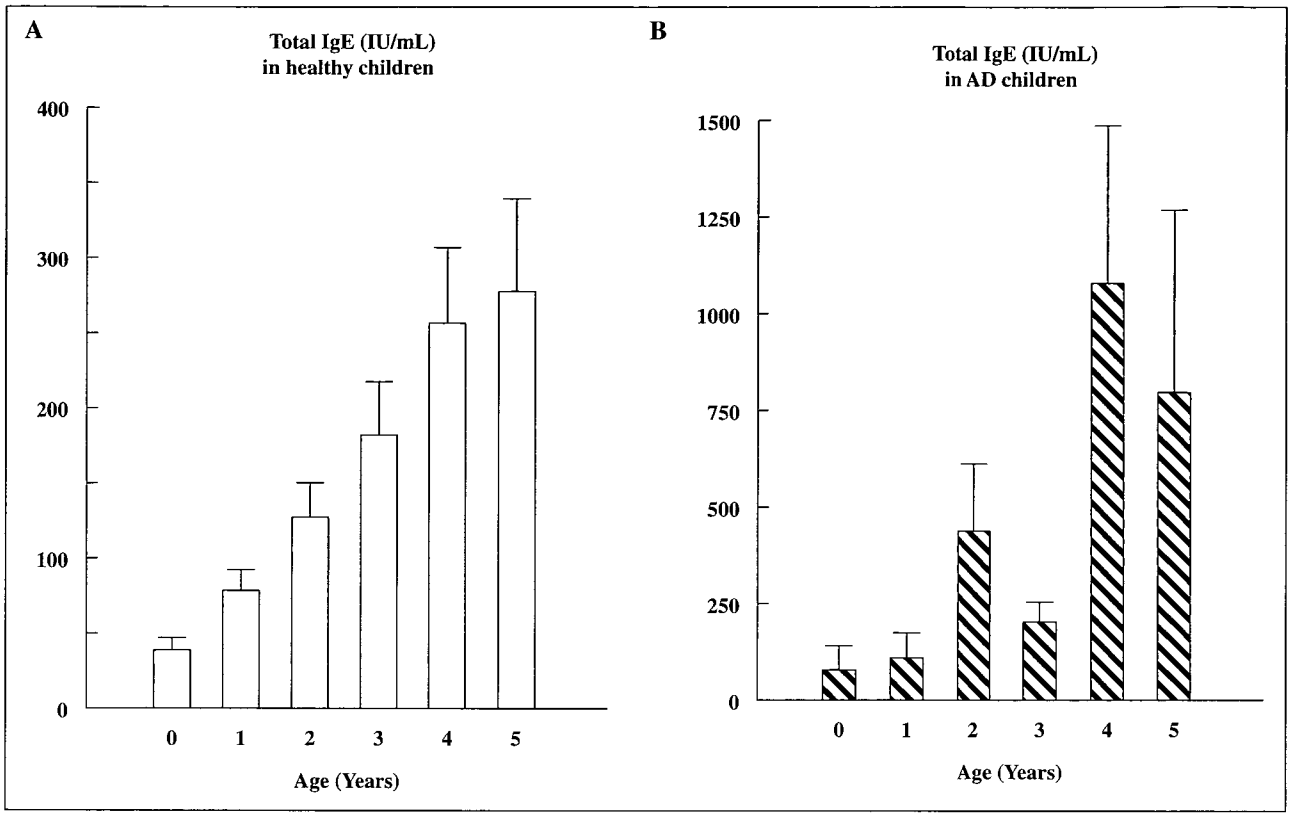

Figure 2. A) Age-related differences in serum total IgE levels of healthy children. The mean IgE (IU/mL) level of the healthy children significantly increased with age (P = 0.0109 by Kruskal-Wallis test). Data are shown as means ± SD. **B)** Age-related differences in serum total IgE levels of children with atopic dermatitis (AD). The mean IgE (IU/mL) level of the AD children did not significantly change with age (P = 0.6641 by Kruskal-Wallis test). Data are shown as means ± SD.

Follow-up study of the natural course of AD

Of the 1359 children examined, 350 were followed in both 2003 and 2004, 44 of them were diagnosed as having AD at the initial physical examination in 2003. Of these 44, 30 were confirmed to have regressed AD in 2004. Of the 306 children without AD, 17 newly developed AD. In 2004, 14 children had sustained AD (Group A), 30 had regressed AD (Group B), 17 had newly developed AD children (Group C), and 289 children were healthy without AD (Group D).

Figure 3 shows the mean serum TARC levels of the sustained, regressed, newly-developed AD and non-AD children in 2003. The mean ± SE serum TARC level in Group A (691.7 ± 84.4 pg/mL) was significantly higher than that of the other groups (569.9 ± 57.6 pg/mL in Group B, 380.1 ± 27.7 pg/mL in Group C, and 506.3 ± 18.1 pg/mL in Group D) (all $P < 0.05$, Group A *vs.* other groups). These findings suggest that a higher TARC level correlates with the sustained AD.

Figure 4 shows the mean serum IgE levels of the sustained, regressed, newly-developed AD and non-AD children in 2003. The mean ± SE serum IgE levels in Groups A, B, and C (800.8 ± 494.1 IU/mL, 461.9 ± 260.1 IU/mL, 369.4 ± 217.2 IU/mL, respectively) were significantly higher than that of Group D (108.3 ± 14.4 IU/mL) (all $P < 0.05$, Group D *vs.* other groups).

Figure 5 shows changes in the mean serum TARC levels of the sustained, regressed, newly-developed AD and non-AD children. In Group A children, the mean ± SE levels of serum TARC in 2003 and 2004 were stably high (691.7 ± 84.4 pg/mL in 2003, 682.0 ± 100.9 pg/mL in 2004) without any significant difference (P = 0.0747). In Group B and D children, the mean ± SE serum TARC levels significantly decreased from 2003 to 2004 (644.2 ± 57.6 pg/mL to 448.7 ± 65.7 pg/mL in Group B, P = 0.0145 and 506.3 ± 18.1 pg/mL to 442.1 ± 10.9 pg/mL in Group D, $P < 0.0001$). In Group C children, the mean ± SE serum TARC levels significantly increased from 2003 to 2004 (380.1 ± 27.7 pg/mL to 491.8 ± 30.4 pg/mL) (P = 0.0203). These findings suggest that an increase in the TARC level correlates with the sustained and developed AD.

Figure 6 shows changes of mean serum IgE levels in the sustained, regressed, newly-developed AD and non-AD children. In Groups A, B, and D children, the mean ± SE serum IgE levels significantly increased from 2003 to 2004 (800.8 ± 494.1 IU/mL to 2375.3 ± 1613.6 IU/mL in Group A, P = 0.0277, 461.9 ± 260.1 IU/mL to 541.4 ± 212.5 IU/mL in Group B, P = 0.0068, and 108.3 ± 14.4 IU/mL to 196.6 ± 27.1 IU/mL in Group D, $P < 0.0001$). In Group C children, even though their AD lesions newly developed, the change of mean ± SE serum IgE levels did not significantly increase from 2003 (369.4 ± 217.2 IU/mL) to 2004 (356.4 ± 90.5 IU/mL) (P = 0.9434). These findings suggest that a change in the IgE level dose not apparently correlate with the regressed AD.

