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（主なもの）

All patients using off-label medication must be informed about the legal consequences, read the manufacturer's consumer information, discuss it with their doctor and give written informed consent.

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Key words: hyperhidrosis axillaris, quetiapine, social phobia

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Proactive treatment appears to decrease serum immunoglobulin-E levels in patients with severe atopic dermatitis

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MADAM, Atopic dermatitis (AD) is a chronic inflammatory skin disease with a broad spectrum of clinical manifestations.[1] Central to the pathogenesis of AD are immunological dysregulation of T-cell function and, frequently, elevated immunoglobulin (Ig) E levels.[2] In severe AD, total serum IgE level can be increased up to 10 000 IU mL^{-1} or even more and may cause several problems in treating allergy.

Recently, proactive treatment, which is long-term, low-dose intermittent application of anti-inflammatory agents to the previously affected skin together with daily application of emollients to unaffected areas, was reported to have several clinical advantages.[3–7] However, there have been no published reports regarding the relationship between IgE level and a proactive treatment approach to AD.

To investigate whether proactive treatment changes serum IgE level or not, we conducted a retrospective study of patients with moderate to severe AD who were treated and followed up in the Division of Allergy, National Center for Child Health and Development (Tokyo, Japan). The inclusion criteria were: (i) admission between January 2004 and July 2007; and (ii) an IgE level above 100 IU mL^{-1} at the first visit, with re-evaluation at least once more after 1–2 years.

In the remission–induction phase, patients applied topical corticosteroids twice daily every day to all affected body areas until visible inflammation disappeared. The maintenance phase consisted of proactive intervention using topical corticosteroids after twice daily skin washing and continuous environmental control: 0·12% betamethasone valerate was applied to the body and extremities, 0·1% hydrocortisone butyrate on the face. According to the tapering protocol of our division (Fig. S1; see Supporting information), the patients were advised to use topical corticosteroids intermittently and proactively on all previously identified affected areas. None of the patients received any additional systemic therapy.

If the patient maintained proactive therapy for 2 years, he or she was assigned to the 'proactive treatment group'. If the patient discontinued the recommended proactive treatments and treated symptoms reactively, he or she was assigned to the 'reactive treatment group'.

Scoring Atopic Dermatitis (SCORAD),[8] safety assessments and height measurements were performed at each hospital visit. Serum total IgE and food-specific IgE levels using an ImmunoCAP Specific IgE kit (Phadia AB, Uppsala, Sweden) were evaluated.

Forty-five patients satisfied the inclusion criteria. All patients achieved remission within 1–2 months of in-hospital treatment. Twenty-five patients continued twice-a-day skin care and proactive treatment and were assigned to the proactive treatment group. Twenty patients failed to continue proactive treatment and were assigned to the reactive treatment group (Fig. S2; see Supporting information). The mean age ± SD was 4·3 ± 3·3 years (proactive group) vs. 5·0 ± 4·0 (reactive group). Baseline SCORAD median (interquartile range) was 82·2 (68·2–85·6) vs. 79·5 (66·8–91·4). Baseline total IgE was 2442 (1263–8330) IU mL^{-1} vs. 2081 (1059–6980). All parameters measured did not show significant differences (Table S1; see Supporting information), but the mean worst SCORAD in the proactive group was lower than that in the reactive group. The application frequency of topical steroid necessary to maintain a clear status was titrated in the proactive group patients, usually 1 day in a week (48% of the proactive group) or 2 days in a week (also 48%).

Serum IgE titre was significantly decreased in the proactive treatment group compared with the reactive treatment group ($P < 0·01$, Mann–Whitney U-test, Fig. 1). In addition, the food-specific IgE level was significantly decreased in the pro-

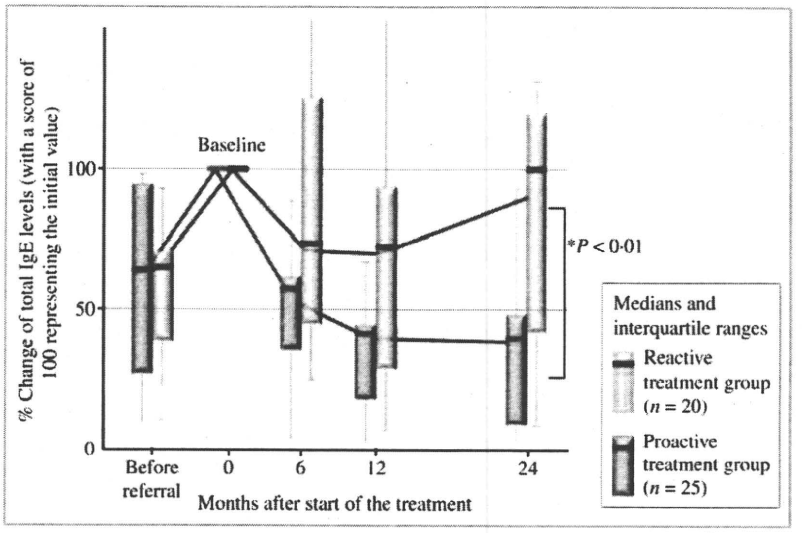

Fig 1. Percentage changes of total immunoglobulin (Ig) E levels during the treatment. Baseline (just before the start of inpatient treatment) total IgE of each patient was determined as 100%. In the proactive group, the total IgE level was reduced by our comprehensive treatment and IgE levels at 2 years after treatment commencement were significantly lower than in the reactive group. *Significant differences between the two groups after 2 years ($P < 0·01$, Mann–Whitney U-test).

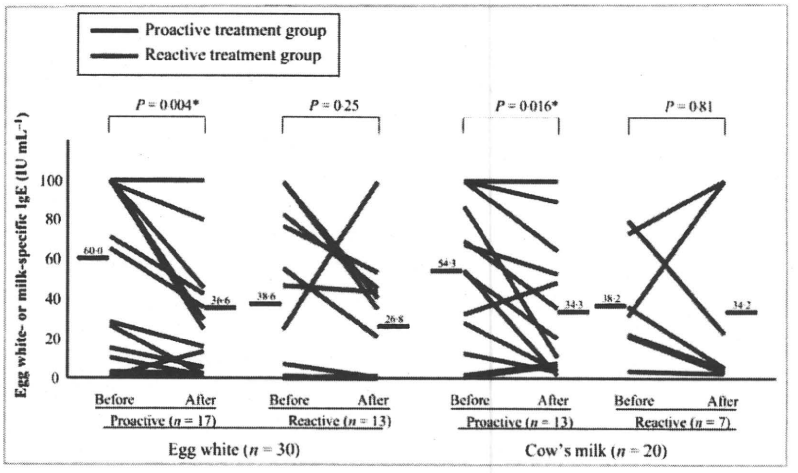

Fig 2. Changes in egg white- and milk-specific immunoglobulin (Ig) E levels after the start of treatment. Food-specific IgE levels in the patients in the proactive treatment group (blue line) decreased significantly during follow-up. No significant decreases were seen in the reactive treatment group patients (red lines). *Significant difference in Wilcoxon signed rank test.

active group compared with the reactive group (Wilcoxon signed rank test, Fig. 2).

There were no serious adverse events in any of the patients during treatment. Eight patients (32%) in the proactive treatment group experienced fungal infection (two patients in reactive group). Skin thinning and striae formation were not seen in any patients. Hypertrichosis was suspected in some patients before titration of frequency of topical steroid, but normalized when the frequency of topical steroid was decreased to twice a week or less. The mean height velocity SD score was relatively high in both groups and did not show any difference.

Inflamed skin of AD bears several kinds of inflammatory cells, including T-helper 2 cells which produce interleukin (IL)-4 and IL-13 and lead to production of IgE in cooperation with B cells. IgE might be synthesized in inflamed skin, its regional lymph node and elsewhere in the body. One can imagine that suppression of inflammatory cells in the skin could lead to disruption of the IgE synthesis mechanism.

We used proactive therapy for the management of severe AD and the serum IgE level appeared to decrease. Continuous close adherence to the proactive treatment may suppress inflammatory cells and lower the serum IgE level. Decrease of egg white- and milk-specific IgE levels was also seen, and may play an important role in alleviating food allergies. This is the first report to evaluate the effectiveness of proactive therapy in reducing the serum IgE level.

