ORIGINAL ARTICLE

Burden of illness, medication adherence, and unmet medical needs in Japanese patients with atopic dermatitis: A retrospective analysis of a cross-sectional questionnaire survey

Kazumasa Kamei[1] 🔘 | Tomohiro Hirose[1] 🔘 | Noritoshi Yoshii[1] | Akio Tanaka[2] 🔘

[1]Inflammation and Immunology Medical Affairs, Pfizer Japan Inc., Tokyo, Japan

[2]Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

Correspondence
Kazumasa Kamei, Inflammation and Immunology Medical Affairs, Pfizer Japan Inc., 3-22-7 Yoyogi, Shibuya-ku, Tokyo 151-8589, Japan.
Email: Kazumasa.Kamei@pfizer.com

Akio Tanaka, Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
Email: tantanakiotan@yahoo.co.jp

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Abstract

Atopic dermatitis (AD) negatively affects patients' daily lives. Poor medication adherence is a major barrier to treatment success. However, factors causing patients' poor adherence are unclear. This study aimed to identify factors associated with improvement of medication adherence in Japanese patients with AD and to evaluate illness burden and unmet medical needs for AD. We retrospectively analyzed Web-based questionnaire surveys conducted in 2018 in patients with AD aged 15 years and above who had been in- or outpatients within the past year from the survey. Quality of life using the EuroQol 5-Dimension (EQ-5D), and work productivity and activity impairment using Work Productivity and Activity Impairment Questionnaire (WPAI) were compared between patients and matched controls who had not visited a hospital for any disease within the past year. Subpopulation analysis was performed to explore factors affecting medication adherence. Unmet medical needs in AD treatment were identified by the percentage of patients who rated issues on the questionnaire as important but who were unsatisfied with them. In this study, we identified 1739 patients with AD. The scores of EQ-5D and WPAI showed that patients had statistically lower quality of life and higher impairment of work and activities than controls. High medication adherence scores were seen in patients with high health literacy levels and those who were well satisfied with communication with health-care providers, information received from them, or explanations of AD. Current unmet medical needs for AD were medical treatment costs, ease of hospital visits and explanations about disease prognosis. Patients tended to put a higher priority on communication with physicians than on that with nurses and pharmacists. In conclusion, we have identified patients' higher health literacy levels and satisfaction with the communication with their health-care provider as potential factors to improve medication adherence.

KEYWORDS
atopic dermatitis, cross-sectional studies, health literacy, medication adherence, quality of life

1 | INTRODUCTION

Atopic dermatitis (AD) is a pruritic eczematous dermatitis with symptoms that fluctuate between remissions and relapses.[1] In most cases, AD presents in childhood and – although the disease may resolve by adolescence – it often becomes a chronic and lifelong condition. Chronic itching impairs patients' health-related quality of life (HRQoL) because of its negative impact on sleep, work productivity, and mental health.[2] Patients with more severe AD have poorer HRQoL; however, AD treatment can improve their HRQoL.[2,3]

Topical corticosteroids (TCS) and tacrolimus ointment are the main anti-inflammatory treatments used for AD.[1,4,5] Patients' interruption and inadequate use of these topical anti-inflammatory drugs can lead to aggravation of AD,[6] and non-adherence to therapy is problematic and has been associated with poor therapeutic outcomes.[7] To improve adherence, health-care providers are expected to explain the importance of medications to patients and motivate them to adhere to treatment.[1]

Health literacy is defined as the ability to access, understand, appraise, and apply health information.[8] Miller et al.[9] conducted a systematic meta-analysis to evaluate health literacy and medication adherence in patients with chronic and acute illness. Although they did not include AD in their analysis, they concluded that health literacy interventions increase medication adherence in patients. If this finding applies to patients with AD, improvement of health literacy may be a useful approach to improve treatment outcome in this disease.

In this study, we retrospectively analyzed the Medilead Healthcare Panel (MHP) database (Medilead Inc.), one of the largest databases in Japan with patient-reported information obtained in a Web-based questionnaire survey.[10] The analysis aimed to evaluate the impact of AD on daily life and how communication between patients and health-care providers or patients' health literacy affects medication adherence in AD. Furthermore, issues that patients felt were important but with which they were unsatisfied (defined as unmet medical needs) were also identified.