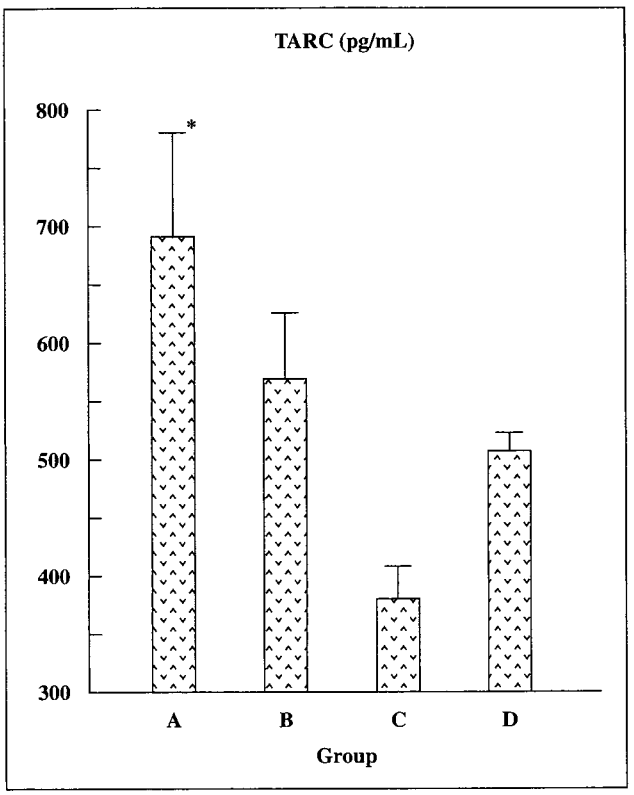

Figure 3. The mean serum thymus and activation-regulated chemokine (TARC) levels of the **(A)** sustained, **(B)** regressed, **(C)** newly-developed atopic dermatitis (AD) and **(D)** non-AD children in 2003. Group A: 14 children who had sustained AD between 2003 and 2004, Group B: 30 children in whom AD regressed form 2003 to 2004, Group C: 17 children who newly developed AD between 2003 and 2004, Group D: 289 healthy, non-AD children between 2003 and 2004. Data are shown as means ± SE.
* means $p < 0.05$ *vs.* other children groups.

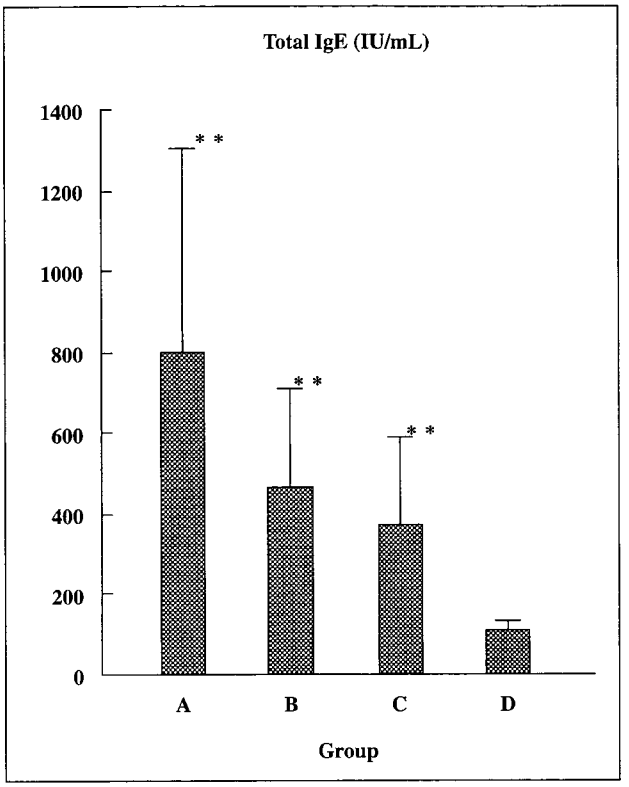

Figure 4. The mean serum IgE levels of the **(A)** sustained, **(B)** regressed, **(C)** newly-developed atopic dermatitis (AD) and **(D)** non-AD children in 2003. Group A: 14 children who had sustained AD between 2003 and 2004, Group B: 30 children in whom AD regressed form 2003 to 2004, Group C: 17 children who newly developed AD between 2003 and 2004, Group D: 289 healthy, non-AD children between 2003 and 2004. Data are shown as means ± SE.
** means $p < 0.05$ *vs.* Group D.

Discussion

AD represents a major public health problem worldwide and usually develops in early childhood [22]. To date, there has been no gold standard for assessing the clinical course of AD. The previous studies on adult AD patients showed that an evaluation has been carried out of the association between the disease activity of AD and serum TARC levels as an objective chemokine marker [10, 11]. In the present study, we demonstrated strong associations between the serum TARC levels and the natural course (newly developed, regressed, and maintained AD) of childhood AD through an analysis of data from our KIDS trial, a population-based cohort study with a large number of children. These findings indicated that serum TARC played an important role in the natural course of AD in children.
Th2 cells and eosinophils are the most prominent cells of allergic inflammation that selectively express CC chemokine receptor (CCR) 4 and CCR3, respectively. TARC, the chemokine ligand of CCR4, implicates the mechanism of inflammation in allergic diseases [23, 24]. Keratinocytes, T cells and dendritic cells are major sources of TARC in AD patients [10, 22]. The serum TARC levels of AD children were significantly higher than those of healthy children in the present study. In a study of adults [10, 25], the increases in serum TARC levels of AD patients were greater in a severely affected patient group than in moderate or mild groups. The TARC levels of adult AD patients decreased after the treatment in accordance with an improvement in clinical symptoms. In addition, the serum TARC levels were significantly correlated with number of eosinophils and other inflammation markers. These results strongly suggest that serum TARC levels are closely related to the disease activity of AD.
In the present study, serum TARC levels of both children with and without AD showed significant correlations with total IgE levels. AD is characterized by the predominant inflammation of mononuclear cells, especially T cells, eosinophils and macrophages in lesional skin and is associated with a high serum level of IgE [11]. Our study showed that serum total IgE level of AD children was significantly higher than that of healthy children. However, we also demonstrated that the changes in the IgE level did not apparently correlate with the regressed AD and healthy children. Moreover, total IgE level of healthy children was confirmed to significantly increase with age, as was found in previous studies [17, 18]. Therefore, serum total IgE would not be an appropriate marker for assessing the natural course of AD in children, although a high IgE level may indicate the possible persistence of AD.

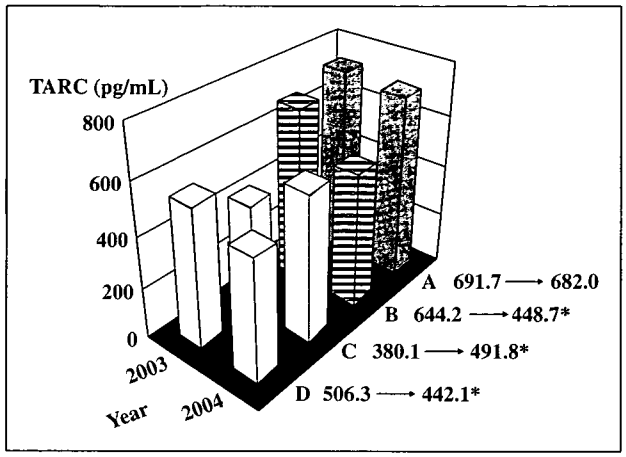

Figure 5. Changes of the mean serum thymus and activation-regulated chemokine (TARC) levels of the **(A)** sustained, **(B)** regressed, **(C)** newly-developed atopic dermatitis (AD) and **(D)** non-AD children. Group A: 14 children who had sustained AD between 2003 and 2004, Group B: 30 children in whom AD regressed form 2003 to 2004, Group C: 17 children who newly developed AD between 2003 and 2004, Group D: 289 healthy, non-AD children between 2003 and 2004. Data are shown as means. * means $p < 0.05$ by Wilcoxon test.