Because this study was retrospective and was designed using therapy adherence as a discriminating factor for assigning the patients, we hope to execute a prospective randomized controlled trial. We also want to understand the mechanism to decrease serum IgE and to change the clinical course of food allergy.

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Key words: atopic dermatitis, food allergy, immunoglobulin E, proactive therapy, topical corticosteroid

Conflicts of interest: none declared.

Supporting information

Additional supporting information may be found in the online version of the article:

Fig S1. Our standard protocol for proactive treatment of atopic dermatitis.

Fig S2. Patient flow.

Table S1. Stratified analysis of the two groups.

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An unusual case of granulomatous cutaneous T-cell lymphoma showing subcutaneous/muscular involvement and a 5q33.1 deletion

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Madam, Granulomatous slack skin (GSS) and granulomatous mycosis fungoides (GMF) are classified as subtypes of mycosis fungoides (MF) according to the recent classifications of haematolymphoid tumours.[1,2] GSS clinically manifests as bulky, infiltrated folds of lax skin in flexural areas, histologically characterized by a granulomatous T-cell infiltrate with abundant macrophages, multinucleated giant cells and loss of elastic fibres.[3] We describe an unusual case of granulomatous cutaneous T-cell lymphoma (CTCL) clinically presenting without typical MF cutaneous lesions and showing histopathological features consistent with GSS, with the absence of elastolysis. Array-based comparative genomic hybridization (aCGH) was also performed showing a unique loss of 5q33.1.

A 34-year-old white man presented with a 5-year history of isolated, deep and painful nodules, rapidly enlarged and localized on the right part of the trunk (Fig. 1a), on the right buttock, on the left thigh (Fig. 1b), left knee and left shoulder. A complete physical examination did not reveal any MF-like typical aspects or lymph node enlargement. His medical and family history was unremarkable. Two previous cutaneous biopsies were not diagnostic for CTCL.

When he presented to us, another biopsy was taken from a skin lesion, and previous histological specimens were reviewed. They showed a focal granulomatous lymphoid infiltrate localized in the dermis and hypodermis (Fig. 1c) and a dense lymphoid infiltrate containing multinucleated giant cells (Fig. 1d) forming granulomas in the subcutis and fascia (Fig. 1e). The atypical proliferating lymphocytes showed small to medium-sized cerebriform and hyperchromic nuclei, typically surrounding the multinucleate giant cells and forming rosette-like features (Fig. 1f); there was also evidence of mild lymphophagocytosis. Immunohistochemically, tumour cells were CD2++, CD3+ (Fig. 2a), CD4+, CD5+/−, CD7−, CD8−, CD30−, CD45RO+, interleukin (IL)-17− and Ki-67+ (Fig. 2b). Multinucleate giant cells were positive for IL-17 (Fig. 2c), interferon (IFN)-γ, tumour necrosis factor (TNF)-α, CD68 and CD163 markers.

Molecular analysis revealed a monoclonal T-cell receptor-γ gene rearrangement (primer V2a, V1-8). A histological diagnosis of GSS was made. Complete haematological staging revealed no abnormalities. Magnetic resonance imaging and a thoracoabdominal computerized tomography scan of the cutaneous lesions showed involvement of only subcutaneous tissue and the muscular layer by the infiltrate.

Genotypic studies of the skin biopsy by aCGH showed a loss of only 5q33.1 containing the *IL17B* and *PCYOX1L* genes

TABLE I. Sensitivity and specificity* for Ara h 2 and whole peanut extract

Test	Cutoff point (kU_A/L)	Sensitivity (%)	Specificity (%)	Correctly classified (%)
Ara h 2	0.30	100.00	90.20	93.75
	0.32	100.00	94.12	95.00
	0.35	100.00	96.08	97.50
	0.38	96.55	96.08	96.25
	0.40	93.10	98.04	96.25
	0.55	93.10	100.00	97.50
	0.87	89.66	100.00	96.25
Whole extract	0.35	96.55	26.92	51.85
	3.91	79.31	84.62	82.72
	5.00	75.86	90.38	85.19
	5.30	75.86	94.23	87.65
	5.96	72.41	94.23	86.42
	7.81	72.41	96.15	87.65
	15.00	55.17	96.15	81.48
	43.86	34.85	98.08	75.31

Analysis included all children with available data (81 for sIgE to whole peanut extract and 80 for sIgE to Ara h 2).

*Sensitivity refers to the proportion of subjects who have peanut allergy and give positive test results. Specificity refers to the proportion of subjects without the target condition and a negative test result for peanut allergy.

peanut allergy and 50 are peanut-tolerant. By using sIgE to component Ara h 2 with a cutoff point of 0.35 kU_A/L, all children with peanut allergy would be correctly classified. The specificity of this test is given as 96.1% (Table I). In this example we expect 2 children who are not allergic to peanuts to be misclassified as having peanut allergy and the other 48 children to have a negative result. By using this cutoff point, 97.5% of the population is correctly classified. A similar proportion of children would be correctly classified by using a cutoff point of 0.55 kU_A/L; however, in this case 3 children with peanut allergy would be misclassified as tolerant. This cutoff point corresponds to a gain in specificity (100%) but a loss in sensitivity (93.1%). Given the importance of not misdiagnosing children with peanut allergy as being tolerant, we propose that the optimal cutoff point in our population is 0.35 kU_A/L.

The cutoff for whole peanut sIgE of 5.30 kU_A/L provides the maximum proportion of correctly classified subjects (87.6%), with a sensitivity of 75.9% and a specificity of 94.2%. However, approximately 24% of children with peanut allergy would be inappropriately classified as peanut-tolerant. The cutoff of 15 kU_A/L has excellent specificity, with 96.2% of children at greater than this level being correctly classified as allergic; however, this decision point has relatively poor sensitivity, with almost half of the subjects with peanut allergy being classified as tolerant. These data suggest that in our population the quantification of whole peanut sIgE has lower accuracy in discriminating peanut allergy from tolerance compared with quantification of sIgE to Ara h 2.

In conclusion, having identified sIgE to Ara h 2 as an important predictor of clinical reactivity to peanut using microarray technology,[5] we have now demonstrated the value of its quantification using a routinely available laboratory test. Among school-aged children in the United Kingdom, a cutoff of 0.35 kU_A/L Ara h 2 IgE confers 100% sensitivity and 96.1% specificity. By using this cutoff point, 97.5% of the subjects in our study population were correctly classified, with all children with peanut allergy given the correct classification. The importance of Ara h 2 has been suggested in studies from other Central and Northern European countries[7,8]; however, in other populations and geographic areas, IgE to other components might be relevant (eg, Ara h 9 in the Mediterranean[9]). Our findings need to be replicated in other populations and age groups before general application.

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Four distinct subtypes of non–IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms

To the Editor:

Although most food allergies are IgE-mediated, there are a number of non–IgE-mediated gastrointestinal food allergies that affect mainly infants and young children.[1,2] Because most such

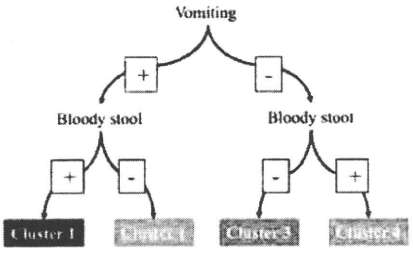

FIG 1. Tree analysis using 2 variables (vomiting and bloody stool at initial presentation) enables assignment of patients into 4 clusters.

patients develop the allergy more than 2 hours after ingestion of the offending food and show negative skin prick tests and/or absence of serum specific IgE against the offending food, these allergies are thought to be cell-mediated. However, the precise pathogenetic mechanisms of these disorders remain poorly understood. Several investigators have described different subtypes of non–IgE-mediated gastrointestinal food allergies: food protein-induced enterocolitis syndrome (FPIES),[3] food protein-induced proctocolitis syndrome (hereafter referred to as "proctocolitis"),[4] food protein-induced enteropathy syndrome (hereafter referred to as "enteropathy"),[5] celiac disease, and allergic eosinophilic gastroenteropathies.