2 | METHODS

2.1 | Data source

For this retrospective study, we purchased and analyzed the MHP database managed by Medilead Inc.[10] The database contains the results of a survey on general health (e.g., current and past symptoms/diseases, HRQoL scores, work productivity loss scores, health literacy scores), and a disease-specific survey (e.g., prescriptions, medication adherence scores, medical expenses) on more than 500 kinds of symptoms/diseases in 347 659 people in Japan. These surveys were conducted from August to November in 2018 in accordance with the Declaration of Helsinki. All respondents filled the consent form for each survey, and data was anonymized not to be able to identify a specific individual.[10] In accordance with the regulations of the Japanese Marketing Research Association, all respondents were 15 years of age or older.

2.2 | Analysis cohorts

Patients with AD (AD patients) were identified as those who answered "AD" to the questions "What is your main disease?" and "Which disease made you an in- or outpatient within the past year?" and completed the AD-specific survey. Among those who answered

"No history" to the question "Which disease made you in- or outpatient in the past year?", we selected control individuals (controls) and matched them with AD patients in a 2:1 ratio on the basis of the demographic variables age, sex, occupation, and district of residence (matching criteria are shown in Table S1).

2.3 | Outcome measures

Generic HRQoL was assessed by the Japanese version of EuroQOL 5-dimension 5-level (EQ-5D-5L), including the subscores for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which ranged 1–5 (worst impairment).[11] The respondents who selected "1" in all subscores were defined as having a full health state with an overall index score of 1. Overall index scores ranged from −0.025 to 1 (best health status).[12]

Impairments in work and activities were assessed by the Japanese version of the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH).[13] This questionnaire assesses absenteeism, presenteeism, overall work impairment, and activity impairment. Respondents with no occupation were instructed to answer the question on activity impairment only.

Health literacy was assessed by the Japanese version of the European Health Literacy Survey Questionnaire (HLS-EU-Q47).[14] This questionnaire produces an overall index score called the general health literacy index (GEN-HL) and three subindices: the health care health literacy index (HC-HL), disease prevention health literacy index (DP-HL), and health promotion health literacy index (HP-HL). In each index, scores range 0–50 (excellent) and respondents' health literacy is classified as inadequate (range, 0–25), problematic (range, >25 to 33), sufficient (range, >33 to 42), and excellent (range, >42 to 50).[14]

Medication adherence was assessed with the Ueno method.[15] Ueno et al.[15] developed the medication adherence scale for Japanese patients with chronic disease, including AD. The total scale ranges 14–70 (excellent) and includes four factors: medication compliance (range, 3–15); collaboration with health-care providers (range, 3–15); willingness to access and use information about medication (range, 5–25); and acceptance to take medication and how taking medication fits the patient's lifestyle (range, 3–15).

The issues which patients felt important but with which they were unsatisfied were defined as unmet medical needs and assessed with the 25 questions originally included in the MHP database (Figure 2). Patients rated the importance level of each topic on a scale of 1–5. Issues were divided into three groups on the basis of patients' ratings: important (score 1 or 2); neutral (3); and not important (4 or 5). Similarly, patients also rated their level of satisfaction with the issues, as follows: satisfied (score 1 or 2); neutral (3); or unsatisfied (4 or 5). The percentage of patients who rated issues as important but who were unsatisfied with them were plotted in a scatter graph.

Patient responses to the original question "Which symptoms made you an in- or outpatient for AD?" were included in the analysis: patients selected all symptoms that applied to them from a list of 17

different symptoms (Table S2) and chose the key symptom that had the most impact on their decision-making.

2.4 | Subpopulation analysis

Atopic dermatitis patients were classified by sex, age, education level, health literacy scores, and their rating of the issues listed in Figure 1. Medication adherence scores were evaluated in each subpopulation.

2.5 | Statistical analysis

Continuous variables are reported as median with range and mean ± standard deviation. Categorical variables were summarized as frequencies and percentages of the study population and by subgroups, where appropriate. Differences in continuous variables between two groups were statistically analyzed with the Wilcoxon

rank-sum test because the data were expected to be non-normal. Differences in continuous variables between more than two groups were statistically analyzed with the Kruskal–Wallis test, and differences in categorical variables with the χ^2-test. All statistical analyses were performed with SPSS version 24.0.0.0 (IBM) and Cross Finder 2 (Cross Marketing).