The TARC gene is located at chromosome 16q13 [26], where total serum IgE level has been reportedly linked [27]. Although a single nucleotide polymorphism (SNP) of TARC gene is a candidate of the genetic factors in allergic diseases, no significant association of the SNP with susceptibility to AD and bronchial asthma was reported [23, 28]. The elevation of serum TARC levels could be induced by other cytokines that enhance the TARC production, but not by this TARC SNP as the promoter.

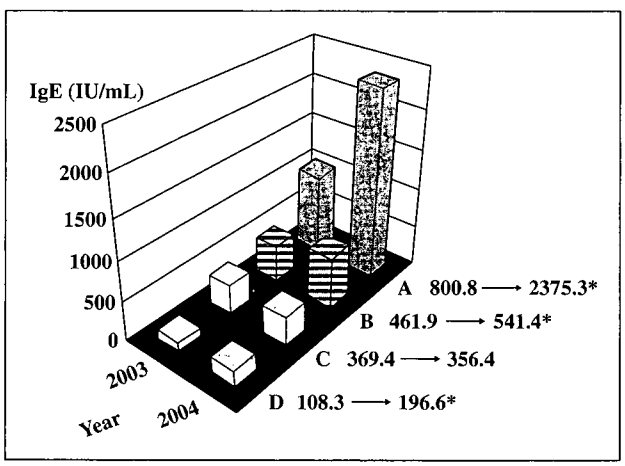

Figure 6. Changes of the mean serum IgE levels of the **(A)** sustained, **(B)** regressed, **(C)** newly-developed atopic dermatitis (AD) and **(D)** non-AD children. Group A: 14 children who had sustained AD between 2003 and 2004, Group B: 30 children in whom AD regressed form 2003 to 2004, Group C: 17 children who newly developed AD between 2003 and 2004, Group D: 289 healthy, non-AD children between 2003 and 2004. Data are shown as means.
* means $p < 0.05$ by Wilcoxon test.

In the present study, we found a significant positive correlation between TARC, total IgE and the natural course of AD. In a study of a murine model of bacteria-induced hepatic failure, TARC mediated infiltration of CCR4 cells in hepatic lesions was inhibited by administration of a monoclonal antibody to TARC [29]. The use of a neutralizing monoclonal antibody to TARC suppresses allergic inflammation and attenuates the accumulation of eosinophils in a murine model of allergen-induced asthma [30]. In addition, basic studies demonstrated the intracellular signaling pathways linked to TARC and CCR4-mediated chemotaxis [31, 32]. In a clinical study, the production of TARC by peripheral blood mononuclear cells in adult AD patients was dramatically inhibited by the administration of an antagonistic drug against the histamine H_1 receptor, Olopatadine [33]. Taken together, chemokine-target treatment may be an effective strategy for the treatment of allergic diseases including AD.

Serum chemokine markers for AD have been extensively studied in both adults and children. Specially, the levels of AD-associated chemokines such as cutaneous T-cell attracting cytokine (CTACK), macrophage-derived chemokine (MDC), and interleukin (IL)-18 were correlated with various clinical signs and severity of eczema in children [5, 34-36]. However, it was not reported which was the most useful for evaluating the disease state. The solution awaits further study.

Our patients diagnosed as AD had not been treated with topical or systematic drugs due to their mild AD lesions. During the present study, we have held the annual educational meetings for their parents, guardians, and school teachers only about the basic management for AD, addressing the skin barrier defect with skin hydration along with identification and avoidance of specific and nonspecific irritating trigger factors [37, 38]. Therefore, this study did not include the children with AD who have received medical interventions.

Japanese investigators reported that the prevalence (17.3%) of AD was significantly higher in the cooler climate of Gifu Prefecture, the middle area of Honshu (main island of Japan), than in the warmer climate of Itoman, Okinawa (3.4%), even after controlling for genetic and environmental factors [39, 40]. In our previous studies [17, 18], the prevalence of AD (6.9%) in children aged 5 years and younger in Ishigaki Island, which is located in the subtropical zone of Japan, was lower than the average rate on the mainland of Japan, possibly suggesting that the AD prevalence can depend on climate state. A worldwide survey has reported that AD is increasing in the developed countries in cooler climates [41], although the reason for the lower prevalence in the warmer climate areas remains to be elucidated.

The limitation of our study is that we did not perform any scoring of AD so that a correlation with the activity or severity has not been carried out, which would increase and strengthen the relevance of the data. In addition, concomitant atopic diseases such as allergic rhinitis or asthma have not been considered in the present analysis. However, we believe that the topic of our study, the relevance of chemotactic signals in the natural course of AD, will be interesting and important for physicians and researchers, because the study power of this longitudinal and population-based approach is very high.

In conclusion, we demonstrated strong associations between serum TARC levels and the natural course of childhood AD in this population-based cohort study with a large number of children. Monitoring serum TARC levels of AD children may be useful for the biological evaluation of AD. ■

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ORIGINAL ARTICLE

Development of atopic dermatitis-specific communication tools: Interview form and question and answer brochure

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ABSTRACT

At first consultation, it is sometimes difficult for patients to decide which questions they want to ask most. We investigated whether an improvement in interview forms would identify the questions that patients want to ask doctors and help patients express their needs. First, we developed a two-part interview form specifically for atopic dermatitis (AD) patients. The first part was related to diagnosis. In the second part, we determined the most frequently asked questions by patients in daily AD clinics and included these in a prompt interview form, which we called "Questions You May Want to Ask". We compared this new interview form with the standard interview one used in our hospital. Then we made a brochure with answers to those questions. Finally, we evaluated the usefulness of these communication tools. The usefulness of the AD-specific interview form and the answer brochure was validated by patients and/or their surrogates. The majority of them recognized the necessity for and usefulness of these tools to communicate appropriately with their doctors. The answer brochure significantly increased their understanding of AD. The AD-specific interview form and the answer brochure are useful communication tools to improve doctor–patient relationships.

Key words: atopic dermatitis, communication tools, consultation, prompt interview form, Q&A brochure.

INTRODUCTION

Treatment of atopic dermatitis (AD) is diverse depending on the patient's condition, and their demands are also varied. Recently, many studies have investigated the quality of life (QOL) of patients with AD. Patients often feel anxieties or dissatisfaction with their treatments because of their possible adverse effects.[1] If not expressed, such fears can decrease the QOL of AD patients. Patients generally want to ask their doctors many questions about the treatment, future clinical course, and inheritance of the disorder. However, it is sometimes difficult for patients, especially during the first consultation with doctors, to decide which questions they want to ask most. Butow *et al.* suggested that a patient's active participation in the discussion of the condition and ability to ask questions are important ways to ensure that patients have understood what their doctors have said.[2] Additionally, for a good quality of care, to reduce anxieties and dissatisfaction with treatments, mutual understanding and cooperation between patients and doctors is necessary because both parties could have different views on health complaints and treatment.[3]

For better mutual partnership, several approaches have been proposed to improve communication between patients and physicians.[2–8] Recent preliminary studies by an Australian oncology group suggested that giving patients prompt sheets with suggested questions might enhance communication during consultations.[2,5–8] Harmsen *et al.* developed a mutual

