 436 patients with acne. Finally, measurements of the skin barrier function (in terms of the transepidermal water loss [TEWL])[11–13] and changes in the skin elasticity were conducted in 15 additional treated volunteers.

Materials and Methods

SA-PEG

A homogeneous and stable 30% SA-PEG formulation (pH 1.16) was provided by Keisei Inc. (Shinagawa, Tokyo, Japan). If prepared under inadequate conditions, SA crystals separate out and this leads to a reduction in the concentration of SA, while the crystals can irritate the skin at the application site.

Animal Experiments

Eight-week-old hairless Skh/hr1 male mice were purchased from Hoshino Laboratory Animals Co. (Saitama, Japan). After cleansing the back of each UVB-irradiated animal (n = 6) with 70% ethyl alcohol, we applied 30% SA-PEG to the right side, while the left side received only the PEG vehicle and served as a control. In 20 minutes, the preparation was rinsed off with distilled water, and the skin was gently dried with cotton gauze. Next, specimens were excised from the two sites on the backs of anesthetized animals. Specimens were obtained immediately following treatment and again at 1, 3, 12, and 24 hours and at 14 days. Each specimen was cut in half, with one-half being snap-frozen in liquid nitrogen, embedded in ornithine carbamyl transferase (OCT) compound, cut into 4-μm-thick slices,

and stained with hematoxylin-eosin. These frozen sections were used to evaluate the morphology of the cornified cells on the surface of the animals' skin and in the hair follicles. The other half of the specimen was fixed with 10% formaldehyde in phosphate-buffered solution (pH 7.2), embedded in paraffin, cut into
4-μm-thick slices, and stained with hematoxylin-eosin. These sections were used to evaluate the histologic characteristics of the animal's skin according to the standards established for paraffin-embedded sections.

Human Patients and Healthy Volunteers

A 33-year-old healthy man received chemical peeling for 5 minutes with 30% salicylic acid in ethanol vehicle on his left forehead and with 30% SA-PEG on the other side in standard protocol. Forty-four Japanese women, aged 44 to 80 years, who presented for cosmetic peeling of the facial skin, were evaluated for aesthetic effect in the procedure shown below. Fifteen healthy Japanese women, aged 19 to 52 years, were evaluated for physiologic functions of their skin in the study. A 24-year-old man was evaluated macroscopically for the cornified plugs during four courses of 30% SA-PEG chemical peeling. A total of 436 Japanese patients with acne, 410 females and 26 males, aged 17 to 46 years (a mean of 32.3 years), were evaluated for clinical effects of the treatment in the study. A total of 2,572 peelings (mean, 5.9/patient) were performed on the patients. All of them were provided informed consent for participation in this study and were asked to report any adverse effects, including stinging or burning of the treated area.

Method of Facial Peeling

The patient's face was cleansed with soap and water, and the lips and eyelids were covered with a layer of petrolatum as protection. Next, 30% SA-PEG was applied to the patient's forehead, nose, and zygomatic area, distally to the chin. Approximately 3 g of the agent was required to completely cover the face. Five minutes later, the peeling agent was carefully wiped off with ice-cold cotton gauze, and the face was rinsed with generous amounts of tap water. Ice-cold cotton gauze was then applied for 5 minutes. Patients were ordered to apply sunscreen and to avoid excessive sun exposure for 48 hours after peeling. They were also instructed to refrain from applying cosmetics for 12 hours. In cases with repetitive treatment, 4-week or longer intervals were set between each application.

Clinical Evaluation

For aesthetic evaluation, each subject received a single application of 30% SA-PEG on the left side of the face only. The results of chemical peeling were evaluated in a representative case by scanning electron microscopy of the skin surface 1 week after peeling. All acne patients were photographed before and after each (single to 12 times) application of SA-PEG chemical peeling. A questionnaire containing 6 questions about adverse effects of the peeling and 11 questions about efficacy of the peeling was filled out by 42 patients, 40 females and 2 males, aged 24 to 46 years (mean, 30.8 years), with acne who had received SA-PEG chemical peeling in a certain month. The evaluation scores for each question were divided into five answer categories: not at all, 0%; a little, 0% to 25%; some, 25% to 50%; quite a lot, 50% to 75%; and very much, 75% to 100%. In representative cases, 1 patient had comedonal and inflammatory acne (Patient 1), and 2 patients had severe inflammatory acne (Patients 2 and 3). Patient 1 was treated with 30% SA-PEG on both sides of the face. Patient 2, who had severe pustular acne, received an oral antibiotic together with a single chemical peeling with 30% SA-PEG on only the left side of the face. Patient 3, who had severe inflammatory nodular acne, received an oral antibiotic and underwent three separate treatments with 30% SA-PEG on both sides of the face.

Physiologic Evaluation

We measured the elasticity and the TEWL of a defined area of the skin before and after treatment. Measurements were carried out before the treatment

and then repeated at 1 hour, 1 day, 1 week, 2 weeks, and 4 weeks after the first chemical peeling. After the second chemical peeling, further measurements were 2 and 4 weeks later. TEWL was determined with a skin evaporative water recorder, TEWL probe (DermaLab, Cortex Technology, Hadsund, Denmark). Measurements were performed for 30 seconds, and the mean value ($g/m^2/hr$) determined of the last stable 8-second period was used as TEWL. The elasticity of the skin was measured with an elasticity probe (DermaLab, Cortex Technology). Measurement of this unit is based on suction applied to the skin surface, whereby the probe provides a vacuum chamber. Calculation of the elasticity module was based on the differential force necessary to elevate the skin surface 1.5 mm between two infrared detection levels inside the probe chamber. Measurements were repeated five times in immediate sequence on the same area. Each value was a mean of the last four measurements (kPa/s).

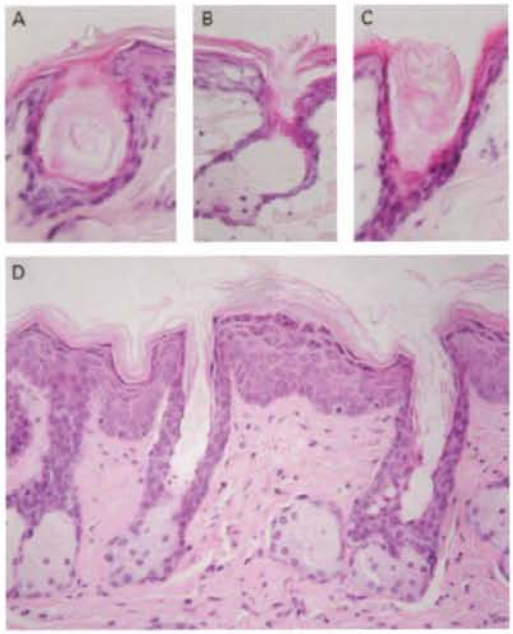

Figure 2. Micrographs of frozen specimens of mouse skin 3 to 12 hours after application of SA-PEG. Immediately after application, the cornified layer becomes detached above the granular cell layer (A). Twelve hours after application, the skin shows a thickening of the granular cell layer. The cornified cells within the hair follicles are almost dissolved and are becoming detached from the follicles (B). Twenty-four hours after application, a new cornified cell layer appears above the granular cells. The cornified cells within the hair follicles, which adhered firmly before peeling, have been removed almost completely (C). Formalin-fixed specimen of UVB-irradiated mouse skin two weeks after the application. The new cornified cell layer consists of fine, regularly arranged cells above the thickened granular cell layer (D).