3 | RESULTS

3.1 | Characteristics of patients with AD

We identified 1739 patients in the MHP database who were treated as in- or outpatients for AD in the year before the 2018 survey; 1516 patients (87.2%) of these patients stated that they were receiving any treatment for AD (Table 1). The sample consisted of 944 women (54.3%) and the mean age of the sample was 42.1 ± 12.1 years. Other demographic information and detailed treatment options are shown in Table 1 and Table S3.
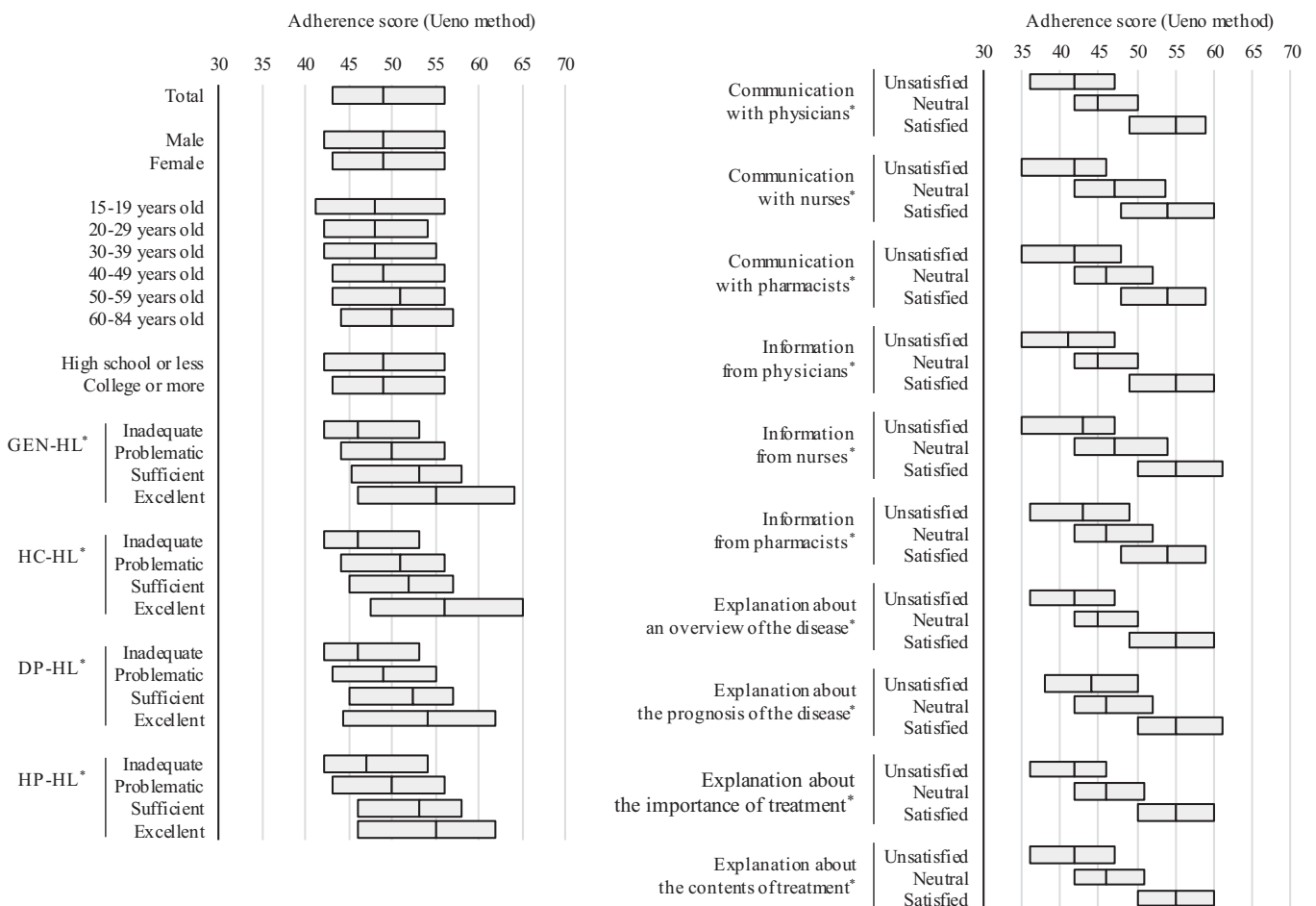