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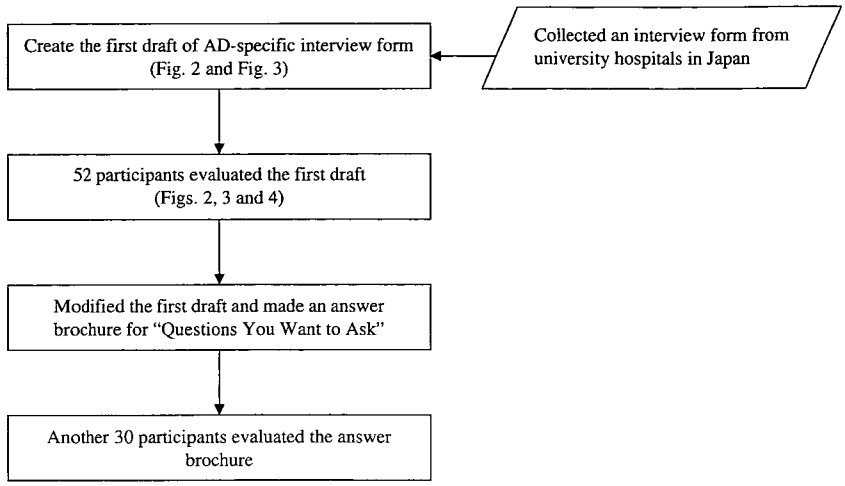


Figure 1. A 4-step procedure of this study: (i) we created the first draft of atopic dermatitis (AD)-specific interview form while collecting an interview form which was used routinely for outpatients from university hospitals in Japan; (ii) we asked 52 AD patients or their surrogates to evaluate the first draft; (iii) we modified it modified the interview form accordingly and made an answer brochure for "Questions You May Want to Ask" on the interview form; and (iv) we asked another 30 AD-patients or their surrogates to assess the answer brochure.

understanding scale to assess the degree of understanding between patients and physicians.[3] For AD, Gore *et al.* explored information needs and decisional role-preferences of parents caring for infants with AD.[9]

Based on issues raised in these studies, we examined the standard interview form which had been used routinely in the dermatology department of our university hospital during initial outpatient consultations. As reported here, we developed a two-part AD-specific interview form that included a prompt questionnaire from the patients' point of view, and investigated whether such a newly developed interview form would assist patients in bringing up the questions they wanted to ask, which would contribute to better understanding of AD by patients.

MATERIALS AND METHODS

Design of the AD-specific interview form

Our AD-specific interview form consisted of two parts, a diagnostic and a prompt-question part (Fig. 1). For the diagnostic part, we selected typical and specific questions about AD (e.g. visual analogue scale for itch, how to apply ointment, interruption of medication) (Fig. 2; all forms originally in Japanese). For this purpose, we collected various interview forms from 41 dermatology clinics in other university hospitals and categorized the questions most frequently asked.

For the latter prompt-question part, we selected questions that patients might want to ask their doctors. Over a period of 2 years we monitored conversations between doctors and patients to determine which questions should be included in the communication tools. We selected 17 representative questions that AD patients or their surrogates asked most frequently to their doctors. The 17 questions were arranged into five categories: (i) treatment in general; (ii) medication; (iii) inheritance, pregnancy and childcare; (iv) daily life; and (v) foods (including dietary avoidance). Figure 3 shows the first draft of the prompt sheet, which is called "Questions You May Want to Ask".

Comparison of the first draft of the AD-specific interview form with the standard interview form

To evaluate the first draft of the AD-specific interview form, we asked patients to compare that interview part (diagnostic part) with the standard interview form that had been used in our university hospital (Fig. 4). Additionally, we asked them whether each question in the prompt question part, "Questions You May Want to Ask", properly represented the problems and concerns of AD patients. Fifty-two patients or their surrogates evaluated these interview forms. For the prompt question part, we asked participants to select questions they wanted to ask most. If they had questions in addition to the 17 questions on the sheet, we asked them to write them in a space entitled "In Addition". After analyzing the 52 replies, we modified the first draft of the prompt interview form to create a final draft of the AD-specific interview form.

- **Your Current Condition**

"*What is your trouble with Atopic Dermatitis?*"

( )

"*When were you diagnosed with Atopic Dermatitis?*" (Age: about_____)

"*On which part of your body is most frequently affected?*" (Please circle the number)

1. Head	2. Face	3. Ears	4. Neck	5. Breast	6. Back	7. Abdomen
8. Arms	9. Palms	10. Buttocks	11. Pubic Region	12. Thigh	13. Legs	14. Whole Body

"*If the most terrible condition that you have had is scored 10, what score would you give your current condition?*"

(/10)

- **Drugs you used during the last 6 months**

"*What kinds of medicines did you use?*"

Ointments	(Name)
Tablets	(Name)
Others	(Name)

"*If you used an ointment, how did you apply it?*"

Part of your body	Ointment	How/How often did you apply it?
(e.g.) Face	Tacrolimus	Twice/day, thin application

- **Concomitant diseases**

"Have you ever been treated for conditions other than Atopic Dermatitis?" (Yes/No)

-If "yes", please fill out the form below

Name of Disease	
Name of Drugs	

- **Your treatment course**

"*Have you ever interrupted the treatment of Atopic Dermatitis?*" (Yes/No)

-If "yes", please check the reason below:

☐Didn't want to use steroid ointments ☐Didn't like the doctor
☐Moved to another area ☐Busy at work or school
☐Other reasons

( )

"*How long did you interrupt the treatment?*" (about years/month)

Figure 2. The AD-specific interview form is composed of two parts: a diagnostic part (shown here) and a section entitled "Questions You May Want to Ask".

"Questions You May Want to Ask"

Do you have any questions today? If so, please read this list of questions and circle those you want to ask your doctor. If you want to ask other questions, please write them in the space "In Addition". If your doctor cannot answer all of your questions today, he/she will answer the remaining questions at the next visit.

♦**Treatment in general**	1) If I/my child go to another doctor (or other doctors) for atopic dermatitis what treatments or advices would be the most appropriate? 2) Is it necessary to have a second opinion to decide the treatment course?
♦**Medicines**	3) How do I apply ointments or take tablets? 4) What kind of side effects could occur when taking steroid or other medicine? 5) How can I discriminate the eruptions from atopic dermatitis from those of other skin diseases? 6) Did I use appropriate medicines (ointment, tablet and so on)? 7) Can I take medicines that are prescribed by other clinics?
♦**Inheritance, Pregnancy and Childcare**	8) Is atopic dermatitis inherited? 9) If I have atopic dermatitis, will it be a problem to breast-feed my baby? 10) I have used steroid ointment for a long time. If I am pregnant, will it affect the fetus?
♦**Daily Life**	11) Are alternative treatments effective? 12) What kind of detergent and bathing remedies (including spa) are good for AD patients? 13) What kind of clothes, bedclothes, carpets, etc. are good for atopic patients? 14) Is it possible to exercise with the current skin condition?
♦**Foods**	15) What are good/bad foods for atopic patients? 16) Is food avoidance therapy effective or necessary for treatment of atopic dermatitis? 17) What cooking method is the most suitable for atopic children?

♦**In Addition (Please use this space for other questions you may have)**

Figure 3. "Questions You May Want to Ask". There are 17 questions which are asked by AD patients very often. There is also a blank space, "In Addition", for extra questions.

Design and evaluation of answer brochure for "Questions You May Want to Ask"

We then created an answer brochure based on "Questions You May Want to Ask" using the same title. We expected that such written material would improve patients' understanding of AD. To determine whether the answer brochure enhanced patients' understanding of AD, another 30 AD patients or surrogates participated in the assessment of the answer brochure. We asked them to evaluate their understanding of AD on the five categories before and after reading the brochure using a visual analog scale (VAS) ranging 0–10.