Presumably because the main target organ of these syndromes is the gastrointestinal tract, patients with non–IgE-mediated gastrointestinal food allergies often exhibit similar symptoms, such as vomiting and diarrhea. However, it remains unclear whether these syndromes have the same pathogenesis and merely differ in severity, or whether the pathogenesis of each is distinct, meaning that they should be classified as separate clinical entities.

We applied cluster analysis to the clinical and laboratory findings to characterize these non–IgE-mediated food allergies and determine whether they are made up of distinct clinical entities. A total of 176 patients with detailed clinical records who had been registered in the database of the Japanese Research Group for Neonatal, Infantile Allergic Disorders from 2007 to 2010 were enrolled. Among them, 136 patients fulfilled 3 of the Powell[6] criteria: (1) a switch to therapeutic milk led to resolution of symptoms, (2) differential diagnosis from other disorders was possible, and (3) there was verified body weight gain. Definitive diagnosis was possible for 46 patients by oral food challenge tests that were performed after complete resolution of the initial symptoms (see this article's Fig E1 in the Online Repository at www.jacionline.org). These 46 patients were subjected to further analysis. Details of food challenge test are available in this article's Food challenge test, method section in the Online Repository at www.jacionline.org. Our total cohort included 15 patients who developed the most severe reactions, including ileus, shock, and developmental retardation. The clinical characteristics of those patients are summarized in this article's Table E1 in the Online Repository at www.jacionline.org. Because of the medical and ethical justification, even though these patients fulfilled 3 elements of the Powell[6] criteria, oral challenge tests were not performed. Thus, these patients were excluded from this cluster analysis of 46 patients. This study was approved by the Ethics Committee of the National Center for Child Health and Development.

We omitted clinical and laboratory findings found only in a few patients and finally selected 5 variables: birth weight, age at first presentation (days after birth), severity of vomiting (ranked as 0, none; 1, 1-2 times a day; 2, 3-5 times a day; and 3, more than 5 times a day or bilious vomiting) and severity of bloody stool (0, none; 1, spotty; 2, intermediate; and 3, massive) at first presentation, and milk-specific IgE antibody titer (class 0-6). Unsupervised cluster analysis and discriminant analysis were performed by using SPSS version 18 software (SPSS, Inc, Chicago, Ill). The Wald minimum-variance hierarchic clustering method was performed by using an agglomerative (bottom-up) approach and Ward's linkage. The squared Euclidean distance was used as a proximity measure. Values were transformed by a maximum magnitude of 1. ANOVA, the Tukey-Kramer test, and the χ^2 test were used for parametric continuous, nonparametric continuous, and categoric variables. As a result, the 46 definitively diagnosed patients were classified into 4 distinct clusters, and a dendrogram was generated (see this article's Fig E2 in the Online Repository at www.jacionline.org).

Stepwise discriminate analysis identified the 2 strongest discriminatory variables for cluster assignment: vomiting and bloody stool (Fig 1). Cluster 1 was the patient group with vomiting and bloody stool at initial presentation. Cluster 2 had vomiting but not bloody stool. Cluster 3 had neither vomiting nor bloody stool. Cluster 4 had bloody stool but not vomiting. One patient initially assigned to cluster 3 in fact had clear bloody stool, and was thus reassigned to cluster 4 in accordance with Fig 1. As a result, clusters 1 through 4 consisted of 14, 16, 5, and 11 patients, respectively.

Table I presents the demographic data for each cluster. Cluster 3 showed a significantly lower birth weight and later onset of disease. Clusters 1 and 4 both had bloody stool, but they had normal birth weight and a somewhat earlier onset (median of 7 days after birth).

The laboratory data generated within the initial several days after onset showed that the peripheral blood eosinophil ratio was high in all clusters, with no significant differences among them. In contrast, eosinophils were found in the stool mainly of patients in clusters 1 and 4, in which all patients, by definition (Fig 1), had bloody stool. The presence of eosinophilia suggests that patients with non–IgE-mediated gastrointestinal food allergies tend to have a T_H2-prone immune deviation at baseline, but some additional factors such as overproduction of eosinophil-attracting chemokines are probably necessary to induce immune responses involving eosinophils in the gut (see this article's Fig E3 in the Online Repository at www.jacionline.org).

A positive milk-specific IgE antibody titer was observed in 37% of the patients, with no statistically significant differences among any of the clusters. In addition, almost all symptoms at initial presentation as well as in oral food challenge tests began to manifest at more than 2 hours after ingestion of the offending food, whereas no patients developed typical IgE-mediated symptoms such as urticaria or wheeze. These results strongly suggest that the presence of milk-specific IgE antibody neither causes the gastrointestinal symptoms nor rules out a diagnosis of non–IgE-mediated gastrointestinal food allergy.

One of the most notable findings of this study was the remarkably high reproducibility of symptoms provoked in the oral food challenge tests and those found at the initial presentation in all 4 clusters, even though the oral challenge tests were performed several months after the initial presentation (Table I). This observation suggests that the upper or lower gastrointestinal tract–specific hypersensitivity and perhaps the responsible

TABLE I. Demographic data of the patients (total = 46) whose diagnosis was confirmed by oral food challenge tests

Clinical characteristics	Cluster 1 (n = 14)		Cluster 2 (n = 16)		Cluster 3 (n= 5)		Cluster 4 (n = 11)		P value
Birth weight (g)	2642 (2410-3030)		2745 (2223-3079)		1008 (907-2491)		2678 (2512-3170)		.03*
Male/female (n)	6/8		9/7		2/3		5/6		.95
Initial presentation									
Day of onset	7.5 (3-23)		16.5 (9.5-33.5)		37 (8.5-132)		7 (2-56)		.17
Vomiting (%)	100		100		0		0		.000*
Bloody stool (%)	100		0		0		100		.000*
Fever (%)	7.1		18.8		20.0		0		.45
(Laboratory data)†	n		n		n		n		
Blood eosinophil ratio (%)‡	13	15 (3.0-23)	14	7 (3.9-19.3)	5	27 (3.2-39.3)	11	14 (4.5-25)	.63
WBC ($\times 10^3$/mL)§	13	18.4 (13.7-22.7)	14	15.7 (11.4-21.9)	5	21.8 (11.0-27.7)	11	13.1 (8.2-18.3)	.64
Total IgE (IU/mL)‖	14	5.2 (4.8-28.3)	16	11.4 (5.0-80.8)	5	7.4 (5.5-653.5)	10	5.0 (2.0-5.8)	.36
Positive for milk-specific IgE (class ≥1) (%)	14	57	16	37.5	5	40	11	9	.28
C-reactive protein (% positive, ≥0.5)	13	46	14	50	5	40	10	30	.47
Stool eosinophil (% positive)	8	50	6	33	3	0	7	100	.01*
Diet (reaction to each milk, %)									
Cow's milk	14	100	16	100	5	100	10	100	1.00
Breast milk	8	38	7	0	2	50	7	27	.40
Hydrolyzed formula	9	0	10	20	2	0	8	63	.02*
Oral food challenge test									
Onset of reaction (h)	6 (1.8-12)		10 (2-24)		48 (24-60)		24 (24-48)		.17
Vomiting (%)	85.7		81.3		0		9.1		.000*
Bloody stool (%)	28.6		6.3		0		72.7		.001*
Diarrhea (%)	21.4		31.3		60.0		18.2		.33

WBC, White blood cell count.
Data are shown as the median and the interquartile range.
*$P < .05$.
†*n*, Number with medical records.
‡Normal range of blood eosinophils is 0% to 4%. However, it is known to rise to some degree in the neonatal period, especially in low-birth-weight infants.[10]
§Normal range of WBC in neonatal period is 7.0 to 25.0 $\times 10^3/\mu L$.
‖Normal range of total IgE in infantile period is less than 20 IU/mL.

immune cells remain in the same part of the gastrointestinal tract even after several months' remission.

Because the patients in clusters 1 and 2 had vomiting that was provoked at relatively early time points, they are likely to be diagnosed as having FPIES, although the bloody stool and eosinophilia seen mainly in cluster 1 patients were not emphasized in earlier reports.[7,8] The nearly simultaneous manifestation of vomiting and bloody stool suggests that FPIES may affect both the upper and lower gastrointestinal tracts.