FIGURE 1 Medication adherence in patients with atopic dermatitis (AD). Medication adherence was evaluated by the Ueno method.[15] A higher score indicates higher medication adherence (range: 14–70). Patients with AD were classified by sex, age, education level, health literacy scores, and the answers to the questions regarding the level of satisfaction. *$p < 0.005$ in the Kruskal–Wallis test. DP-HL, disease prevention health literacy index; GEN-HL, general health literacy index; HC-HL, health-care health literacy index; HP-HL, health promotion health literacy index

TABLE 1 Characteristics of patients with atopic dermatitis and the matched controls

	AD patients (n = 1739) n (%)	Controls (n = 3478) n (%)	p^a
Sex			
Male	795 (45.7)	1590 (45.7)	1.000
Female	944 (54.3)	1888 (54.3)	
Age group, years			
15–19	46 (2.6)	86 (2.5)	0.998
20–29	230 (13.2)	459 (13.2)	
30–39	430 (24.7)	862 (24.8)	
40–49	588 (33.8)	1179 (33.9)	
50–59	314 (18.1)	621 (17.9)	
60–84	131 (7.5)	271 (7.8)	
Medication for atopic dermatitis			
Yes	1516 (87.2)	N/A	N/A
No	223 (12.8)	N/A	
Detailed medication for atopic dermatitis			
Moisturizer	754 (43.4)	N/A	N/A
Topical tacrolimus	404 (23.2)	N/A	
Weak TCS[b]	5 (0.3)	N/A	
Mild TCS[b]	499 (28.7)	N/A	
Strong TCS[b]	105 (6.0)	N/A	
Very strong TCS[b]	499 (28.7)	N/A	
Strongest TCS[b]	22 (1.3)	N/A	
Systemic corticosteroid	8 (0.5)	N/A	
Cyclosporin	2 (0.1)	N/A	
Phototherapy	4 (0.2)	N/A	
Unknown (no answer)	312 (17.9)	N/A	

Abbreviations: AD, atopic dermatitis; N/A, not applicable; TCS, topical corticosteroid.

[a]χ^2-Test.

[b]In Japan, TCS are generally classified into 5 ranks.[1]

Table 2 shows the AD symptoms for which patients sought treatment as in- or outpatients. Most patients named itchy skin as the symptom that made them seek the treatment (60.0%). When patients were allowed to name multiple symptoms, 93.1%, 72.1%, and 57.2% named itchy skin, rough skin, and dry skin, respectively.

3.2 | Controls

The controls were 3478 persons who had no history of visiting hospital for any disease in the past year. In the matched sample, sex (p = 1.000), age (p = 0.998), district of residence (p = 1.000), and occupation (p = 1.000) showed no significant difference between AD patients and controls (Table 1 and Table S2), indicating that they were appropriately matched for confounding covariates.

3.3 | Health-related quality of life

The median EQ-5D-5L score was lower in the AD patients than in the controls (p < 0.005) (Table 3). Furthermore, the percentage of respondents reporting full health (indicated by "no problem" in all domains) was 40.0% in the AD patients and 59.3% in the controls (p < 0.005).

3.4 | Impairments in work and activities

Atopic dermatitis patients had higher presenteeism, activity impairment, and overall work impairment than controls (p < 0.005; Table 3). On the other hand, absenteeism was not statistically significantly different between the two groups (p = 0.320).

3.5 | Health literacy

The median GEN-HL total health literacy score was 29.1 (interquartile range [IQR], 22.0–33.3) in AD patients and 28.8 (IQR, 19.4–33.3) in controls (Table 4). The subindex HC-HL was slightly higher in AD patients than in controls (p = 0.007), but no statistical difference was found in DP-HL (p = 0.063) or HP-HL (p = 0.904).