Statistical analysis

Results were analyzed by the paired *t*-test. A *P* value less than 0.05 was considered to be statistically significant. The analysis was performed using SPSS® software version 11.0J for Windows® (SPSS®, Chicago, IL, USA).

RESULTS

Comparison of the AD-specific interview form with the standard interview form

We asked 52 AD patients or surrogates to compare the two-part AD-specific interview form with the

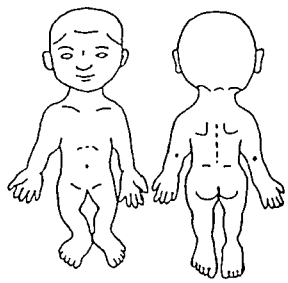
Please fill out this form.

1. Your symptom

   (1) Onset date: about _____(year)_____(month)_____(day) (age:)

   (2) Distribution: Please mark affected areas on the drawing of the human body.

   (3) Symptoms: pain, itch, redness, blister, tumor, pigment spot, others ( )



2. Previous treatments

   "Have you ever been treated for this condition?"

   (1) Yes → previous medicines:

   treatment duration:

   (2) No

3. History

   "In addition to this condition, have you ever had any other disease?"

   (1) Yes → name of disease:

   medicines you used:

   (2) No

4. Family history

   "Does anyone in your family have skin diseases?"

   (1) Yes → name of disease:

   Please circle the affected member(s).

   grandfather, grandmother, father, mother, older brother, older sister, younger brother, younger sister, your children

   (2) No

5. Drug allergy

   "Have you ever been allergic to any medicine?"

   (1) Yes → name of medicine:

   (2) No

6. Alcohol/cigarette

   (1) Alcohol: about ( )/Day

   (2) Cigarette: about ( )/Day

Figure 4. This form is used routinely for outpatients at the Dermatological Department of Kyushu University Hospital. We asked AD patients or their surrogates to compare this form with our AD-specific interview form and then answer the questionnaire.

standard form by answering questions, some of which are described below.

Of the 52 responders to the question "Which interview form do you want to use?", 41 chose (78.8%) the AD-specific interview form while 11 (21.2%) preferred the standard interview form.

For the question "Why did you choose the two-part AD-specific interview form?", the main reasons

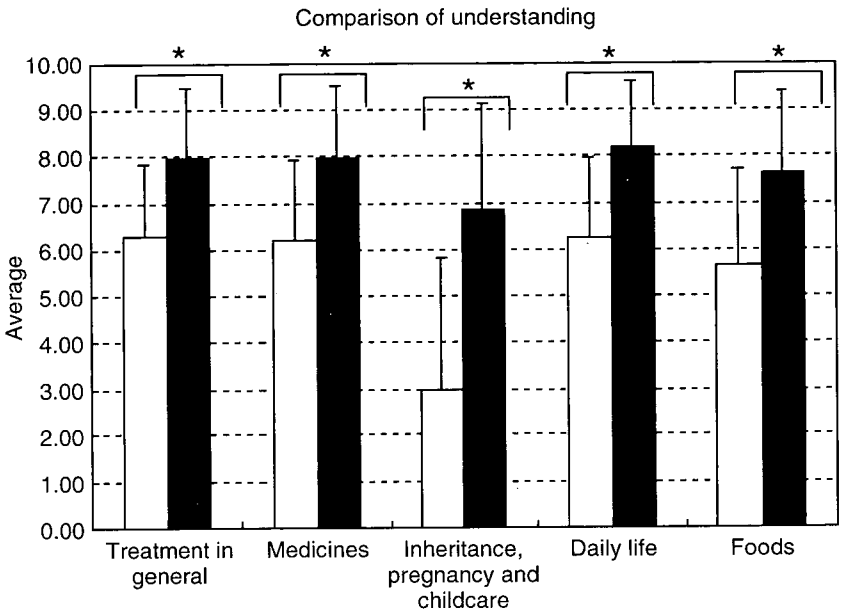


Figure 5. Statistical analysis of information provided by 30 AD patients or their surrogates. They estimated their level of understanding of AD before (□) and after (■) they read the answer brochure by five categories: (i) treatment in general; (ii) medicines; (iii) inheritance, pregnancy and childcare; (iv) daily life; and (v) foods in the brochure.

why the 41 responders selected the two-part interview form were: "It made it easier to ask doctors specific questions than did the standard form" (14; 34.1%); "Questions were from the patient's point of view" (13; 31.7%); and "It made it easier to communicate with doctors" (8; 19.5%). Although the latter part, "Questions You May Want to Ask", was appraised highly, three of 11 responders (27.3%) who did not choose our AD interview form pointed out that it was time-consuming to read all of the questions and the two of the 11 responders (18.2%) mentioned they were worried that a very detailed interview form would keep doctors from discussing issues other than those on the interview form with patients.

Evaluation of the first draft of the prompt form

Each responder selected the questions they wanted to ask doctors from the 17 prompt questions. All 17 questions were selected by responders at least once. Frequently selected questions were "What are good/bad foods for AD patients?" (33; 63.5%), "What kind of detergent and bath remedies (including spa) are good for AD patients?" (28; 53.8%) and "What kind of side-effects could occur when applying steroids or other ointments?" (26; 50.0%). All 52 responders agreed that the 17 questions on the prompt form represented their concerns about AD. Reflecting their comments, we made minor typographical and grammatical changes in the 17 questions and made a final version of the prompt form, "Questions You May Want to Ask".

Enhancement of patients' understanding through use of the answer brochure

We next prepared a brochure containing the answers to the 17 questions on the prompt interview form. The answer brochure was also called "Questions You May Want to Ask." Information in this answer brochure was based on "Guidelines for Therapy for Atopic Dermatitis 2004" by the Japanese Dermatological Association[10] and some booklets about AD edited by expert dermatologists. We asked another 30 AD patients or their surrogates to evaluate this brochure. After they read the brochure, their understanding in all the five categories was significantly improved (Fig. 5; $P < 0.01$). All 30 participants stated that the brochure helped their understanding of AD.

DISCUSSION

Several approaches have been proposed for improving communication between patients and physicians. In oncology consultations, a prompt sheet endorsed by the physician is an effective means of encouraging

patients' involvement in the cancer consultation.[8] Patients who expressed a desire for involvement in medical decision-making spent more time asking questions and making statements.[2] Also, patients who used the prompt sheet asked apparently more questions in general than those without and, in particular, asked more questions about tests and treatments.[8] In oncology consultation, doctors usually withheld detailed information regarding cancer diagnosis, prognosis and treatment options in the belief that such information would cause the patient excessive fear, anxiety and loss of hope, thus worsening patient outcomes. However, recently, cancer patients who are informed of their diagnosis are increasingly unwilling to adopt a traditional, passive role in the medical consultation. Patients commonly seek information to enable them to make decisions about treatment, to understand prognostic issues and to be clear about side-effects of treatment.[11–13] Prompt sheets are, therefore, suitable communication tools to encourage patients to participate in the discussion of the condition and to understand what is said during the consultation.