The main symptoms of the patients in cluster 3 were poor weight gain and diarrhea and were similar to those found in patients with enteropathy. The significantly lower birth weight and marked eosinophilia characteristically found in cluster 3 patients imply the involvement of immature gastrointestinal function in the pathogenesis of this syndrome.

Bloody stool was the main symptom of the patients in cluster 4. Some patients in this cluster had no systemic manifestation other than bloody stool, whereas others also had diarrhea and/or poor weight gain. Therefore, these patients may be diagnosed as having proctocolitis or early onset of allergic eosinophilic gastroenteropathies, respectively. However, the pathogenetic similarity and/or disparity of proctocolitis and allergic eosinophilic gastroenteropathies need to be studied further.

In our cohort, 3 children with exclusive breast-feeding have developed FPIES. This information is available in this article's Breast-feeding and FPIED section in the Online Repository at www.jacionline.org.

Elevated serum C-reactive protein levels were found in 30% to 50% of patients with non–IgE-mediated gastrointestinal food allergies. In addition, some patients developed a fever during oral food challenge tests, suggesting that TNF-α and other proinflammatory cytokines may be involved in the pathogenesis of these syndromes.[9]

To confirm the results of cluster analysis, we performed the same analysis for the aforementioned 136 patients who fulfilled 3 of the Powell[6] criteria (consisting of the 46 patients definitively diagnosed by oral food challenge and 90 patients not subjected to oral food challenge; Fig E1). We obtained exactly the same results: the patients were assigned to 4 clusters in accordance with the tree analysis shown in Fig 1. The patients' demographics (see this article's Table E2 in the Online Repository at www.jacionline.org), birth weight (see this article's Fig E4 in the Online Repository at www.jacionline.org) and peripheral blood eosinophils (see this article's Fig E5 in the Online Repository at www.jacionline.org) confirmed the earlier cluster analysis findings.

In our ongoing cohort, 52% of the patients acquired tolerance to the offending food by 1 year of age, 88% by 2 years, and 94% by 3 years. Therefore, assuming that identification and elimination of the offending food had been done properly, it can be assumed that most patients outgrew their allergy by the age of 2 to 3 years. On the other hand, just like patients with severe IgE-mediated food allergy, patients with non–IgE-mediated gastrointestinal food allergies may develop severe reactions

(Table E1). Thus, early diagnosis is very important, and refinement of the diagnostic method is truly necessary.

Our findings clearly demonstrated that patients with these non–IgE-mediated gastrointestinal food allergies showed similar T_h2-prone laboratory data (eosinophilia and presence of specific IgE antibody), but the disease entities of each cluster had distinct clinical features and may have different pathogenetic mechanisms.

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ORIGINAL ARTICLE

Impact of Sedative and Non-Sedative Antihistamines on the Impaired Productivity and Quality of Life in Patients with Pruritic Skin Diseases

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ABSTRACT

Background: The impairment that pruritic skin diseases have on patient productivity at work, in the classroom, and in daily activities is substantial and needs to be characterized. The objective of this study was to determine how pruritic skin diseases impact patient productivity and quality of life (QOL), in order to improve the measurement of these endpoints to allow the influence of treatment options including sedative and non-sedative antihistamines to be analyzed.

Methods: The impact of pruritic skin diseases and the effect of antihistamine therapy on work, classroom, and daily productivity were evaluated using the Work Productivity Assessment Index-Allergy Specific Questionnaire. The intensity of itch and patient QOL were assessed using a visual analogue scale and Skindex-16, respectively.

Results: Pruritic skin diseases resulted in significant impairment of work, classroom, and daily productivity. The severity of overall work impairment in atopic dermatitis (AD), urticaria, and prurigo was higher than for other diseases analyzed. However, classroom activity was more adversely affected in patients with urticaria relative to other diseases. All pruritic diseases in this study negatively impacted daily activity to a similar degree. Impaired productivity was significantly improved in patients taking non-sedative antihistamines for 1 month, and the improvements correlated with the alleviation of itch and improved QOL.

Conclusions: These results indicate that pruritic skin diseases reduce patient productivity at work, in the classroom, and during daily activities, and that non-sedative antihistamines may offer an advantage over sedative antihistamines for alleviating certain negative consequences of these skin diseases.

KEY WORDS

antihistamine, productivity, pruritic, quality-of-life, skin diseases, WPAI-AS

INTRODUCTION

The impaired quality of life (QOL) and diminished work and classroom productivity of individuals with pruritic skin diseases is a matter of public concern.[1,2] Furthermore, estimates of the impact of pruritic skin diseases on the economic loss in businesses and school performance records have attracted a great deal of interest worldwide.[3,4] Similar unfavorable impacts were identified for certain skin diseases, such as chronic idiopathic urticaria, psoriasis, and chronic hand dermatitis.[5-8] The Work Productivity Assessment Index (WPAI) is commonly used to determine the impact of health and disease on certain parameters related to patient productivity. According to the WPAI, the estimated percent of overall work impairment due to psoriasis, urticaria, and chronic hand dermatitis is 15%, 25%, and 29%, respectively.[5,6,8]

Itching is a key characteristic of allergic skin diseases that dramatically affects a patient's quality of

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life.[9,10] Thus, it is possible that itching alone would affect patient performance in the work place. The allergy specific WPAI (WPAI-AS) can be used to more effectively assess productivity in these patients as itching is a common symptom of allergy-related skin diseases. Recently, we reported the effect of antihistamines on productivity of patients with pruritic skin diseases using the WPAI-AS assessment questionnaire.[11,12] On average, pruritic skin diseases impaired overall workplace productivity, classroom productivity, and daily activity by 39%, 45%, and 42% at baseline, respectively.[12] Furthermore, non-sedative antihistamines (mainly fexofenadine) reduced the intensity of itch and improved work productivity. In contrast, sedative antihistamines failed to improve work productivity, but significantly decreased itch intensity.[12] However, the relative impact of different pruritic diseases on work productivity has not been assessed. In this report, the WPAI-AS evaluation system was applied to each subgroup of patients with different diagnoses of pruritic skin diseases, and the degree of impairment for each disease at baseline was compared using a linear least-squares method. Furthermore, itch severity and patient QOL were assessed using a visual analogue scale (VAS) and Skindex-16, respectively. Finally, after validating the relationships between these parameters, we propose a method to approach the treatment of pruritic skin disease that will improve overall productivity in the workplace, in the classroom, and in daily activities.

METHODS

PATIENTS AND STUDY DESIGN

This study was conducted between April, 2008 and March, 2009. After obtaining approval from the Institutional Review Board (IRB), patients with pruritic skin diseases (n = 216) from Osaka University Hospital or its affiliated hospitals, gave informed consent to participate in this study. The final number of valid responses was n = 206 (male : female=93 : 113; mean age ± SD: 52 ± 20 years). Patients with skin diseases associated with underlying systemic diseases (e.g., serious liver disease, renal dysfunction, and blood diseases), history of epilepsy, history of a previous drug allergy, or women who were pregnant or lactating were excluded from this study. Participants received no medical attention during the week before study initiation. The selection of therapy for each patient, such as oral antihistamines versus external medicine (e.g., steroid ointments, tacrolimus ointments, or certain moisturizers), was left to the physician's discretion (open-label trial). Fexofenadine (n = 72) and loratadine (n = 2), anti-histamines for which the package insert contained no cautionary statement regarding sedative actions, were categorized as "non-sedative". All other antihistamines were classified as "sedative".

STUDY INSTRUMENTS

The Skindex-16 quality-of-life instrument[13] was used to measure the effect of pruritic skin diseases on QOL. The magnitude of the itch sensation was assessed using a VAS (0-100, "0" indicates no-symptom, and "100" indicates most severe symptom). Work and classroom productivity were assessed with the WPAI-AS instrument (score range, 0-100%; higher percentages indicate higher productivity).[11] Work productivity, classroom productivity, and daily activity impairment (%I) were calculated by the effects of the pruritic skin diseases on productivity while working/attending class or other daily activities during the past 7 days. The percentage of work/classroom time missed (%TM = TM/TW) was calculated by the number of work/classroom hours missed due to allergy (TM) and the usual number of hours worked/attending class (TW). Finally, the percentage overall impairment was calculated as follows: %TM + ([100 - %TM] × I%) = % overall impairment.[11] These instruments were patient-administered before (baseline) and 1 month after treatment initiation.