3.6 | Factors associated with medication adherence in patients with AD

The total medication adherence score was 49.2 ± 10.2 in male AD patients and 49.3 ± 10.2 in female ones. To examine which factors affect medication adherence, we performed a subpopulation analysis. As shown on the right-hand side of Figure 1, medication adherence was high in patients who were satisfied with the communication with health-care providers (physician, nurses, and pharmacists), the information given to them from these providers, and the explanation of its content (disease overview, prognosis of disease, importance of treatment, and treatment options). Furthermore, patients with higher health literacy showed better medication adherence (shown in the lower left part of Figure 1). On the other hand, when patients were divided according to demographic characteristics such as age, sex, and education level, no significant differences were found in any subpopulation.

3.7 | Unmet medical needs for atopic dermatitis

The X-axis in Figure 2 shows the percentage of patients who rated the 25 issues on AD as important. The top three issues were communication with physicians (74.4%), ease of hospital visit (71.8%), and information from physicians (70.0%). The results for items 1–3 (Figure 2) showed that patients tended to place greater importance on communication with physicians (item 1, 74.4%) than on

TABLE 2 Trigger symptoms that made patients seek in- or outpatient treatment for atopic dermatitis

Symptoms	Decision-making symptoms[a]	All trigger symptoms[b]
Non-visible symptoms		
Itchy skin	882 (60.0)	1370 (93.1)
Skin pain	66 (4.5)	408 (27.7)
Visible symptoms		
Rough skin	240 (16.3)	1061 (72.1)
Dry skin	34 (2.3)	842 (57.2)
Reddened skin/something similar to moles and freckles occurred	81 (5.5)	635 (43.2)
Skin swelling	47 (3.2)	393 (26.7)
Red spot on the skin	76 (5.2)	368 (25.0)

[a]Patients selected one symptom that made them seek in- or outpatient treatment for atopic dermatitis (AD). Symptoms with a response rate of 1% are shown.

[b]Patients selected all symptoms that made them seek in- or outpatient treatment for AD. Symptoms with a response rate of 10% are shown.

TABLE 3 Health-related quality of life and work productivity and activity impairment in patients with atopic dermatitis and controls

	AD patients, median (IQR)	Controls, median (IQR)	p[a]	AD patients, mean (SD)	Controls, mean (SD)
EQ-5D-5L	0.895 (0.823–1.000)	1.000 (0.867–1.000)	<0.005	0.879 (0.137)	0.898 (0.182)
WPAI					
Absenteeism	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.320	6.3 (19.1)	6.5 (20.0)
Presenteeism	20.0 (0.0–50.0)	10.0 (0.0–50.0)	<0.005	27.4 (27.8)	24.9 (27.7)
Overall work impairment	20.0 (0.0–51.0)	20.0 (0.0–50.0)	<0.005	30.4 (30.7)	28.0 (30.8)
Activity impairment	30.0 (0.0–50.0)	20.0 (0.0–50.0)	<0.005	31.4 (28.8)	25.6 (27.7)

Abbreviations: AD, atopic dermatitis; EQ-5D-5L, EuroQOL 5-dimension 5-level; IQR, interquartile range; SD, standard deviation; WPAI, Work Productivity and Activity Impairment.

[a]Wilcoxon rank-sum test.

TABLE 4 Health literacy score of patients with atopic dermatitis and controls

	AD patients, median (IQR)	Controls, median (IQR)	p[a]	AD patients, mean (SD)	Controls, mean (SD)
GEN-HL	29.1 (22.0–33.3)	28.8 (19.4–33.3)	0.047	28.8 (9.7)	28.1 (11.2)
HC-HL	29.2 (21.9–33.3)	28.1 (18.8–33.3)	0.007	28.7 (9.8)	27.9 (11.5)
DP-HL	31.1 (22.6–34.9)	30.6 (20.0–34.4)	0.063	30.0 (10.6)	29.3 (11.7)
HP-HL	28.1 (19.8–33.3)	28.1 (17.8–33.3)	0.904	27.7 (10.6)	27.6 (11.6)

Abbreviations: AD, atopic dermatitis; DP-HL, disease prevention health literacy index; GEN-HL, general health literacy index; HC-HL, health care health literacy index; HP-HL, health promotion health literacy index; IQR, interquartile range; SD, standard deviation.