Gore *et al.* explored the information needs and preferred level of involvement in treatment decisions by parents caring for infants with AD.[9] The authors mentioned that many parents felt that their baby's condition was not taken seriously, leading to delayed diagnosis and difficulty in receiving appropriate treatment. In light of this perceived indifference, and faced with a highly visible condition and visible distress, parents found they had to be more active than they wished to obtain information about the condition and its treatment. These findings suggest the need for improved awareness among health professionals of the problems associated with AD. Therefore, it is necessary to develop written information specifically for parents with regard to decision-making and to improve the partnership with physicians during consultations.[9]

Baron *et al.* compared the treatment patterns for AD by dermatologists in Japan with those in the US and the UK, and reported that the use of alternative remedies (e.g. traditional herbs, acidic water) was highest in Japan.[14] It is possible that the negative propaganda against topical steroids in Japan contributes to the tendency to resort to alternative remedies that appear more natural and are usually marketed as having no side-effects. According to Nakagawa's observation, patient anxiety over topical corticosteroids is also a factor in this phenomenon.[14] The mass media's negative propaganda, and social problems like the "atopy business",[15] enhance fear, anxiety and loss of hope in patients with AD in Japan. Therefore, it is very important for AD patients to understand and receive appropriate treatment. Bruera *et al.* has reported that a disease-specific prompt sheet provided before medical encounters is perceived to significantly assist in communication between patients and doctors.[16] This is why we decided to develop an AD-specific interview form to promote understanding of, and participation in, standard AD treatment by patients.

In the present study, we investigated whether an AD-specific two-part interview form could clarify the questions patients want to ask doctors, help patients with AD express their needs, as well as provide doctors with diagnostic information. We also made a brochure with answers to each question, because we thought that such written material would help patients better understand the answers or explanations by doctors during the consultation. Results of the evaluations showed that both tools helped patients ask their questions in the majority of occasions and significantly increased their understanding of AD. However, some participants felt that there was not a sufficient number of questions in the part of the interview form "Questions You May Want to Ask" and in the answer brochure. We certainly understand that 17 questions cannot account for every question that a patient might want to ask or address every patients' concerns, but this communication tool did include representative questions on AD that were observed to be frequently asked in daily AD clinics. We allowed space for patients to write down questions that were not included on the prompt form. Through the evaluation of the prompt interview form and the answer brochure, we found that these communication tools significantly increased patients' understanding of AD and helped them express their concerns to doctors. Limitations exist within the study. Our communication tools were developed from the patient's point of view as is our main objective. However, we think it is also necessary to evaluate these tools on the doctor's side.

Further studies are necessary regarding whether the prompt interview form may improve doctor–patient communication from the doctor's point of view.

In conclusion, most patients and/or their surrogates recognized the usefulness of the AD-specific interview form and the answer brochure to communicate their needs, fears and other feelings to their doctor. These communication tools may be useful in clinical practice of AD, especially with regard to patients who engage in multi-doctor consultation because of intense anxiety and who do not have a standard by which to judge information given to them. As future tasks, we will use our prompt interview form and the brochure in the AD consultation and research the effect on the doctor's side.

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1．小児アトピー性皮膚炎への0.03%タクロリムス軟膏の治療

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KEY WORDS　アトピー性皮膚炎，タクロリムス軟膏

はじめに

アトピー性皮膚炎の治療において，外用療法は極めて重要な位置を占める。ステロイド軟膏やタクロリムス軟膏の副作用に対する恐怖感や忌避感は，治療ガイドラインの普及に伴って下火になっているとはいえ，払拭されたとは言いがたい。外用療法の有用性をただただ強調するだけでは，患者のコンプライアンスはあがらない。その使用法や使用量に対してより具体的な分かりやすい説明を行うことが肝要となる。また小児アトピー性皮膚炎の治療では，患者のみならず家族のQOLを含めた十分な説明が必要である。アトピー性皮膚炎の治療に関するEBMはhttp://www.kyudai-derm.org/atopy_ebm/index.htmlに掲載されている。また患者向けのサイトは，「アトピー性皮膚炎について一緒に考えましょう」(http://www.kyudai-derm.org/atopy/）を参照されたい。治療ガイドラインの詳細については，皮膚科専門医を対象とした日本皮膚科学会治療ガイドライン(http://web.kanazawa-u.ac.jp/~med24/atopy/therapy.html）ならびに一般臨床医を広く対象とした厚労省治療ガイドライン(http://www.mhlw.go.jp/new-info/kobetu/kenkou/ryumachi/index.html）を参照していただきたい[1]。タクロリムス軟膏の有効性のEBMについては，上記EBMのホームページに詳述してあるので，本稿では「得られたEBMに基づいた患者への具体的な説明」に焦点を当てて論じたい。

Ⅰ．タクロリムス軟膏外用のEBMと副作用

小児アトピー性皮膚炎治療におけるタクロリムス軟膏のEBMに関しては，先に述べたEBMのウェブサイトで佐伯らによって詳述されているので参照されたい。ここでは，我が国で行われた大規模臨床試験についてまとめてみたい。2～15歳の221例による2重盲検パラレルRCT（基剤群；75例，0.03%タクロリムス群；75例，0.1%タクロリムス群；71例）では，3週間外用後の著明改

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善率は基剤群；12.7％，0.03％タクロリムス群；66.7％，0.1％タクロリムス群；75.7％であった。血中濃度は0.03％群で5/134サンプル（最大値；0.85 ng/mℓ）に，0.1％群で20/139サンプル（最大値；1.78 ng/mℓ）に検出された[2]。2～15歳の214例によるオープンパラレルRCT（0.03％タクロリムス群；104例，0.1％タクロリムス群；110例）では，1年間外用後の中等度改善以上は36週以降52週まで両群ともに90％以上に認められている。0.03％タクロリムス群の有害事象は，皮膚刺激感；50％，皮膚感染症；33.7％，合併症；5.8％で，0.1％タクロリムス群では皮膚刺激感；62.4％，皮膚感染症；22％，合併症；8.3％に認められた。血中濃度が3 ng/mℓ以上で検出されたのは2例のみであった。血中濃度は皮膚症状の改善とともに低下し，全身性副作用は認められなかった[3]。ついで上記2試験の継続試験が134例（2～15歳）で行われ，0.03％タクロリムス外用（うち増悪時に0.1％タクロリムス外用を行ったのは17例のみ）が継続された。観察期間は，平均；792日，最長観察期間；1060日であった。中等度改善以上は52週以降90％が維持された。有害事象は，皮膚刺激感；41％，皮膚感染症；41％，合併症；11.2％であった。3 ng/mℓ以上の血中濃度が検出された症例はなかった（最大値；2.24 ng/mℓ）。95％以上の症例では，血中濃度は検出限界以下（0.5 ng/mℓ以下）であった[4]。幼小児期の場合，0.03％と0.1％製剤で有効率に差がないことから，我が国では，0.03％タクロリムス軟膏が小児用として保険適応になった。0.03％タクロリムス軟膏小児用の長期外用でも血中濃度が検出されることはごくまれであった。このような大規模試験の結果から，①小児アトピー性皮膚炎に対してタクロリムス軟膏は高い臨床効果を発揮すること，②通常の外用量であれば血中濃度が連続して検出されることはほとんどないこと，③平均2年以上の外用観察期間中に重篤な副作用を認めていないことがわかる。後述するように，外用量を基準内に守ることと2歳未満では試験データがないので使用しないことが大切である。