STATISTICAL ANALYSIS

The one-sample t-test was used for analysis of differences between two groups. Pearson's product-moment correlation coefficient was used to determine the significance of correlations between two parameters (Table 1, 2). To examine the significance of the contingency between the certain categorical data, Fisher's exact test (for evaluating the significance between the two kinds of classifications) and Cochran-Mantel-Haenszel general association statistics (for evaluating more than 3 kinds of classifications) were performed (Table 3). The bias of evaluative consequences to one variable was analyzed using univariate analysis (Table 4). A linear least-squares method was used to evaluate the degree of impairment in each disease at baseline. Because heterogeneity of starting values was inevitable, the effect measures illustrated in Figure 1 were evaluated using linear models. The results and confidence intervals for the improvement variations were compared visually for each parameter using a forest plot. Improvement variations (change ratios) were calculated as follows: change ratio = (evaluated value 1 month after the initiation of treatment-baseline value)/(baseline value). In all tests, values of $P < 0.05$ were considered statistically significant.

RESULTS

STUDY POPULATION CHARACTERISTICS

A total of 216 patients with pruritic skin disease entered the study, and data from 206 patients (average age of 52 ± 20 years) who completed the study were used for analysis. Company employees and part-time workers represented 48% of the patients (n = 99), and retired seniors and unemployed individuals ac-

Table 1 Correlations between baseline parameters and patient outcomes

	Correlations to baseline patient parameters [*P*-value, Pearson's coefficient of correlation (r), *n*]		
Allergic pruritic skin diseases (AD and urticaria)	Itch VAS	Skindex-16 score	Activity impairment
Overall work productivity impairment	NS ($r = 0.2443$, $n = 52$)	$P < 0.001$ ($r = 0.5674$, $n = 51$)	$P < 0.001$ ($r = 0.6712$, $n = 52$)
Overall classroom productivity impairment	NS ($r = 0.1948$, $n = 14$)	NS ($r = 0.0915$, $n = 13$)	NS ($r = 0.1833$, $n = 14$)
Activity impairment	$P = 0.006$ ($r = 0.2893$, $n = 89$)	$P < 0.001$ ($r = 0.7051$, $n = 84$)	- -
Non-allergic skin diseases (All other excluding AD and urticaria)			
Overall work productivity impairment	NS ($r = 0.2904$, $n = 44$)	$P < 0.001$ ($r = 0.4813$, $n = 46$)	$P < 0.001$ ($r = 0.8584$, $n = 47$)
Overall classroom productivity impairment	NS ($r = 0.2604$, $n = 4$)	NS ($r = 0.7963$, $n = 4$)	$P = 0.0014$ ($r = 0.9986$, $n = 4$)
Activity impairment	$P < 0.001$ ($r = 0.3332$, $n = 107$)	$P < 0.001$ ($r = 0.5170$, $n = 109$)	- -

NS, not statistically significant; vs., versus.

Table 2 Correlative relationships between antihistamine treatment groups and the improvement ratio of itch VAS scores to Skindex-16, overall work productivity impairment, and activity impairment

	Correlations to baseline patient improvement ratios by treatment group [*P*-value, Pearson's coefficient of correlation (r), *n*]	
	Non-sedative AH	Sedative AH
Skindex-16 score vs. itch VAS	$P < 0.001$ ($r = 0.5769$, $n = 69$)	NS ($r = 0.2360$, $n = 99$)
Overall work productivity impairment vs. itch VAS	$P = 0.0042$ ($r = 0.4539$, $n = 38$)	NS ($r = 0.2462$, $n = 46$)
Activity impairment vs. itch VAS	$P = 0.0046$ ($r = 0.3448$, $n = 66$)	NS ($r = 0.1203$, $n = 92$)

NS, not statistically significant; AH, anti-histamines; VAS, visual analogue scale.

counted for 43% ($n = 89$). Students made up a relatively small fraction of the study group ($n = 18$, 9%). Patients diagnosed with eczema/dermatitis had the highest representation (36%) among participants, followed in decreasing order by patients with urticaria, atopic dermatitis (AD), pruritus, prurigo, and psoriasis (Table 5).

ASSESSMENT OF WORK, CLASSROOM, AND ACTIVITY IMPAIRMENT

Table 6 shows the baseline work, classroom, and daily activity WPAI-AS productivity scores. Due to the relatively small sample size of each disease group, statistically significant differences in impairment between disease groups were not detected (Fig. 2). However, the results indicate that the overall impairment of work, classroom, and daily activity productivity tended to be larger in the atopic dermatitis, eczema/dermatitis, and urticaria disease groups (Fig. 2). There were also some interesting group-specific observations. Prurigo showed higher overall impairment of work productivity and daily activity. Individuals with urticaria had relatively higher percentages of impairment of overall classroom productivity than that observed in other skin diseases. Daily activity was impaired at high percentages for individuals with AD.

CORRELATION BETWEEN PRODUCTIVITY IMPAIRMENT AND SKINDEX-16, OR LOSS OF DAILY LIFE PRODUCTIVITY

To check the validity of the assessment procedures in this study, we looked for correlations between impaired productivity at work, in the classroom, and in daily activities. In addition, correlations between overall activity impairment, the magnitude of itch sensation as assessed by VAS, and QOL measures as assessed by Skindex-16 were analyzed (Table 1). As shown in Table 1, correlation analyses were divided between allergic (atopic dermatitis and urticaria) and non-allergic skin diseases (all other diagnosis groups). Results specific for allergic skin diseases indicated that impairment in overall work productivity showed a positive correlation with the itch VAS, Skindex-16, and the impairment in daily activity. A correlation between impairment in overall classroom

Table 3 Distribution of patient characteristics in the sedative and non-sedative antihistamine treatment groups

Background factors		Non-sedative AH		Sedative AH		*P*-value*
		n	%	*n*	%	
Age	<50	42	56.8	55	45.8	0.183
	≥50	32	43.2	65	54.2	
Gender	Male	37	50.0	48	40.0	0.183
	Female	37	50.0	72	60.0	
Disease	AD	20	27.0	22	18.3	0.515
	Ec/der	26	35.1	45	37.5	
	Urticaria	16	21.6	33	27.5	
	Other	12	16.2	20	16.7	
Occupation	Worker	45	60.8	51	42.5	0.017
	Student	8	10.8	10	8.3	
	Other	21	28.4	59	49.2	
Duration of disease	<5 years	46	62.2	74	61.7	1.000
	≥5 years	21	28.4	34	28.3	

*Differences in the distribution of patients between sedative and non-sedative antihistame groups was determined by the Fisher's exact test for age, gender, and duration of disease and by the Cochran-Mantel-Haenszel general association statistic for disease diagnostic group and occupation. AH, antihistamines; AD, atopic dermatitis; Ec/der, eczema/dermatitis.

Table 4 Impact of background factors on the improvement of WPAI-AS score

Patient characteristics	Impact of patient characteristics on overal productivity impairment (*P*-value)		
	Overall work impairment	Overall classroom impairment	Daily activity impairment
Age	0.345	0.2986	0.3556
Gender	0.4454	0.5464	0.2615
Disease	0.0646	0.5349	0.4118
Duration of disease: <5 years, ≥5 years	0.0053	0.4793	0.2528
Occupation: worker, student, other	N/A	N/A	0.5097

N/A, not applicable.

productivity and itch VAS, Skindex-16 score, and activity impairment was not observed for the allergic skin diseases (Table 1). However, in the allergic skin disease subgroup there was a positive correlation between the impairment in daily activity and the magnitude of itch and Skindex-16 scores.

Similar analyses were performed on the subgroup of patients with all other skin disease diagnoses except atopic dermatitis and urticaria. This group was designated the non-allergic skin disease group even though varying causative conditions including allergic and non-allergic mechanisms could be responsible for symptoms related to eczema/dermatitis. As shown in Table 1, the correlation profile of this subgroup was very similar to that of the allergic skin disease subgroup with one major difference. There was a significant correlation between overall classroom productivity and activity impairment in the non-allergic skin disease subgroup (Table 1).