[a]Wilcoxon rank-sum test.

communication with nurses (item 2, 45.9%) or pharmacists (item 3, 57.5%). A similar tendency was also observed regarding the healthcare providers who provide information to patients: physicians (item 4, 70.0%), nurses (item 5, 43.1%), and pharmacists (item 6, 57.7%).

The Y-axis in Figure 2 shows the percentage of patients who stated that they were unsatisfied with issues regarding AD. The top three issues were medication costs (item 18, 22.4%), launch of new drugs that can prevent disease onset (item 21, 21.2%), and launch of new drugs that can cure the disease or make it possible to have a normal daily life (item 20, 19.3%). Three issues ranked in both the top 10 of important issues and the top 10 of unsatisfied issues: medical treatment costs, explanation about prognosis of disease, and ease of hospital visit (items 9, 17, and 18), suggesting that these are unmet medical needs in AD.
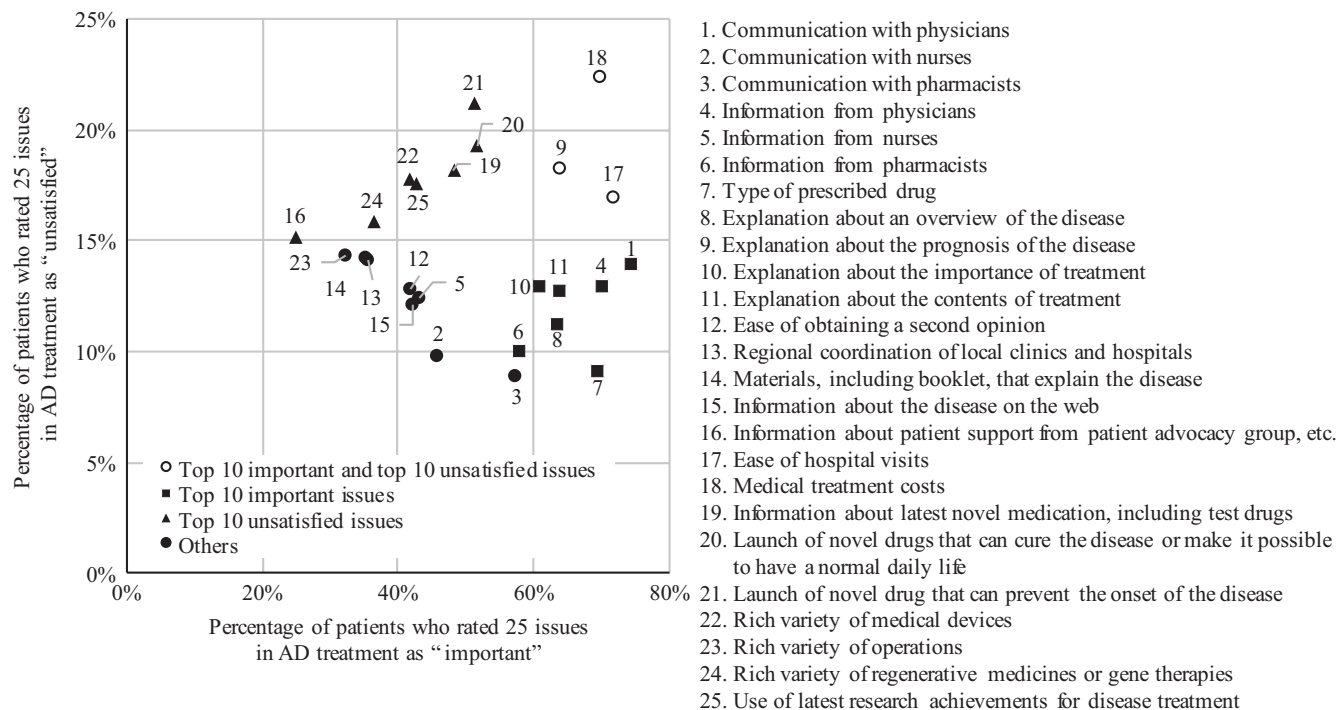
1. Communication with physicians
2. Communication with nurses
3. Communication with pharmacists
4. Information from physicians
5. Information from nurses
6. Information from pharmacists
7. Type of prescribed drug
8. Explanation about an overview of the disease
9. Explanation about the prognosis of the disease
10. Explanation about the importance of treatment
11. Explanation about the contents of treatment
12. Ease of obtaining a second opinion
13. Regional coordination of local clinics and hospitals
14. Materials, including booklet, that explain the disease
15. Information about the disease on the web
16. Information about patient support from patient advocacy group, etc.
17. Ease of hospital visits
18. Medical treatment costs
19. Information about latest novel medication, including test drugs
20. Launch of novel drugs that can cure the disease or make it possible to have a normal daily life
21. Launch of novel drug that can prevent the onset of the disease
22. Rich variety of medical devices
23. Rich variety of operations
24. Rich variety of regenerative medicines or gene therapies
25. Use of latest research achievements for disease treatment