Results

Experimental Observations

Immediately after the application of SA-PEG to the skin of hairless mice, the cornified cell layer showed a temporary thickening. Beneath that layer, vacuolar changes were occasionally seen and the cornified cell layer became detached (Figure 2A). Three hours after application, the epidermis showed a marked thinning. The cornified cells that plugged the hair follicles became macerated and then became detached above the granular cells. Twelve hours after the application, the cornified cell layer, which adhered firmly before peeling, had almost disappeared. The skin showed hypertrophy with a thickening of the granular cell layer and occasional mitosis of the basal cells. The cornified cells within the hair follicles were almost dissolved and became detached from the follicles (Figure 2B). At 24 hours after the application, a new cornified cell layer appeared above the granular cells. The cornified cells within the hair follicles, which adhered firmly before peeling, had nearly been removed (Figure 2C). Two weeks after the application, a cornified cell layer consisting of new, fine, and regularly arranged cells appeared above the hypertrophic granular cell layer (Figure 2D). Adhesion of the cornified cell layer to the epidermis was not seen. No inflammatory changes were observed in the epidermis or dermis.

Clinical Response in Volunteers

Chemical peeling with SA-PEG on one side of the face produced marked cosmetic improvement within 1 week compared with the other, untreated side of the face (not shown). There were no complaints of

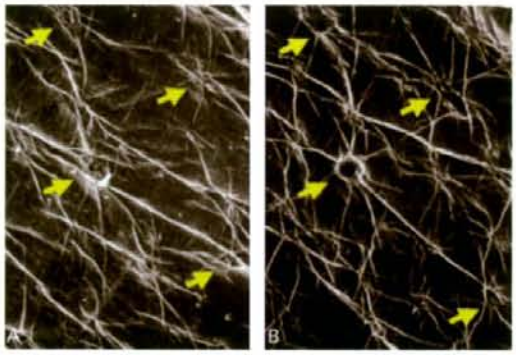

Figure 3. Scanning electron micrographs of a 75-year-old Japanese woman with typical aged skin. The surface of the skin before treatment shows numerous adherent cornified cells masking the regular grooves of the skin surface (A). One week after treatment with SA-PEG, there is a restoration of the regular grooves in the skin surface, and the adherent cornified cells have been removed from the hair follicles (B).

pain, burning, or stinging and no signs of edema, bleeding, crusting, or postinflammatory pigmentation. Scanning electron microscopy of the treated skin surface 1 week after chemical peeling revealed a restoration of the regular grooves (glyphics) of the skin and the removal of the cornified plugs from the hair follicles (Figure 3). Adherent cornified cells have been removed from the skin surface and hair follicles. Macroscopically, cornified plugs were also removed, and the appearance of facial pores was minimized after peeling four times (Figure 4).

The SA-PEG preparation achieved the desired rejuvenated appearance of aging skin in the majority (98%) of subjects, who showed a smoothing of texture, an increase in elasticity, and an improvement in color of the skin. Follow-up for 1 to 3 months showed that the majority of subjects were satisfied with the results. Only 2% showed no change.

The skin barrier function, evaluated by TEWL, did not show significant changes, which provides further evidence of the safety of this preparation (Figure 5). Significant improvement in the skin elasticity was proved by this measurement (Figure 6).

Clinical Response in Acne Patients

None of the 436 acne patients treated by SA-PEG complained of pain, and there were no adverse effects such as erythema, bleeding, crusting, or

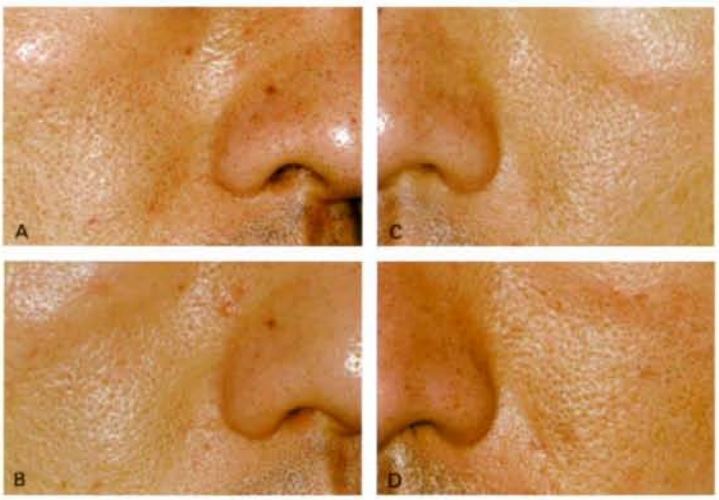

Figure 4. Macroscopic effect of SA-PEG chemical peeling on cornified plugs and facial pores. The cornified plugs were evaluated macroscopically in a 24-year-old man before (A) and 2 weeks after four peelings with SA-PEG (B) on the right side of his face. As a control, the left side (C) was not treated with SA-PEG (D).

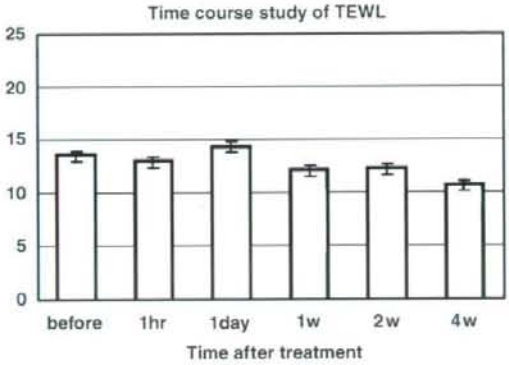

Figure 5. TEWL ($g/m^2/h$) after chemical peeling with SA-PEG. No significant change was observed during the 4-week period of observation, a favorable outcome.

postinflammatory pigmentation of the skin.
The results of the questionnaire survey on perceived efficacy of SA-PEG chemical peeling indicate that the vast majority of 42 respondents noted a clinical improvement in acne, satisfaction in the treatment, and a spontaneous improvement in skin texture and color (Table 1). Some patients desired and received continuous treatment for cosmetic improvement after they were satisfied with a complete healing of acne.

Within 1 month of treatment, chemical peeling with 30% SA-PEG considerably reduced the development of comedones and papules in the patients.

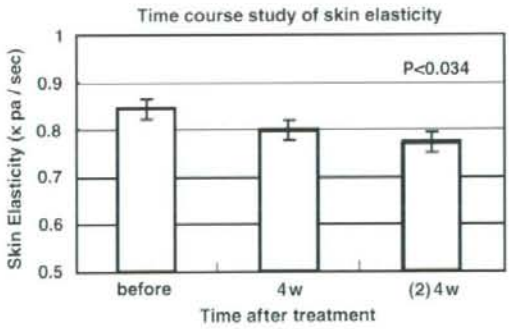

Figure 6. Elasticity (kPa/s) of skin after chemical peeling with SA-PEG. The results indicate a significant improvement during the 8-week period of observation.

However, areas of inflammation consisting of erythema, papules, and pustules still persisted in Patient 1, who was treated with SA-PEG on both sides of the face (Figure 7). Patient 2 received an oral antibiotic and underwent a single chemical peeling with SA-PEG on only the left side of the face. Treatment produced marked improvement (Figures 8C and 8D) within 2 weeks compared with the right, untreated side (Figures 8A and 8B). The treated side exhibited a clearing of the pustules, papules, and comedones accompanied by a reduction in oiliness and in roughened, enlarged pores (Figure 8).
Patient 3, who had severe acne (Figure 9A), received an oral antibiotic together with the administration of three separate chemical peeling treatments on both sides of the face, given monthly for 3 months. After 3 months of the combined oral antibiotic–topical chemical peeling treatment, the pustules, papules, and comedones dissappeared, accompanied by a decrease in sebum and an improvement in skin texture and color (Figure 9B). All three individuals spontaneously reported an improvement in skin texture and color.