IMPACT OF ANTIHISTAMINES ON PATIENT OUTCOMES

Patients were treated with non-sedative antihistamines (n = 74), sedative antihistamines (n = 121), or external medication (n = 11) for a duration of 1 month (Table 7). The patient characteristics in the physician-assigned treatment groups of sedative and non-sedative antihistamines were all well-matched with the exception of occupation (Table 3). We previously reported that the impaired productivity in pruritic skin diseases was significantly improved in patients taking non-sedative antihistamines.[12] Interestingly, for patients taking non-sedative antihistamines in this study, the improvement ratio as assessed using the VAS score showed a significant correlation with improvements in the Skindex-16 score, the reduction in overall work productivity impairment, and the reduction in daily activity impairment. No significant correlations were found among patients taking sedative antihistamines (Table 2).

To eliminate the bias for starting value dispersion, the effects of non-sedative and sedative antihistamines on overall work productivity, daily activity, and overall classroom productivity were corrected by grouping according to background factors or baseline value using the linear least-squares methods (Fig. 1A). Results indicated that non-sedative antihistamines produced greater overall improvements in pro-

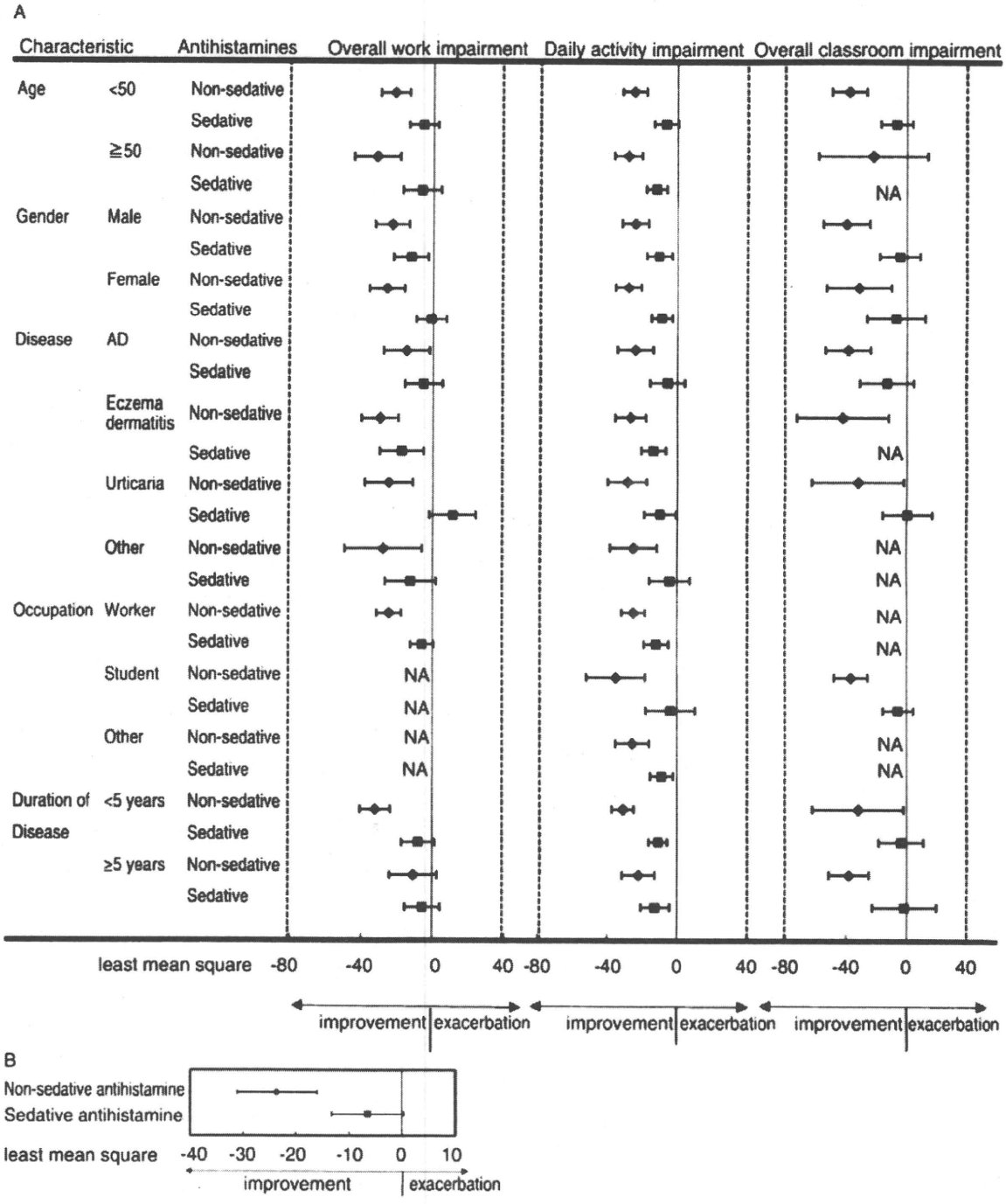

Fig. 1 **A.** The impact of antihistamines on overall work productivity impairment, activity productivity impairment, and overall classroom productivity impairment per-certain parameters of pruritic skin diseases. Changes in the evaluated value of certain parameters from baseline were adjusted with background factors and the initial value (a linear model). Results are shown in a forest plot. Horizontal lines indicate 95% confidence intervals. The rhomboid or square dot on center of the horizontal line indicates the point estimate. Significance is indicated by horizontal lines that do not overlap with the vertical line of least mean square = 0. NA, not applicable. **B.** Comparison of overall work impairment (amount of change) adjusted by background factor (disease duration).

Table 5 Characteristics of patient population by pruritic skin disease diagnostic group

Disease	(*n*)	Male	Female	Average age (yrs ± SD)	Average duration of disease (yrs ± SD)
Atopic dermatitis	43	21	22	33.7 ± 10.1	17.1 ± 13.2
Eczema/dermatitis	75	33	42	61.9 ± 17.8	3.1 ± 8.1
Urticaria	50	17	33	47.3 ± 16.3	5.4 ± 10.1
Pruritus	14	9	5	64.3 ± 18.1	3.4 ± 3.6
Prurigo	8	6	2	59.8 ± 16.6	2.1 ± 1.5
Psoriasis	7	4	3	49.3 ± 19.6	1.1 ± 1.4
Others[†]	9	3	6	54.7 ± 18.2	10.8 ± 14.9

[†] Includes patients with systemic lupus erythematodes, tinea pedis, toxicoderma, polymorphic light eruption, von Recklinghausen disease, tuberous sclerosis, scabies, bullous pemphigoid, and lupus erythematodes.

Table 6 Baseline WPAI-AS productivity scores (Mean ± SD)

	AD	Ec/Der	Urticaria	Pruritus	Prurigo	Psoriasis	Others
Work	(*n* = 31)	(*n* = 31)	(*n* = 21)	(*n* = 2)	(*n* = 5)	(*n* = 3)	(*n* = 6)
Work productivity impairment	38.7 ± 26.3	41.0 ± 24.8	33.8 ± 25.8	20.0 ± 0	36.0 ± 18.2	26.7 ± 25.2	23.3 ± 29.4
Work time missed	4.9 ± 11.4	2.6 ± 10.3	10.6 ± 26.8	0	12.2 ± 21.7	2.2 ± 3.8	0
Overall work productivity impairment	40.4 ± 26.8	41.3 ± 25.2	41.8 ± 29.5	20.0 ± 0	42.9 ± 24.8	28.9 ± 21.7	23.3 ± 29.4
Classroom	(*n* = 8)	(*n* = 1)	(*n* = 6)	(*n* = 1)	(*n* = 0)	(*n* = 1)	(*n* = 1)
Classroom productivity impairment	41.3 ± 25.3	50.0	63.3 ± 15.1	0	-	0	10
Classroom time missed	0	0	14.5 ± 17.8	0	-	0	0
Overall classroom productivity	41.3 ± 25.3	50.0	70.1 ± 10.5	0	-	0	10
Activity	(*n* = 43)	(*n* = 72)	(*n* = 46)	(*n* = 14)	(*n* = 8)	(*n* = 7)	(*n* = 9)
Activity impairment	50.2 ± 26.9	41.8 ± 23.0	37.6 ± 26.4	37.9 ± 20.1	46.3 ± 22.0	44.3 ± 28.8	34.4 ± 29.2

AD, atopic dermatitis; Ec/Der, Eczema/Dermatitis; SD, Standard deviation.

ductivity in patients with skin diseases than sedative antihistamines (Fig. 1A). Non-sedative antihistamines significantly improved work productivity under almost all background conditions with the exception of disease duration. Sedative antihistamines only had a significant impact on the subpopulation of patients that were male or those that had a diagnosis of eczema/dermatitis (Fig. 1A).