II．タクロリムス軟膏によるステロイド外用療法へのインパクト

我々は成人期アトピー性皮膚炎における調査から，タクロリムス軟膏が登場したことによって，①コントロール不良群が明らかに低下したこと，②ステロイド軟膏の使用量の低下に伴って，ステロイド外用に由来する頬部の血管拡張や多毛などの副作用が6カ月間で半減したことを報告した[5][6]。アトピー性皮膚炎の炎症を抑える外用薬としてステロイド外用薬しかなかった時には，長期外用に伴う局所性副作用をいかに少なくするかに腐心していた。タクロリムス軟膏が登場したことによって，ステロイド外用薬の使用量を確実に減少させることができる時代となった。ステロイド外用量が少なくなると，すでに発現していたステロイド外用薬の副作用も消失していくことも分かった[6]。このような臨床的観察は，外用療法を長期に行わなければならない患者にとって福音となるばかりか，日常診療に携わる皮膚科臨床医にも安堵感を与える事実である。たしかにステロイド外用の副作用である顔面の血管拡張が減少した群と減少しなかった群のステロイド外用量を調べてみると，減少しなかった群では6カ月間の顔面のステロイド外用量が有意に多かった[6]。

免疫抑制作用を有するタクロリムスとステロイドの併用外用療法によって皮膚感染症が増加することがとても危惧されたが，治療前後の皮膚感染症の頻度を見てみると，皮膚感染症を増加させている明らかな証拠は今のところ見出せていない。むしろタクロリム外用

によって特に顔面の皮疹が改善するためと思われるが，皮膚感染症は全般的に減少する[6]。ただし，顔面・頸部の単純疱疹ウイルス感染症が治療前の2.8％から治療6カ月後4.7％に増加していた。タクロリムス外用薬の市販前の調査では思春期・成人期の3.5％に単純疱疹ウイルス感染症が認められたことを考えると[5][6]，明らかな増加とするべきかどうか今後の調査が待たれる。ちなみにFleischerらはタクロリムス軟膏によって皮膚感染症の増加は認められなかったと報告している[7]。

III. タクロリムス軟膏の利点と副作用

タクロリムス軟膏はステロイド外用と異なり，皮膚萎縮をきたすようなホルモン作用はない[8]。しかしながら総じてステロイド軟膏よりは効力が弱く，外用部位に灼熱感を呈する。現時点ではステロイド軟膏とタクロリムス軟膏をいかに上手に組み合わせて，副作用が少なく，しかも効力を最大限にできるかを患者ごとに工夫する必要がある。保湿剤との組み合わせを考えると，様々なバリエーションを患者ごとに試用することになる。実はこのように多彩な組み合わせを用いた治療が可能になったことが，極めて大きな利点であり進歩である。2003年に公表されたInternational Consensus Conference on Atopic Dermatitis IIによる治療手順では，タクロリムス軟膏の維持療法としての重みは，ステロイド外用薬よりも高い位置に据えられている[9]。一方，ステロイド外用薬は急性病変の寛解導入としての重みづけが従来よりも明確になっている。ステロイド外用薬よりも効果は弱いが，タクロリムス軟膏はホルモン作用による副作用がなく，灼熱感も外用継続で消失し，長期外用でも効力の低下が認められないことから当然のことと思われる。日本皮膚科学会治療ガイドラインでも，タクロリムス軟膏はステロイド軟膏と並んで，アトピー性皮膚炎の炎症を抑える主要な外用薬の中に組み込まれている。特に，経皮吸収の良い顔面・頸部の皮疹に対して高い適応のある薬剤として位置づけられている[1]。

2005年3月，米国Food and Drug Administrationがタクロリムス軟膏（外用カルシニューリン阻害薬）による発癌の可能性について注意を喚起した（http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01343.html）。動物実験やこの薬剤の基礎的作用機序，これまでの臨床症例検討からあくまでも可能性として指摘したものである。発癌に関する結論は10年以上の臨床データの蓄積のうえに判断されるべきであると結論付けている。この注意が喚起された背景には，2歳未満の患者への処方が諸外国で急増したことも挙げられている。

本邦のガイドラインで強調されているように，タクロリムス外用薬を用いる場合，一回塗布量が0.1％成人用では成人で1回5g，0.03％小児用では，2～5歳（20kg未満）では1g，6～12歳（20kg以上50kg未満）では2～4g，13歳以上（50kg以上）5gを超えないようにする。1日の使用回数は，1～2回までとする。おおむね体重10kgあたり1回1g以内の外用を指示するように記憶していると簡便である。広範囲に用いる場合，皮疹の程度に合わせて他のステロイド外用剤を併用するなど使用方法を工夫することが大切である[1]。

IV. finger tip unit（FTU）と副作用の説明のしかた

成人の第2指の先端から第1関節部まで5gチューブから軟膏を出すと大体0.5gとなり，この量が成人の手2枚分の患部面積に対する外用適量である（図）[10][11]。これをfin-

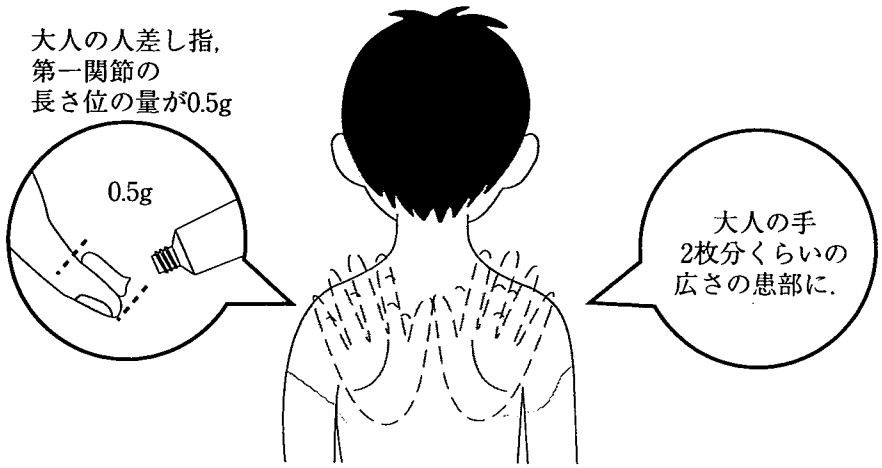

図　塗り薬の使用量の目安（フィンガーチップユニット）

ger tip unit（FTU）と呼ぶ。分かりやすい言い方をすると，5gチューブ1本でお母さんの手の面積20枚分である。たとえば，アトピー性皮膚炎のお子さんで悩んでいるお母さんに，著者は以下のような説明をていねいに行い，十分な理解が得られるように努力している。

＃タクロリムス軟膏は2歳未満のお子さんには塗ることができません。

＃使用量は体重10kgあたり1回1g，1日2回までに制限されています。

＃でも1gでお母さんの手の面積の4枚分を塗ることができます。朝夕，違う場所に塗る場合には手の面積8枚分の患部に塗ることができますので十分な量です。しっかりと塗ってください。5gチューブ1本でお母さんの手の面積20枚分に塗るのが適量です。

＃ステロイド軟膏よりは少し弱いので，タクロリムス軟膏で効果がない場合や塗る範囲が広い場合にはステロイド軟膏に切り換えて，症状がある程度軽くなったらタクロリムス軟膏にしてください。

＃タクロリムス軟膏はステロイドホルモンではないので，ホルモン作用による副作用はありませんが，塗りはじめにヒリヒリしたりほてったりするのが最大の副作用です。でも我慢して3日間塗り続けるとヒリヒリ感はほとんどなくなってきます。十人に一人くらいのお子さんがヒリヒリのためにどうしてもタクロリムス軟膏を塗ることができません。その場合には，今までどおりステロイド軟膏と保湿剤で加療します。

＃使用量の制限を守れば，皮膚から吸収されたタクロリムスが血液の中で継続して検出されることはまずありませんので，説明書に書いてあるリンパ腫が発生する危険性は非常に低いです。