Discussion

This study showed that chemical peeling with SA-PEG was very effective in eradicating relatively

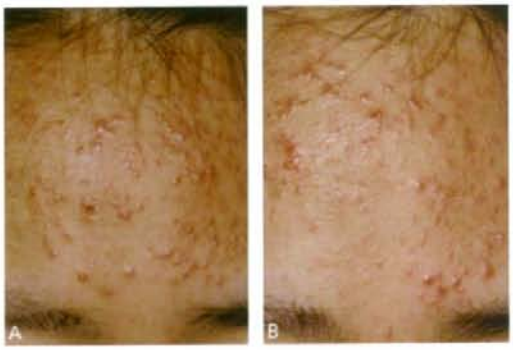

Figure 7. Photographs of Patient 1, a 16-year-old Japanese girl with papular inflammatory acne (A). One month after facial peeling with SA-PEG, there was an obvious reduction in the number of comedones and papules. However, inflammation still persists (B).

TABLE 1. The Results of a Questionnaire Survey on Adverse Effects and Perceived Efficacy of SA-PEG Chemical Peeling in 42 Patients (40 Females and 2 Males) with Acne*

	Not at All	*A Little*	*Some*	*Quite a Lot*	*Very Much*
Adverse effects					
Bleeding	42	0	0	0	0
Pain on peeling	35	7	0	0	0
Pain after peeling	41	1	0	0	0
Rush	41	0	1	0	0
Dryness	35	6	1	0	0
Pigmentation	42	0	0	0	0
Efficacy on the skin					
Nascent acne decreased	0	1	0	4	37
Acne healed	0	0	1	6	35
Acne scar minimized	0	0	4	7	31
Excess oil disappeared	0	1	5	11	25
Pores shrank	0	0	7	12	23
Skin turned smooth	0	0	1	4	37
Elasticity increased	0	0	2	3	37
Skin color improved	1	3	6	10	22
Skin clarity improved	0	1	5	14	23
Skin turned comfortable for makeup	0	0	0	4	36
Degree of satisfaction	0	0	0	0	42

*The question about makeup was asked only of female patients.

severe comedones and papules in patients with acne. Furthermore, new lesions were slow to emerge during repetitive treatments, even these were done only once a month. The combination of an oral antibiotic and chemical peeling produced excellent clinical results in both cases of acne with preexisting severe inflammation. There was no stinging or burning, even immediately after application of the prepara-

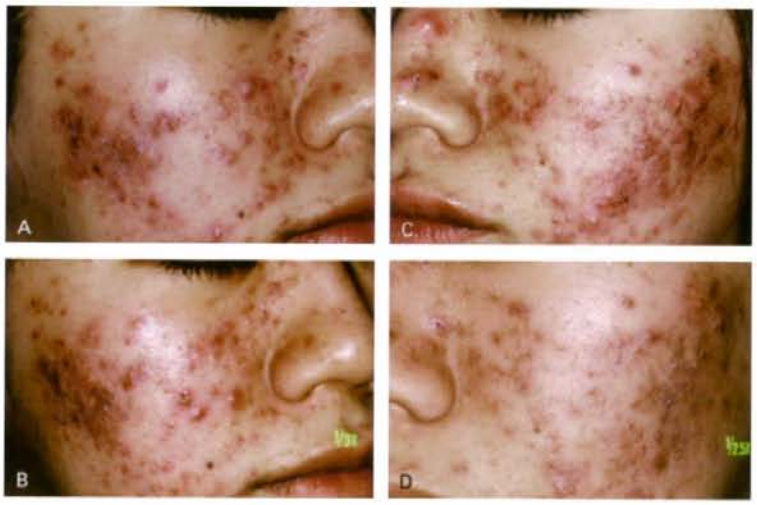

Figure 8. Photographs of Patient 2, a 20-year-old Japanese woman with papular and pustular inflammatory acne on the right (A) and left (C) sides of the face before treatment. Two weeks after the administration of an oral antibiotic, the comedones and papules persist on the untreated right side (B). Left side of face 2 weeks after a single application of SA-PEG with the concomitant administration of an oral antibiotic. The number of comedones and papules is now markedly reduced (D).

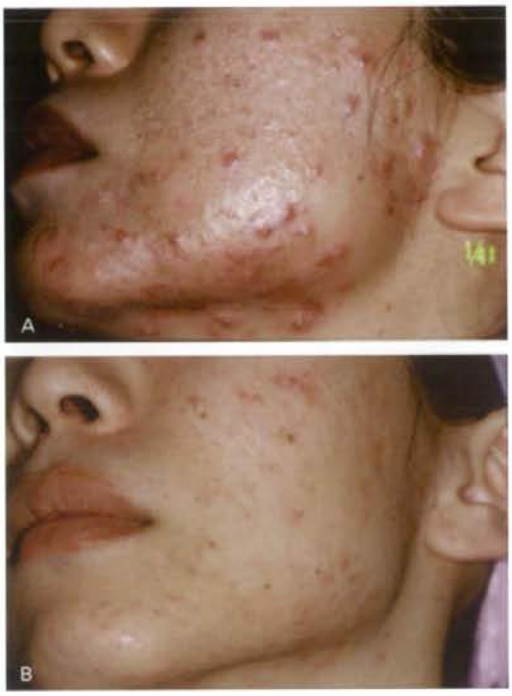

Figure 9. Photographs of Patient 3, a 22-year-old Japanese woman with nodular acne with severe inflammation (A). Two months after the third chemical peeling treatment with SA-PEG plus an oral antibiotic, the comedones and the inflammation have disappeared. The oiliness of the skin has decreased and the texture and color of the skin have improved (B).

tion, nor other adverse effects including scaling, crusting, or postinflammatory pigmentation. Although some patients felt a minimum tingling, the degree of pain was comparably weaker than the penetrating pain caused by salicylic acid in ethanol.

We previously reported that chemical peeling with SA-PEG in animals leads to an alteration in epidermal morphology by inducing a loss of cornified cells.[5–7] Inflammatory infiltrates are occasionally seen in areas of skin treated with 30% salicylic acid in ethyl alcohol vehicle.[1,5] However, treatment with SA-PEG infrequently produces such infiltrates.[5–7] PEG has a high affinity for salicylic acid and therefore binds this agent, releasing only a small amount into the living tissue layer of the epidermis.[6] This may explain why SA-PEG does not cause the burning pain that is usually encountered with the ethyl alcohol vehicle.[1–3] This may also help to explain why patients undergoing chemical peeling with the new preparation do not immediately experience pain, in contrast to those treated with the ethyl alcohol vehicle.

Our studies on using radiolabeled salicylate in animals have shown plasma levels of radioactivity well below the toxic level and demonstrated by microautoradiograms that the highest level of radioactivity was present in the cornified cell layer of the hair follicles. One may anticipate that this new formulation of salicylic acid may be used as a chemical peeling agent without the risk of inducing salicylism.[7] No clinical evidence of salicylism was observed in any of our treated subjects to date.

In addition to a disappearance of comedones and papules, the acne patients showed an improvement in skin texture after treatment. Similarly, the 44 volunteers reported a smoother skin texture. There was also an obvious increase in skin elasticity and an improved skin color. In 15 additional volunteers, measurement of TEWL showed little change in water barrier function, and a significant improvement in skin elasticity was demonstrated. We previously showed that peeling with SA-PEG leads to the production of new collagen fibers in the papillary dermis of UV-irradiated mouse skin.[6] This observation may explain how this chemical peeling serves to improve the texture of the skin.

In conclusion, SA-PEG used for facial peeling in patients with acne was safe and effective when used in conjunction with an oral antibiotic. Although few procedures have been employed to remove comedones, this innovative preparation, which can specifically remove the cornified layer even on infundibulum with little absorption, offers significant adjunctive benefits for all acne patients affected at various degrees of severity without exception. The skin of middle-aged or elderly volunteers without acne showed cosmetic improvement in repetitive,

long-time treatment without any adverse effects. This preparation will present an advantage in chemical peeling especially for Asian patients who tend to develop hyperpigmentation or keloids related to acne inflammation.