The duration of disease was the only baseline patient characteristic that could significantly influence or bias the outcomes seen from administration of antihistamines (Table 4). Therefore, we compared the amount of change in the overall work impairment in the sedative and non-sedative antihistamine treatment groups after adjusting for the baseline duration of disease (Fig. 1B). These results confirmed that non-sedative antihistamines significantly improved the overall work impairment, while sedative antihistamines did not (Fig. 1B). Evaluation of impact of antihistamines on daily activity impairment and overall classroom impairment also demonstrate the superiority of non-sedative antihistamines over sedative antihistamines (Fig. 1A). Interestingly, sedative antihistamines failed to improve overall classroom productivity in all the patient population groups analyzed (Fig. 1A).

THE EFFECT OF ANTIHISTAMINES ON ATOPIC DERMATITIS

The effect of antihistamines on atopic dermatitis is still controversial.[14,15] Therefore, the treatment effects specifically for patients with atopic dermatitis (*n* = 43) were analyzed independently from other diagnostic groups (Fig. 3). As expected, treatment with antihistamines significantly reduced itch intensity in atopic dermatitis, while external medicines were ineffective (Fig. 3A). No differences were found between patients taking non-sedative versus sedative antihistamines (Fig. 3A). The impact of all treatments on the Skindex-16 QOL measure was similar to that for the itch VAS, with a significant effect for all antihistamines, but not for topical medications (Fig. 3B). Both non-sedative, and sedative antihistamines improved overall work impairment without statistical significance (Fig. 3C). Alternatively, the non-sedative antihistamine significantly reduced activity productivity impairment, whereas the trend towards improvement seen with sedative antihistamines did not reach statistical significance (Fig. 3D). These patients were prescribed concomitant external medications, but there were no remarkable differences between the non-sedative and sedative antihistamines treatment groups (Fig. 3E).

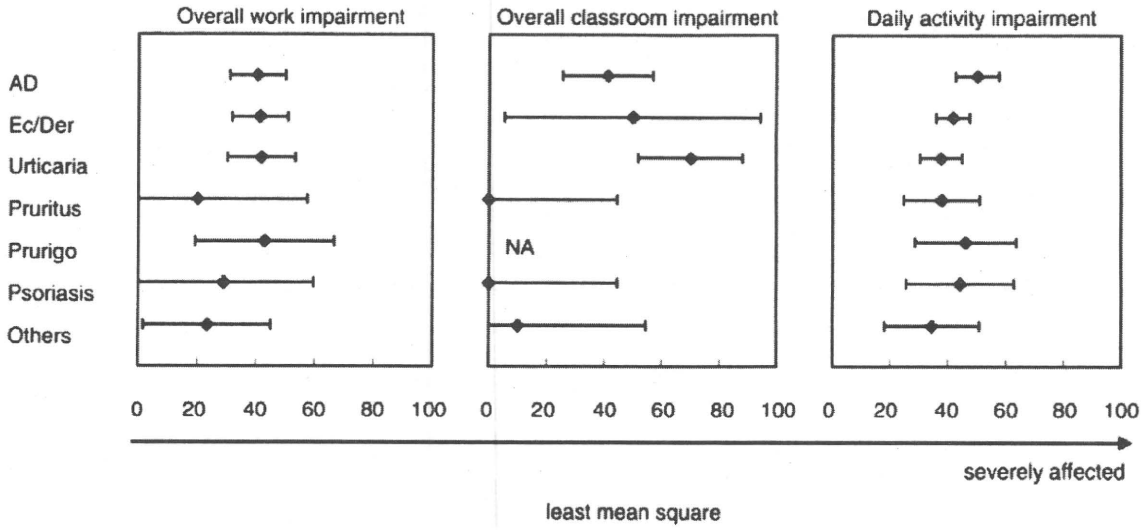

Fig. 2 Forest plots demonstrating the degree of impairment in each disease at baseline was evaluated using a linear least-squares method. Horizontal lines represent 95% confidence intervals. The rhomboid dot on the center of horizontal line indicates the point estimate. NA, not applicable.

Table 7 Number of patients from each skin disease diagnostic group assigned to indicated treatments

	Sedation	*n*	AD	Ec/Der	Uriticaria	Pruritus	Prurigo	Psoriasis	Others
Fexofenadine	NS	72	20	26	14	5	1	1	5
Loratadine	NS	2	0	0	2	0	0	0	0
Olopatadine	S	53	8	18	18	2	3	3	1
Epinastine	S	8	3	3	0	0	0	2	0
Cetirizine	S	9	2	6	0	0	1	0	0
Ebastine	S	11	1	7	1	1	0	0	1
Other 2nd generation	S	19	5	5	7	1	0	0	1
1st generation	S	21	3	6	7	2	2	1	0
External medicine	-	11	1	4	1	3	1	0	1
Total	-	206	43	75	50	14	8	7	9

AH, anti-histamines; NS, non-sedative; S, sedative; AD, atopic dermatitis; Ec/Der, Eczema/Dermatitis.

DISCUSSION

This study demonstrates that allergic skin diseases may have detrimental effects on productivity at work, in the classroom, and during daily activity. Previous reports demonstrated that allergic rhinitis impaired mean overall productivity at work, in the classroom, and in daily activity by ratios of 27-48%, 33-47%, and 42-51%, respectively.[16-19] In the present study, work performance and daily activities were highly and similarly impaired in patients with allergic skin diseases. However, WPAI-AS baseline scores in our study were slightly high relative to previous reports of WPAI (unidentified version) baseline scores for chronic idiopathic urticaria, psoriasis, and chronic hand dermatitis.[5,6,8] It is not currently clear why the present study generated different WPAI baseline scores, but further investigation is warranted.

According to the WPAI-AS values for the various pruritic skin diseases, the impairments in classroom productivity and overall classroom productivity were higher for patients with urticaria (Fig. 2). To clarify the reason why urticaria affected classroom productivity, cases of students with urticaria were analyzed independently for correlations with certain parameters (data not shown). Only the Skindex-16 was significantly associated with classroom impairment in this group ($P = 0.0075$, $r = 0.9282$, $n = 6$). Presumably, urticaria may impair a student's classroom productivity by negatively impacting their QOL.

In previous reports, WAPI scores of overall work impairment in patients with psoriasis were lower than those for patients with chronic idiopathic urticaria and chronic hand dermatitis.[5,6,8] Pearce and colleagues[6] discussed the observation that QOL measures did not exhibit the same trend as WPAI score in