＃日焼けに対してですが，海水浴・スキー・運動会・遠足などのように日光に過度に当たる日には，タクロリム軟膏は塗らないでステロイド軟膏を塗るようにしてください。通常の通学や遊びの時は外用していただいて構いません。

おわりに

白内障，網膜剝離などの眼合併症には細心の注意を要する。掻破に伴って眼球が機械的に圧迫されるためか顔面皮疹の重症例で発生しやすい。アトピー性皮膚炎と白内障の合併が初めて報告されたのは1921年で，1936年にはBrunstingによって，アトピー性皮膚炎のおよそ10％に若年性の白内障が併発することが明らかにされた[12]。10～20歳代の患者に発生しやすく，急速に失明に至り手術を要することも多い。白内障の合併は，ステロイド外用剤の副作用であると安易に診断さ

れることがあるが，ステロイド外用剤が初めて臨床応用されたのはBrunsting論文の14年後の1952年であり，アトピー白内障は確固とした独立疾患として対処せねばならない。アトピー性白内障は顔面の皮疹の重症度と関連しているため，顔面の皮疹をできるだけ早く軽快させる必要性がある[13)14)]。タクロリムス軟膏は，経皮吸収のよい顔面の発疹には著効するため，白内障の発生予防にも一定の役割を演ずる。ベリーストロングランクステロイド外用とタクロリムス軟膏の間欠投与療法は，ベリーストロングランクと保湿薬との間欠投与療法よりも，苔癬化を有意に抑制する[15)]。タクロリムス軟膏の灼熱感は保湿ローションの前投与で有意に抑制される[16)]。繰り返しになるが，タクロリムス軟膏の登場によって，様々な外用方法を患者と相談しながら組み立てていけるようになったことは，アトピー性皮膚炎の診療に大きな転換期をもたらした。ステロイド軟膏が初めて臨床に供されたのが1952年のことであるので[17)]，成人用（1999年）および小児用（2003年）タクロリムス軟膏が上市されたのは実に50年ぶりのこととなる。本剤が多くの小児アトピー性皮膚炎患者の福音となり，今後の薬剤開発の起爆剤となったことは疑いようのない事実である。

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コラム

1．丘疹をみたときに

丘疹は表面が隆起した小さな病変で，通常は粟粒大・米粒大から豌豆大位までのものを指す。それより大きいと結節と表現される。丘疹の多くは炎症性変化により隆起性病変となるものであり，炎症が軽快すると発疹も消退する。一方，腫瘍性病変では消退することはなく，小さいものでも小結節と表現した方がよい。

このように丘疹は隆起するためには炎症性の細胞成分が増える必要がある。組織学的にどのような部位に炎症がみられるのかによって，表皮性丘疹，表皮真皮性丘疹，真皮性丘疹の3つに分けられる。それぞれ炎症の場が異なるので，自ずと症状に違いがでることを理解すべきである。表皮性丘疹は尋常性疣贅のように表皮特に角質の肥厚によるものや，湿疹病変のように表皮内への滲出や炎症細胞浸潤によるものがある。表皮真皮性丘疹には扁平苔癬のような表皮の肥厚と真皮などの炎症がみられるものである。真皮性丘疹は表皮に所見はなく，真皮内の炎症細胞浸潤によるもので，光沢苔癬など多くの炎症性疾患がある。

このように丘疹が主体となる症例をみた場合には，発疹の性状を詳細に観察することが重要であり，さらに，発疹の分布に特徴があるかどうか，発疹の出現の仕方が急性であるか慢性であるか，痒みなどの自覚症状の有無，全身症状の有無，考えられる誘因があるかどうか，丘疹以外に他の皮膚症状があるかどうか，発症年齢などを総合して診断する。通常の皮膚疾患に当てはまるものがなければ，皮膚生検を行い，病理組織学的に検討し，さらには全身検索を必要とすることもある。

痒みのある丘疹を安易に湿疹と診断することは避けるべきで，湿疹にはそれに特徴的な症状があることを知っている必要がある。

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セミナー

ステロイド軟膏の標準的な使い分け

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はじめに

さまざまな皮膚疾患の治療において，ステロイド外用療法は極めて重要な位置を占める。しかしステロイドの副作用に対する恐怖感や忌避感が世間一般に広がっている現状では，その有用性をただただ強調するだけでは，患者のコンプライアンスはあがらない。その使用法や使用量に対してより具体的な分かりやすい説明を行うことが肝要となる。たとえば，アトピー性皮膚炎の治療では乳児期から成人期まで幅広い年齢を対象とし患者数も多く，患者のみならず家族のQOLを含めた十分な説明が必要である。アトピー性皮膚炎の治療に関するEBMはhttp://www.kyudai-derm.org/atopy_ebm/index.htmlに掲載されている。また患者向けのサイトは，「アトピー性皮膚炎について一緒に考えましょう」(http://www.kyudai-derm.org/atopy/) を参照されたい。治療ガイドラインの詳細については，皮膚科専門医を対象とした日本皮膚科学会治療ガイドライン (http://web.kanazawa-u.ac.jp/~med24/atopy/therapy.html) ならびに一般臨床医を広く対象とした厚労省治療ガイドライン (http://www.mhlw.go.jp/new-info/kobetu/kenkou/ryumachi/index.html) を参照していただきたい[1]。

ステロイド軟膏の多彩な薬理作用

ステロイドは血管収縮作用を含め多彩な薬理作用によって抗炎症作用を発揮する。皮膚炎の場合，表皮細胞・線維芽細胞・肥満細胞などの炎症の場を構成する組織細胞だけでなく，浸潤してきた炎症性免疫細胞（T細胞，単球，好中球，好酸球など）の活性化や種々のサイトカインの産生を抑制することによって炎症の遷延化を抑制すると考えられる。特にT細胞の活性化を抑制するいわゆる免疫抑制作用がさまざまな炎症性皮膚疾患に有効性を示す理由と考えられる。

ステロイド外用薬のランクおよび剤型による使い分け

ステロイド外用剤のランクおよび皮疹の重症度に合わせた選択の仕方を，**表1**，**表2**に示した[1]。軟膏，クリーム，ローション，テープ剤などの剤型の選択は，病変の性状，部位などを考慮して選択する。外用回数は1日2回（朝，夕：入浴後）を原則とする。ただし，ステロイド外用剤のランクを下げる，あるいはステロイドを含まない外用剤に切り替える際には，1日1回あるいは隔日投与などの間欠投与を行いながら，再燃のないことを確認する必要がある。外用量については，ベリーストロングクラスのステロイド外用剤の長期使用試験結果より，通常の成人患者では充分量である1日5gないし10g程度の初期外用量で開始し，症状に合わせて漸減する使用法であれば3ヶ月間使用しても，一過性で可逆性の副腎機能抑制は生じうるものの，不可逆性の全身的副作用は生じない。3ヶ月以上にわたって1日5ないし10g程度のステロイド外用剤を連日継続して使用することは極めて例外的であるが，そのような例では全身影響に対する十分な検査を定期的に行う必要があり，個々の患者でステロイド外用剤の減量を可能ならしめるような適切な対応が検討されるべきである。乳幼児，小児においては，より少量の初期外用量で通常開始されるが，体重をもとに1日使用量を成人での使用量から換算し目安とする。

炎症症状の鎮静後にステロイド外用剤を中止する際には，急激に中止することなく，症状をみながら漸減あるいは間欠投与を行い徐々に中止する。ただ

Key words　アトピー性皮膚炎，治療ガイドライン，ステロイド軟膏，外用量

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