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Address correspondence and reprint requests to: Teruki Dainichi, MD, PhD, Department of Dermatology, Kurume University School of Medicine, 67 Asahimachi, Kurume, Fukuoka 830-0011, Japan, or e-mail: dainichi@med.kurume-u.ac.jp

COMMENTARY

In a time when new laser technologies appear to be the wave of the future, it is interesting to see something new in the world of chemical peeling. Salicylic acid peeling is an old therapy, but this article shakes up some of the traditional ideas of its use. These authors have methodically examined, in detail, the clinical and histologic effects of this particular chemical peel solution. Rarely have we seen this much science behind a peeling agent. They have effectively shown that much of what we thought was required for chemical peeling to be effective (i.e., redness, stinging, peeling) is completely unnecessary.

It is a very intriguing concept that keeping salicylic acid from penetrating deeply into the skin does not negate its positive effects, only its side effects. It would be interesting to see if continued application of this peel over a series of 8 to 10 treatments would give cumulative clinical benefits for photoaged skin, particularly rhytides.

MARK G. RUBIN, MD
Beverly Hills, CA

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Original Article

Efficacy and Safety of a Traditional Herbal Medicine, *Hochu-ekki-to* in the Long-term Management of *Kikyo* (Delicate Constitution) Patients with Atopic Dermatitis: A 6-month, Multicenter, Double-blind, Randomized, Placebo-controlled Study

Hiromi Kobayashi[1], Masamitsu Ishii[1], Satoshi Takeuchi[2], Yoichi Tanaka[3], Takahiro Shintani[4], Atsushi Yamatodani[5], Tadashi Kusunoki[6] and Masutaka Furue[2]

[1]Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, [2]Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, [3]Tanaka Clinic, Nagasaki, [4]Research Institute of Oriental Medicine, Kinki University, Osaka-Sayama, [5]Department of Medical Physics and Engineering, Graduate School of Allied Health Sciences, Faculty of Medicine, Osaka University, Osaka and [6]Department of Pharmacoepidemiology, Faculty of Medicine, University of Tokyo, Tokyo, Japan

Hochu-ekki-to is a traditional herbal (Kampo) medicine that has been shown to be effective for patients with *Kikyo* (delicate, easily fatigable, or hypersensitive) constitution. Previous case reports have suggested that this herbal drug was effective for a certain subgroup of patients with atopic dermatitis (AD). We aimed to evaluate the efficacy and safety of *Hochu-ekki-to* in the long-term management of *Kikyo* patients with AD. In this multicenter, double blind, randomized, placebo-controlled study, 91 *Kikyo* patients with AD were enrolled. *Kikyo* condition was evaluated by a questionnaire scoring system. All patients continued their ordinary treatments (topical steroids, topical tacrolimus, emollients or oral antihistamines) before and after their protocol entry. *Hochu-ekki-to* or placebo was orally administered twice daily for 24 weeks. The skin severity scores, total equivalent amount (TEA) of topical agents used for AD treatment, prominent efficacy (cases with skin severity score = 0 at the end of the study) rate and aggravated rate (more than 50% increase of TEA of topical agents from the beginning of the study) were monitored and evaluated. Seventy-seven out of 91 enrolled patients completed the 24-week treatment course (*Hochu-ekki-to*: $n = 37$, placebo: $n = 40$). The TEA of topical agents (steroids and/or tacrolimus) was significantly ($P < 0.05$) lower in the *Hochu-ekki-to* group than in the placebo group, although the overall skin severity scores were not statistically different. The prominent efficacy rate was 19% (7 of 37) in the *Hochu-ekki-to* group and 5% (2 of 40) in the placebo group ($P = 0.06$). The aggravated rate was significantly ($P < 0.05$) lower in the *Hochu-ekki-to* group (3%; 1 of 37) than in the placebo group (18%; 7 of 39). Only mild adverse events such as nausea and diarrhea were noted in both groups without statistical difference. This placebo-controlled study demonstrates that *Hochu-ekki-to* is a useful adjunct to conventional treatments for AD patients with *Kikyo* constitution. Use of *Hochu-ekki-to* significantly reduces the dose of topical steroids and/or tacrolimus used for AD treatment without aggravating AD.

For reprints and all correspondence: Hiromi Kobayashi, MD, PhD, Department of Dermatology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan.
Tel: +81-6-6645-3826; Fax: +81-6-6645-3828;
E-mail: hiromik@med.osaka-cu.ac.jp

Keywords: atopic dermatitis – *Hochu-ekki-to* – Kampo medicine – randomized controlled trial – steroid – tacrolimus – (traditional) herbal medicine

Introduction

Atopic dermatitis (AD) is a common, chronic, relapsing eczematous skin disease with severe pruritus (1–3). The incidence of AD appears to be increasing worldwide (4,5), among which the percentage of adolescent- and adult-type AD cases have also been increasing (6,7). The precise pathogenesis of AD remains obscure and appears complex. Topical steroids, topical tacrolimus, emollients and oral antihistamines are used as the first-line treatments in standard therapeutic guidelines for AD (2,3,8). However, long-term application of topical steroids could induce local adverse effects such as skin atrophy and telangiectasia in a substantial number of patients. Topical tacrolimus is a potent calcineurin inhibitor that does not exhibit the hormonal adverse effects associated with steroid therapy (9,10). The major adverse effect in using topical tacrolimus is sensation of skin burning or irritation after application (11). In addition, the Food and Drug Administration (FDA) has issued a public health advisory to inform healthcare professionals and patients of a potential cancer risk by the use of topical calcineurin inhibitors (http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01343.html). This concern is based on animal studies, case reports with a small number of patients, or knowledge of the drug's action mechanism as immunosuppressant. According to the FDA statement, it may take human studies of 10 years or longer to determine if the use of topical calcineurin inhibitors is actually linked to cancer development in human. These adverse effects and emotional fear of long-term use of topical steroids and/or tacrolimus have caused topical steroid/tacrolimus phobia in substantial number of patients with AD worldwide who would like to avoid these topical agents if possible (12). Moreover, clinical experience has shown that some of AD patients are really refractory to these conventional treatments, and indeed current AD therapeutic guidelines recommend further intensive treatments such as ultraviolet phototherapy or oral cyclosporine for such patients (8).

In Japan, an alternative approach has been pursued to treat these grave and/or refractory AD patients with traditional herbal medicine such as *Saiko-seikan-to*, *Shohu-san*, *Oren-gedoku-to*, *Byakko-ka-ninjin-to*, *Tokaku-joki-to*, *Unkei-to*, *Hochu-ekki-to* and so on (13–33). These prescriptions comprise several elemental herbs, combined use of which is thought to help increase the treatment effects and to diminish adverse reactions of each individual herb. Among these prescriptions, formula like *Tokaku-joki-to* are mainly aimed at eliminating disease factors, whereas *Hochu-ekki-to* is aimed at correcting abnormal homeostasis of the body. Each prescription is selected individually according to the pharmacological features and the constitution of each patient. *Hochu-ekki-to* is composed of hot water extracts from 10 species of herbal plants and is used for patients with *Kikyo* constitution. *Kikyo*, or deficiency of *Ki*, is defined as delicate, easily fatigable, or hypersensitive constitution typically associated with poor gastrointestinal functions, anorexia and night sweats (34). In experiments using animal models, orally administered *Hochu-ekki-to* exhibits various immunopharmacological effects, especially anti-allergic properties. They include suppression of serum IgE level and eosinophil infiltration and improvement of dermatitis through controlling Th1/Th2 balance possibly by inducing interferon γ production from intraepithelial lymphocytes (35–42). In addition, *Hochu-ekki-to* helps to correct leukocytopenia of mice treated with anti-cancer agents and augments the resistance against bacterial infections (43,44). These results suggest that *Hochu-ekki-to* may be applicable to the treatment of AD patients who have *Kikyo* constitution. Although accumulating reports have shown clinical efficacy of *Hochu-ekki-to* for AD patients (13,15,17,20,21,25,27,29–33), no placebo-controlled study has previously been conducted.