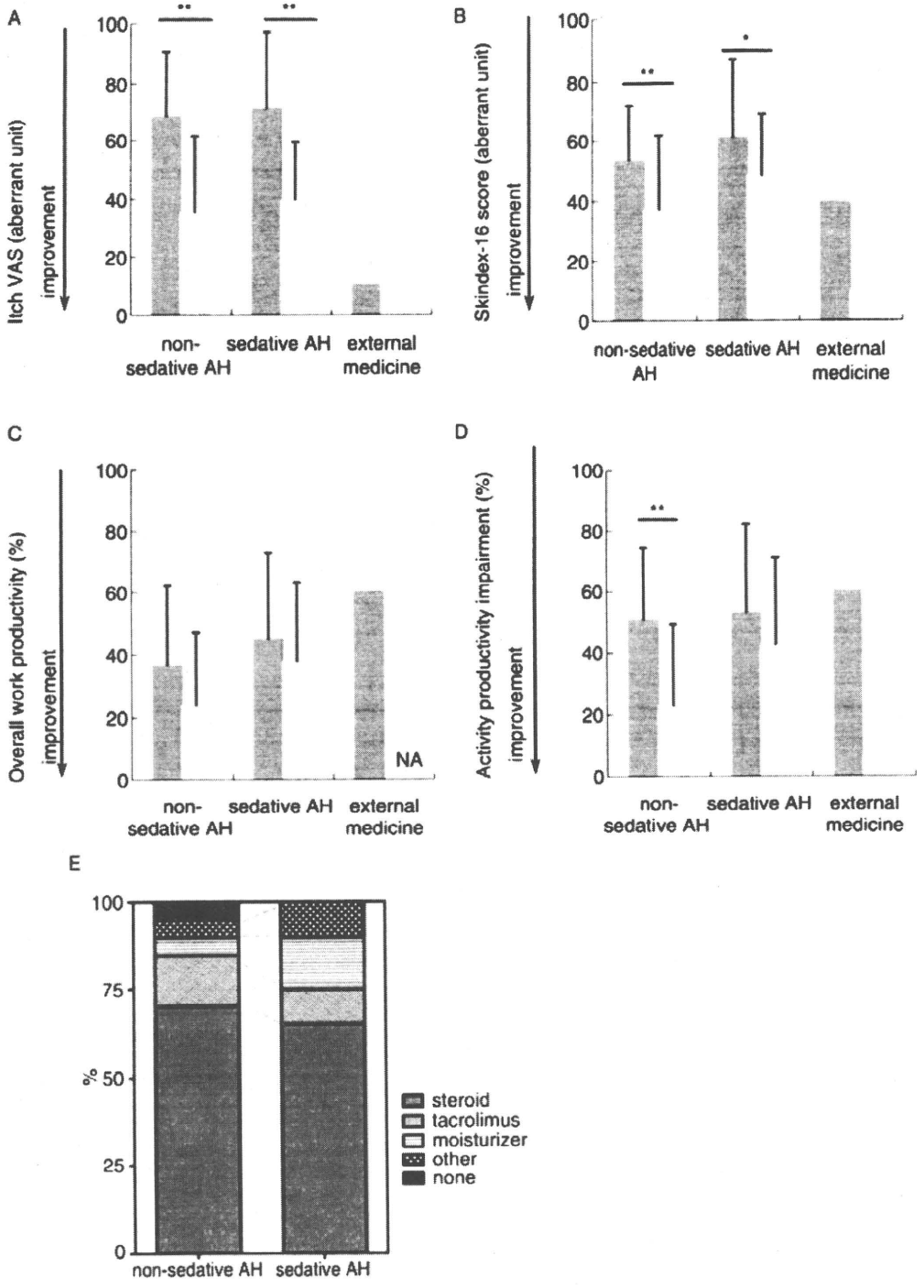

Fig. 3 The impact of antihistamines on (**A**) itch VAS, (**B**) skindex-16 score, (**C**) overall work productivity impairment, and (**D**) daily activity productivity impairment in atopic dermatitis. The data of baseline assessment (dark gray bar) and post treatment assessment (light gray bar) are shown as mean ± SD. **Statistically significant improvement compared with the data of baseline assessment ($P < 0.001$), *$P < 0.01$. NA, not applicable; AH, antihistamines. (**E**) Concomitant external medicine for cases with atopic dermatitis. "Other" includes vitamin D3 or non-steroidal anti-inflammatory ointment.

patients with psoriasis, and indicated that estimating the impact of psoriasis on social life seemed to be difficult. Indeed, as the number of patients with psoriasis was low in this study, which may indicate that our data are not representative of the general population of patients with psoriasis.

Concerning WPAI-AS scores in patients with atopic dermatitis, the total loss of daily activities was relatively higher than for patients with other skin diseases (Table 6, Fig. 2). It has been said that the intensity of itch might be increased in a relaxed environment, such as coming home or at nighttime.[20] In support of this, daily activity in patients with atopic dermatitis or pruritus was severely impaired compared with the impairment in overall work productivity (Table 6). Thus, daily activity may be highly susceptible to impairment in patients with atopic dermatitis and pruritus.

The differences between patients taking non-sedative versus sedative antihistamines was also addressed. As previously reported, sedative antihistamines failed to reduce work productivity impairment despite decreasing itch VAS values and Skindex-16 measures.[12] Impaired performance as an adverse effect of sedative antihistamines may be a major factor in these divergent results. In fact, in patients treated with sedative antihistamines, the improvement ratio for itch VAS scores did not significantly correlate with either the Skindex-16 QOL measure, the reduced impairment in overall work productivity, or the reduced impairment in daily activity (Table 2). Additionally, the extent of impairment in overall work productivity can be predicted by the Skindex-16 measures (Table 1). Nevertheless, clinicians should keep in mind that they could overestimate the effect of sedative antihistamines to improve on work productivity by relying solely on patient itch-intensity and QOL values. For these reasons, non-sedative antihistamines have substantial value in the treatment of patients with pruritic skin diseases.

However, the criteria for selecting antihistamines differ from disease to disease and vary worldwide. It is well known that non-sedative antihistamines, but not sedative antihistamines, are recommended as first-line agents for urticaria treatment.[21-25] In contrast, many previous published reviews, guidelines, and position papers on the care of atopic dermatitis state that the antihistamines are no more than a supportive management for pruritus, and their sedative properties offer an advantage for reducing the magnitude of itch in atopic dermatitis.[14,15,26,27] Thus, there is a tendency worldwide to recommend sedative antihistamines for the treatment of atopic dermatitis with intense itch or sleep disturbance.[14,15,26] Our data challenge this trend, since non-sedative antihistamines reduced the impairments in daily activity in patients with atopic dermatitis, while sedative antihistamines were ineffective (Fig. 1A, 3). Accordingly, the criteria for selecting antihistamines in certain skin diseases should be reconsidered.

Limitations of this study include the number of patients in each group and the potential influences of the adverse global economic conditions. Nonetheless, this report may highlight a new goal in the treatment of pruritic skin diseases and provide a rationale for shifting the choice of treatment options to non-sedative antihistamines.

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Olopatadine Hydrochloride Improves Dermatitis Score and Inhibits Scratch Behavior in NC/Nga Mice

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Key Words
Olopatadine hydrochloride · Atopic dermatitis · Model animal · Neurite outgrowth · Inflammation · Itch

Abstract
Background: Control of itch is an important issue in the treatment of atopic dermatitis (AD). Itch is mediated by a variety of pruritogens, including histamine, and promoted by neurite outgrowth in the epidermis of AD patients, probably due to the release of nerve growth factor. ***Objectives:*** We investigated the effects of orally administered olopatadine hydrochloride (olopatadine) on itching, itching mediators, and neuritogenic action in a mouse model. ***Materials and Methods:*** NC/Nga mice were treated topically with *Dermatophagoides farinae* body (Dfb) extract twice weekly for 4 weeks to induce AD-like lesions. They were concomitantly given oral olopatadine, distilled deionized water, or topical tacrolimus during the last 2 weeks. ***Results:*** Olopatadine significantly suppressed scratching, improved the dermatitis score, inhibited neurite outgrowth, and decreased the elevated inflammatory markers, growth factors and histamine content in the lesional skin, and serum concentration of Dfb-specific IgE. Notably, olopatadine treatment increased semaphorin 3A expression in the epidermis. ***Conclusions:*** Our study confirms the pleiotropic effects of olopatadine, i.e. inhibition of inflammation and neurite extension into the epidermis.

Introduction

Itch is a major symptom in allergic skin diseases that affects patients' quality of life [1]. Itch is induced by specific nonmyelinated C-fiber stimulation and the magnitude of itch is modulated by changes in stimulus frequency [2]. In atopic dermatitis (AD) skin lesions, increased epidermal nerve fiber density is frequently observed [3–5]. Substances found to be pruritogenic in AD include histamine, serotonin, prostaglandins, bradykinin, proteinases, opioids, cytokines and leukotrienes [2, 6–13]. Histamine, in particular, has been implicated as a cause of itch, inflammation and tissue remodeling in AD [7, 14–17], primarily through H_1 receptor activation [7]. Histamine

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