In this double-blind, placebo-controlled, randomized clinical trial, we address a question of whether *Hochu-ekki-to* has beneficial effects for *Kikyo* patients with AD who have been treated with conventional modalities.

Methods

Hochu-ekki-to

Hochu-ekki-to fine granules of 7.5 g contain hot water extract (6.4 g) from 10 species of medicinal plants including *Ginseng radix* (4.0 g), *Atractylodis rhizoma* (4.0 g), *Astragali radix* (4.0 g), *Angelicae radix* (3.0 g), *Zizyphi fructus* (2.0 g), *Bupleuri radix* (2.0 g), *Glycyrrhizae radix* (1.5 g), *Zingiberis rhizoma* (0.5 g), *Cimicifugae rhizoma* (1.0 g) and *Aurantii nobilis Pericarpium* (2.0 g).

Assessment of *Kikyo* Condition

Kikyo condition was evaluated by a questionnaire scoring system. As shown in Table 1, the scoring questionnaire consisted of one 'must have' major sign (10 points) and 10 minor signs (2 points each). The patients who had the

Table 1. Questionnaire scoring system for Kikyo constitution

Items	Signs and conditions	Scores
Major sign (must-have)	Easy fatigability or lack of perseverance	10
Susceptibility to infections	Susceptible to cold	2
	Delayed recovery from cold	2
	Vulnerable to other infectious diseases (herpes virus etc)	2
	Susceptible to suppuration	2
Anorexia	Recent very little eating	2
	Appetite loss	2
	Easily-becoming full stomach	2
	Nahrungsverweigerung	2
Digestive symptom	Diarrhea (laxity)	2
Others	Easy drowsiness especially after meals	2
Total scores		30

Patients who have the major sign and earn 18 points or more in this questionnaire scoring system are determined as Kikyo constitution.

major sign and earned 18 points or more using the questionnaire were determined as *Kikyo* constitution.

Study Population

Patients (20–40 years of age) with *Kikyo* constitution who fulfilled the diagnostic criteria of Japanese Dermatological Association for AD were eligible for this study. All the 91 AD patients enrolled had been treated with topical steroids (mild, strong, or very strong rank) and/or topical tacrolimus for more than 4 weeks prior to the study, and were expected to continue the same therapeutic regimen after the initiation of the study. Patients were not eligible for the study if they had been treated with only weak topical steroids (without stronger topical steroids or tacrolimus), strongest topical steroids, systemic steroids, oral suplatast tosilate, allergen desensitization therapy, or any other herbal medicines for <4 weeks prior to the study. The study was approved by the responsible ethics committee and was performed in accordance with the Declaration of Helsinki and with Good Clinical Practice. An informed witnessed consent was obtained from all the patients.

Study Protocols

The study was performed in a multicenter, double blind, randomized, placebo-controlled parallel-group design. The patient number was randomly assigned a treatment code of either *Hochu-ekki-to* or placebo using a block size of 10 (5 per each group) by an independent controller of the investigators. This code was concealed from the investigators. During trial period, patients were randomized to receive twice daily either *Hochu-ekki-to* fine granules (Kracie Co., Ltd, Tokyo, Japan) or its inactive placebo which were indistinguishable by its appearance, odor and savor. The daily doses were 7.5 g. All patients continued their ordinary treatments such as topical steroids (other than strongest class), topical tacrolimus, emollients or oral anti-histamines. The skin severity score, amounts of topical agents, adverse effects and laboratory examination including serum IgE, lactate dehydrogenase (LDH) or eosinophil counts were monitored at pre (0-week)-, mid (12-week)- and post (24-week)-treatment. The prominent efficacy (skin severity score = 0 at the end of the study) rate and the aggravated rate (more than 50% increase of amounts of topical agents from the beginning of the study) were also evaluated.

Assessment of Skin Severity Scores

The skin severity scores of AD patients were assessed using the scoring system by the Atopic Dermatitis Severity Evaluation Committee of Japanese Dermatological Association (issued 2001). The skin severity scores were composed of eruption intensity score and affected skin area score. The body surface was divided into five sites, namely head and neck, anterior trunk, posterior trunk, upper extremities and lower extremities. The eruption intensity and affected skin area were evaluated and scored. Eruption intensity scores were evaluated using three eruption items: (i) erythema/acute papules, (ii) oozing/crusts and excoriation and (iii) lichenification/chronic papules and nodules) in the severest area scored from 0 to 3 points (0 = absent, 1 = mild, 2 = moderate, or 3 = severe) for each item in each body site. The affected skin area was also evaluated and scored in each body site as 0, 1, 2, 3 points when affected skin area was absent, less than one-third, one-third to two-third, more than two-third of each body site, respectively. Thus, the skin severity score ranges from 0 to 60 points.

Assessment of the Dosage of Topical Steroids and Topical Tacrolimus

At each patient visit, the actual amounts used of topical steroids and/or topical tacrolimus were measured by weighing the returned ointment tubes from examinees. The amount of topical agents (steroids and tacrolimus) per day was expressed as total equivalent amount (TEA) (gram arbitrary unit; gau) by multiplying potency equivalent factors as follows; weak rank steroids = $\times 1$, mild rank steroids = $\times 2$, strong rank steroids = $\times 4$, very strong rank steroids = $\times 8$, tacrolimus = $\times 4$. Percent change of TEA to that of the beginning of the study

was calculated for each patient at 12th and 24th week of treatment using the following formula:

$$\text{Percentage changes of TEA} = \frac{\text{TEA at 12th or 24th week} - \text{Initial TEA}}{\text{Initial TEA}} \times 100\ (\%)$$

Statistical Analysis

Statistical analysis was performed using SAS statistical software (version 8.02; SAS Institute, Cary, NC) under the Windows XP operating system. Data were expressed as the means ± standard deviation (SD) or standard error (SE). A P-value of <0.05 was considered to indicate statistical significance. Treatment efficacy was analyzed by comparing the difference between *Hochu-ekki-to* and placebo control groups using unpaired Student's t-test or Fisher's exact test.

Results

Patient Enrollment and/or Exclusion

In total, 91 patients were enrolled and randomized in this trial from February to November 2002. Seven out of the initial 91 enrolled patients were excluded from subsequent analysis for the following reasons; agreement acquisition violation ($n = 4$), eligibility violations ($n = 2$) and failure to take trial medicine at all ($n = 1$). Thus the number of patients who actually received medication (hereafter termed 'full analysis set: FAS' group) and who were analyzed was 84 (*Hochu-ekki-to*: $n = 40$, placebo: $n = 44$). Seventy-seven out of the 84 patients completed the 24-week treatment course (Fig. 1), including a patient in whom TAE of topical agents could not be assessed because of the insufficient descriptions on the item. There were no statistically significant differences between *Hochu-ekki-to*- and control groups in terms of age, sex, physique, duration of AD morbidity, incidence of past- or present history of other allergic or non-allergic diseases, *Kikyo* score, skin severity score, initial TAE of topical agents per day (Supplementary data 1). Two out of the 7 dropped-out cases during the trial (One each in placebo and *Hochu-ekki-to* group) were excluded because of a significant aggravation of skin eruption and occurrence of headache, respectively. Others were found unfit for further analyses (dismissal of medication etc).

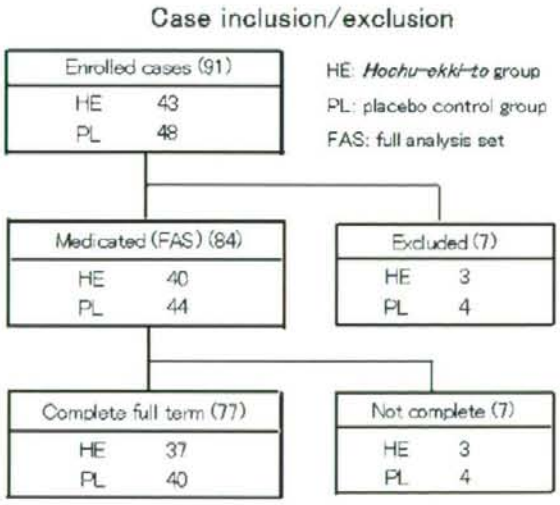

Figure 1. The chart of case enrollment and exclusion. Among the 91 enrolled AD patients, 84 patients were medicated and 77 out of the 84 patients completed full term (for 24 weeks) of trial.

Clinical Efficacy of *Hochu-ekki-to*

The overall skin severity score gradually decreased as examination went on and was slightly lower in *Hochu-ekki-to* group (closed circle) than in placebo group (open circle) at 24th week (Fig. 2). The TEA of topical agents gradually increased in the placebo group during the trial period, whereas such increase of TEA was minimal to unchanged in the *Hochu-ekki-to* group. The percent change of TEA at 24th week was significantly ($P < 0.05$) lower in the *Hochu-ekki-to* group (closed circle) than in the placebo control group (open circle) (Fig. 3).

Since *Hochu-ekki-to* was thought to be a slow-acting herbal medicine and the present trial was relatively long-term, we wondered if a striking beneficial effect was observed in a certain population of patients by long-term use of *Hochu-ekki-to*. Therefore, we analyzed a prominent efficacy rate, the rate of patients whose skin severity

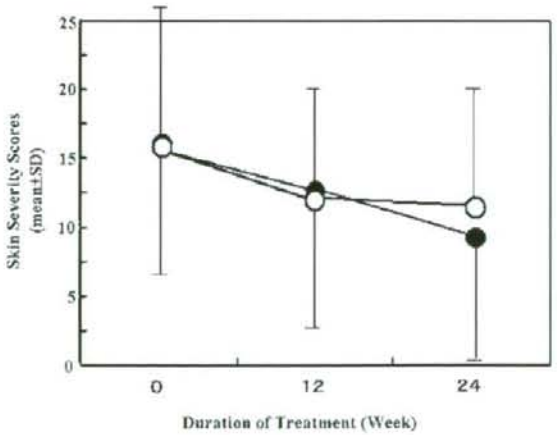

Figure 2. The time course change of skin severity score during examination. Skin severity scores were assessed at pre-, mid (12-week)- and post (24-week)-treatment in *Hochu-ekki-to*- (closed circle) and placebo group (open circle). Data were expressed as the mean ± SD.

score became 0 at the end of the study. The prominent efficacy rate was indeed moderately higher in the *Hochu-ekki-to* group (19%; 7 of 37) than in the placebo group (5%; 2 of 40), although there was not a significant difference ($P = 0.06$). Furthermore, the aggravated rate, defined as ratio of patients whose TEA had increased more than 50% at 24 weeks from the beginning of the study, was significantly lower in the *Hochu-ekki-to* group (3%; 1 of 37) than in the placebo group (18%; 7 of 39) ($P < 0.05$). There was no significant difference in the serum IgE, LDH, or eosinophil counts in peripheral blood in both groups (data not shown).

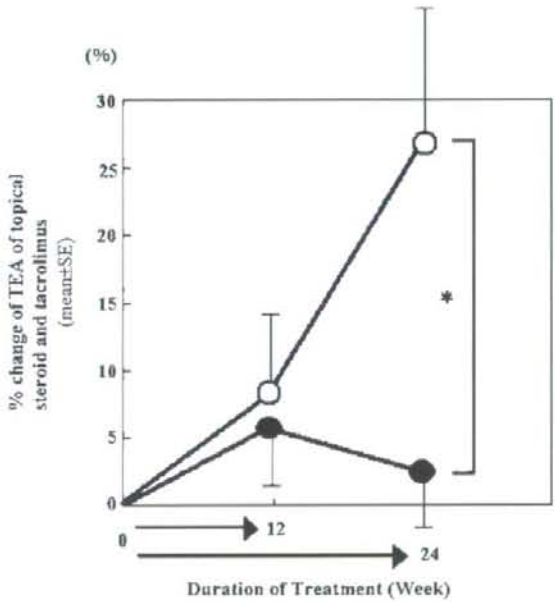

Figure 3. The time course change of equivalent dosage of topical agent during examination. The percent changes of TEA of topical agents were assessed at pre-, mid (12-week)- and post (24-week)-treatment in *Hochu-ekki-to* (closed circle) and placebo group (open circle). Data were expressed as the mean ± SE. The TEA of topical agents gradually increased in the placebo group as trial went, while such increase was minimal to unchanged in the *Hochu-ekki-to* group. $^*P < 0.05$.

Adverse Events and Abnormal Laboratory Findings

The adverse events, including those of unclear causality with treatment using tested agents, were observed in 13 of 40 patients (32.5%, total 33 events) in the *Hochu-ekki-to* group and in 12 of 44 patients (27.3%, total 20 events) in the placebo group. All the adverse events were moderate symptoms such as nausea and diarrhea etc or slight increase or decrease of laboratory data (Table 2).

Discussion

The present study demonstrates that 24-week oral administration of *Hochu-ekki-to* has a substantial benefit over placebo in the treatment of *Kikyo* patients with AD. The administration of *Hochu-ekki-to* significantly reduces dosage of topical steroids and/or tacrolimus, compared with placebo, although there was no significant difference in the mean skin severity scores between both groups. These results indicate that the patients in the placebo group need significantly more topical steroids and/or tacrolimus in order to control their skin conditions. In keeping with this notion, the post-treatment prominent efficacy rate tends to be higher in the *Hochu-ekki-to* group than in the placebo group. In contrast, the aggravated rate was significantly lower in the *Hochu-ekki-to* group than in the placebo group. It was surprising that 19% of patients in the *Hochu-ekki-to* group were devoid of skin eruption after the 24-week treatment. Considering the long-term history of the majority of the 7 'eruption-free' patients (10–34 years, mean ± SD: 21.9 ± 8.0), this marked improvement would indicate the beneficial effects of *Hochu-ekki-to*, as 'spontaneous' healing was not likely to take place in those severe AD patients during the course of trial.

Hochu-ekki-to, however, did not seem to be effective for all the AD patients in this trial. Individual difference of intestinal flora has been proposed to be one of the major reasons for such disparity of the efficiency of Kampo therapy. It is because active components of orally administered herbal drugs are known to be assimilated through the intestinal mucosa under the influence of the intestinal flora (45). Although we generally advise patients to choose traditional Japanese diet in usual

Table 2. Adverse effects

	The number of cases with adverse effects	Adverse effects (the number of cases if not one), including those of unclear causality with treatment using tested agents
Hochu-ekki-to group	13/40 (32.5%)	Symptoms: nausea (2), diarrhea (2), stomach discomfort (2), enlarged feeling of abdomen, epigastralgia, anorexia, loose stools, right hypochondrium pain, malaise, dizziness, headache, light-headed feeling, rhinitis, acne pustulosa, feverish thirstiness, dental caries.
		Laboratory data: eosinophilia (3), GPT elevation, IgE elevation, BUN decline, serum K elevation.
Placebo-control group	12/44 (27.3%)	Symptoms: ovarian disorder (2), diarrhea, epigastric discomfort, anorexia, malaise, hives, insomnia, feverish limbs.
		Laboratory data: eosinophilia (4), LDH elevation (2), GOT elevation (2), γ-GTP elevation, serum total protein decline, hemoglobin decline.

Kampo treatment as intestinal flora can be affected by daily diet, we have avoided intensive intervention during this trial period, assuming that such intervention could be a considerable stress for certain patients and could significantly influence their clinical course of skin symptoms by increasing itch sensation etc. The clinical action of *Hochu-ekki-to* appears to be rather mild and limited; however, the present study clearly demonstrates an add-on beneficial effect of this herbal drug over the conventional treatments. Kampo herbal drugs are broadly classified into two categories, immediate acting- and slow acting ones. Since *Hochu-ekki-to* is considered to work in the latter manner, supporting the inactive *Kikyo* body to become warm and active. Thus, it needs to be administered for a long time to be shown effective. A long-term (for 24 weeks) administration was adopted in our protocol design because of the relatively slow acting profile of *Hochu-ekki-to*. The significant clinical benefits indeed appeared at 24th week rather than 12th week, as shown by the reduction of TEA of topical agents and of the reduced aggravated rates.

Kampo herbal drugs are usually prescribed according to patient's *Sho* (constitution/condition) such as *Yin* (negativity) and *Yang* (positivity) or *Kyo* (deficiency) and *Jitsu* (fullness) and to target components to treat such as *Ki* (energy, spirit and function), *Ketsu* (blood and organs) and *Sui* (fluid), all of which are considered to be basic components constituting human body. *Hochu-ekki-to* is recommended to be used for *Kikyo* condition, a state of functional deficiency. In our trial, only AD patients with *Kikyo* constitution were selected eligible by using the questionnaire scoring system. This selection may favorably contribute to carve in relief of the clinical significance of *Hochu-ekki-to* over placebo, thus it remains to be tested if the herbal drug has such beneficial effect on AD patients without *Kikyo* constitution.

Although considerable attention has been paid on traditional herbal medicines as a treatment option for AD (13–33), there are only a few reports examining their efficacy in a randomized, double blind manner, as reviewed by Armstrong and Ernst (46). Sheehan *et al.* (47–49) have reported the usefulness of the composite herbs of Zemaphyte® in a randomized, double blind cross-over trial, where it was shown that the Zemaphyte's composite herbs possess anti-inflammatory and anti-congestive function (48). However, a subsequent trial by Fung *et al.* (50) failed to confirm its superiority over placebo. Although efficacies of herbal medicines are now being recognized even outside the Asian countries (51), there has been no report of double-blind, randomized and placebo-controlled trial of herbal drugs as treatment for AD other than Zemaphyte® before the present study.

In conclusion, our results indicate that *Hochu-ekki-to* is a useful adjunct to conventional treatments for *Kikyo* patients with AD. We contend that it can reduce the dosage of topical steroids and tacrolimus without aggravating the clinical course of AD.

Supplementary Data

Supplementary data are available at *eCAM* online.

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日本皮膚科学会ガイドライン

日本皮膚科学会アトピー性皮膚炎診療ガイドライン

日本皮膚科学会アトピー性皮膚炎診療ガイドライン作成委員会
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中村　敏明[6]　佐々木りか子[7]　須藤　　一[8]　竹原　和彦[9]

I. はじめに

アトピー性皮膚炎は日常診療上頻繁に遭遇する疾患であると同時に，患者への十分な説明や治療へのコンプライアンス・アドヒアランスを考慮すべき疾患として，近年世界的に治療ガイドラインが整備されている．本症の治療ガイドラインはすべて近似した疾患概念，治療体系の上に構築されている．すなわち，アトピー性皮膚炎の病態を，皮膚の生理学的機能異常を伴い，複数の非特異的刺激あるいは特異的アレルゲンの関与により炎症を生じ慢性の経過をとる湿疹としてとらえ，その炎症に対してはステロイド外用薬やタクロリムス軟膏による外用療法を主とし，生理学的機能異常に対しては保湿・保護剤外用などを含むスキンケアを行い，瘙痒に対しては抗ヒスタミン薬，抗アレルギー薬の内服を補助療法として併用し，悪化因子を可能な限り除去することを治療の基本とするコンセンサスが確立されている．日本皮膚科学会によるアトピー性皮膚炎の診断基準は1994年に[1]，重症度分類は1998年の中間報告を経て[2]，2001年に策定された[3]．日本皮膚科学会アトピー性皮膚炎治療ガイドラインは2000年に初めて策定され，その後2003年，2004年に改訂されている[4]~[6]．このガイドラインはホームページ上（http://www.dermatol.or.jp/medical/guideline/pdf/114020135j.pdf）でも公開されている．さらに，暮しの手帖社より，一般患者向けのガイドライン解説書『専門医がやさしく語るアトピー性皮膚炎』も出版され，本症に対する正しい理解の普及がなされてきた．今回，アトピー性皮膚炎の診断基準，重症度分類，治療ガイドラインを統合したものとして，アトピー性皮膚炎診療ガイドラインを策定した．また，アトピー性皮膚炎治療における evidence-based medicine（EBM）については，「アトピー性皮膚炎—よりよい治療のためのEBMデータ集—」（http://www.kyudai-derm.org/atopy_ebm/index.html）が公開されている．

なお，本ガイドラインは，アトピー性皮膚炎の診療において，プライマリーケアの段階から高度の専門性が要求される段階までの患者を診療する，皮膚科診療を専門とする医師を対象としたものである．

II. 病　　態

アトピー性皮膚炎は表皮，なかでも角層の異常に起因する皮膚の乾燥とバリアー機能異常という皮膚の生理学的異常を伴い，多彩な非特異的刺激反応および特異的アレルギー反応が関与して生じる，慢性に経過する炎症と瘙痒をその病態とする湿疹・皮膚炎群の一疾患であり，患者の多くはアトピー素因を持つ．アトピー素因とは，①家族歴・既往歴（気管支喘息，アレルギー性鼻炎・結膜炎，アトピー性皮膚炎のうちいずれか，あるいは複数の疾患）があること，または②IgE抗体を産生しやすい素因をさす．

また，一般に慢性に経過するも適切な治療により症状がコントロールされた状態に維持されると，自然寛解も期待される疾患である．

III. 診断基準

1. 診断基準

1994年に策定された日本皮膚科学会「アトピー性皮膚炎の定義・診断基準」（今回改訂している）に基づき，

[1]九州大学大学院医学研究院皮膚科学（委員長）
[2]東京大学大学院医学系研究科皮膚科学（副委員長）
[3]和歌山県立医科大学皮膚科学
[4]広島大学大学院医歯薬学総合研究科皮膚科学
[5]自治医科大学皮膚科学
[6]大阪大学大学院医学系研究科皮膚科学
[7]国立成育医療センター皮膚科
[8]順天堂大学医学部皮膚科学
[9]金沢大学大学院医学系研究科皮膚科学
別刷請求先：（〒812-8582）福岡県福岡市東区馬出3—1—1　九州大学大学院医学研究院皮膚科学
古江　増隆

表1　アトピー性皮膚炎の定義・診断基準（日本皮膚科学会）

アトピー性皮膚炎の定義（概念）

アトピー性皮膚炎は，増悪・寛解を繰り返す，瘙痒のある湿疹を主病変とする疾患であり，患者の多くはアトピー素因を持つ．

アトピー素因：①家族歴・既往歴（気管支喘息，アレルギー性鼻炎・結膜炎，アトピー性皮膚炎のうちいずれか，あるいは複数の疾患），または②IgE抗体を産生し易い素因．

アトピー性皮膚炎の診断基準

1．瘙痒

2．特徴的皮疹と分布

①皮疹は湿疹病変

- 急性病変：紅斑，湿潤性紅斑，丘疹，漿液性丘疹，鱗屑，痂皮
- 慢性病変：浸潤性紅斑・苔癬化病変，痒疹，鱗屑，痂皮

②分布

- 左右対側性

好発部位：前額，眼囲，口囲・口唇，耳介周囲，頸部，四肢関節部，体幹

- 参考となる年齢による特徴

乳児期：頭，顔にはじまりしばしば体幹，四肢に下降．

幼小児期：頸部，四肢関節部の病変．

思春期・成人期：上半身（頭，頸，胸，背）に皮疹が強い傾向．

3．慢性・反復性経過（しばしば新旧の皮疹が混在する）

：乳児では2カ月以上，その他では6カ月以上を慢性とする．

上記1，2，および3の項目を満たすものを，症状の軽重を問わずアトピー性皮膚炎と診断する．そのほかは急性あるいは慢性の湿疹とし，年齢や経過を参考にして診断する．

除外すべき診断

- 接触皮膚炎
- 脂漏性皮膚炎
- 単純性痒疹
- 疥癬
- 汗疹
- 魚鱗癬
- 皮脂欠乏性湿疹
- 手湿疹（アトピー性皮膚炎以外の手湿疹を除外するため）
- 皮膚リンパ腫
- 乾癬
- 免疫不全による疾患
- 膠原病（SLE，皮膚筋炎）
- ネザートン症候群

診断の参考項目

- 家族歴（気管支喘息，アレルギー性鼻炎・結膜炎，アトピー性皮膚炎）
- 合併症（気管支喘息，アレルギー性鼻炎・結膜炎）
- 毛孔一致性の丘疹による鳥肌様皮膚
- 血清IgE値の上昇

臨床型（幼小児期以降）

- 四肢屈側型
- 四肢伸側型
- 小児乾燥型
- 頭・頸・上胸・背型
- 痒疹型
- 全身型
- これらが混在する症例も多い

重要な合併症

- 眼症状（白内障，網膜剥離など）：とくに顔面の重症例
- カポジ水痘様発疹症
- 伝染性軟属腫
- 伝染性膿痂疹

（文献1より引用，改変）

1）瘙痒，2）特徴的皮疹と分布，3）慢性・反復性経過の3基本項目を満たすものを，症状の軽重を問わずアトピー性皮膚炎と診断する．疑診例では急性あるいは慢性の湿疹とし，年齢や経過を参考にして診断する（http://www.dermatol.or.jp/medical/guideline/pdf/114020135j.pdf）[1]．この診断基準の英訳は1995年に公表されている[7]．なお，今回の改訂で除外すべき診断として新たに，皮膚リンパ腫，乾癬，免疫不全による疾患，膠原病（SLE，皮膚筋炎），ネザートン症候群が付け加えられた（表1）．除外すべき診断としてあげられ

た疾患を十分に鑑別でき，重要な合併症としてあげられた疾患について熟知していることが必要である．

＜参考＞世界的には1980年に作成されたHanifin&Rajkaの診断基準が頻用されている（参考表1）[8]．日本皮膚科学会による診断基準がHanifin&Rajkaの診断基準と異なる点は，アトピー疾患の既往歴・家族歴を基本項目から参考項目にした点であるが，アトピー性皮膚炎の定義（概念）としてアトピー素因が明記されている．Hanifin&Rajkaの診断基準における23の小項目症状はいずれも本症でしばしば観察される特徴的な症状であるが，その発現頻度はさまざまで，抽象的表現を用いた項目もあり，日本皮膚科学会による診断基準では省いてある．その後，"簡易版Hanifin & Rajkaの診断基準"ともいうべきものが2003年に公表されている（参考表2）[9]．

2. 検診における診断基準

日本皮膚科学会「アトピー性皮膚炎の定義・診断基準」を使用する．その際，自覚症状や経過の問診の信頼性が期待できない幼小児の検診では，「特徴的皮疹と分布」によって診断することが可能であるが，その旨を明記して公表する．

＜参考＞問診・調査表による全国調査

1994年にU. K. Working Partyによってアトピー性皮膚炎診断のための質問表が作成され[10]，世界的に使われている．日本でも邦訳版が作成され，その有用性が示された[11]．6～10歳児用の邦訳版を参考表3に示す．また，The International Study of Asthma and Allergies in Childhood（ISAAC）によって作成された質問表に基づいて，アトピー性皮膚炎を含む湿疹のグローバルな疫学調査が定期的に実施されている（http://isaac.auckland.ac.nz/Index.html）[12]．現在使用されている6～7歳児用の邦訳版を参考表4に示す[13][14]．

IV. 重症度分類

1. 臨床試験に有用な重症度分類

日本皮膚科学会アトピー性皮膚炎重症度分類検討委員会によるアトピー性皮膚炎重症度分類は統計学的信頼性と妥当性が検証されており，臨床試験に用いることが可能である（図1）（最高点数60点）[3]．本委員会の検討による簡便法として，全身を頭頸部，前体幹，後体幹，上肢，下肢の5部位に分け，各部位のグローバル評価の総和を求める方法も提示されている（図2）（最高点数20点）[2]．

＜参考＞さらに簡便な方法として，厚生労働科学研究班により重症度のめやすも提案されている（http://www.mhlw.go.jp/new-info/kobetu/kenkou/ryumachi/index.html）（参考表5）．世界的にはEuropean Task Force on Atopic DermatitisによるSeverity Scoring of Atopic Dermatitis（SCORAD）（参考図1）（最高点数103点）あるいは米国のEczema Area and Severity Index（EASI）（参考表6）（最高点数72点）が頻用されている[15][16]．

＜参考＞皮疹の経過を加味した重症度分類

皮疹の経過を加味した重症度分類としてRajka & Langelandによる重症度分類が頻用されている（参考図2）[17]．また上記のISAACの調査表（参考表4）では，「最近12カ月のあいだに，平均してどのくらいの頻度で，あなたのお子さま（あなた）は，このかゆみを伴った皮疹（ひしん）のために，夜間起きていることがありましたか？」という質問を用いて「1週間に1晩かそれ以上」で眠れないことがある場合は重症と判断している[12]～[14]．

＜参考＞痒みの評価

痒みの評価にはVisual analogue scale（VAS）が有用である[18]．VASは痒みの程度に応じて10cmの線分上の1点に印を付け，左端の「痒みなし」を0，右端の「最もひどい痒み」を100として，左端から印を付けた部位までの距離（mm）を痒みの尺度値として評価する方法である．SCORADでも記載されているように（SCORADでは0～10で評価）VASは睡眠障害に対しても用いうる（参考図1）．文章表現による痒みの評価で，エビデンスレベル2以上の臨床試験に用いられたものを参考表7に示す[19][20]．

＜参考＞Quality of Life（QOL）による評価

Skindex-16（参考表8）ならびにDermatology Life Quality Index（DLQI）（参考表9）が統計学的に詳細に解析され，その邦訳が出版されている[21]～[27]．

2. 個々の皮疹の重症度

治療の主体である外用療法の選択は「個々の皮疹の重症度」（表2）により決定される．すなわち，範囲は狭くとも高度な皮疹には十分に強力な外用療法が選択されるが，範囲は広くとも軽度の皮疹には強力な外用療法は必要としない．よって，外用療法の選択のためには「個々の皮疹の重症度」が最も重要であり，重症度判定はその判断を下し，さらには治療効果を予測しう