FIGURE 2 Percentages of patients with atopic dermatitis (AD) who responded "important" or "unsatisfied" regarding the 25 issues (listed on the right-hand side)

4 | DISCUSSION

In this study, we obtained and retrospectively analyzed survey-based data to examine the effects of AD on the daily life of Japanese patients and the effects of various factors on medication adherence. We showed that Japanese patients with AD have impaired HRQoL, work productivity, and activity, which supports the findings of previous studies.[16–19] For example, Arima et al.[16] reported that in Japanese patients with AD absenteeism, presenteeism, overall work impairment, and activity impairment were 4.0 ± 12.3%, 28.6 ± 25.3%, 30.6 ± 27.2%, and 32.2 ± 27.9%, respectively. In our study, the respective values were 6.3 ± 19.1%, 27.4 ± 27.8%, 30.4 ± 30.7%, and 31.4 ± 28.8%, indicating that the participants in our study represented typical Japanese patients with AD. These findings suggest the need for controlling patients' symptoms so that they can achieve a satisfactory HRQoL.[1]

Medication adherence and persistence are the cornerstones of effective treatment of AD. In our study, medication adherence was positively associated with patients' health literacy and their satisfaction with communication with health-care providers and the information provided by them. Nakayama et al.[14] reported that Japanese health literacy was lower than that of Europeans: this difference may be partly due to issues related to the Japanese primary health-care system. Furthermore, it is difficult for patients in Japan to access reliable and understandable health information because no comprehensive national online platform exists.[14] Health literacy can be improved by provision of information, effective communication, and structured education.[20,21] Therefore, physicians should identify patients with lower health literacy and support them, in cooperation with other health-care providers, in developing a better understanding of their condition.

In this study, we evaluated medication adherence by the Ueno method and the scores were lower than those with chronic diseases reported by Ueno et al.[15] The result is supported by the results of Furue et al.,[22] who showed that medication adherence was lower in patients with AD than in those with urticaria, psoriasis or tinea. Their group also identified messiness of treatment, forgetfulness, and feeling better as the major reasons for forgetting to take topical medication.[23] To avoid recurrence, advising patients to continue topical treatment is regarded as helpful even after they think their skin lesions have cleared up.[23] We found that patients with AD tended to put a higher priority on communication with physicians than on that with nurses and pharmacists. In Japan, the duration of consultations with physicians is often limited.[24,25] Such short consultations make it difficult for physicians to have enough time to explain the condition of AD and treatment methods until their patients understand them completely. One of the realistic solutions to this problem is that, besides physicians, nurses and pharmacists also explain these issues to patients, while acknowledging that patients would prefer to receive explanations from physicians.

Explanation about prognosis of the disease and medical treatment costs were identified as two unmet medical needs. The latest Japanese guidelines for AD recommend explaining the disease and treatment goal to patients before initiating treatment.[1] However, our results suggest that, in most cases, these issues are not adequately

explained to patients. Furthermore, some patients might think that treatment for AD is not worth the cost because they do not fully understand how their skin inflammation will be controlled by the treatment. Further study is required because this possibility remains purely speculative.

Our results showed that patients with AD tended to decide to visit physicians not because of symptoms affecting their appearance but because of itchy skin. Because severe itching disturbs patients' daily life,[2] we speculate that they seek treatment to alleviate it. At present, in daily clinical practice most physicians ask their patients if they have itching.[24] In addition to that, physicians can utilize quantitative tools to evaluate the intensity of the itch, for example with the Numerical Rating Scale or Visual Analog Scale.[26]

The treatment landscape of AD has been changing in the last 2 years because an anti-interleukin-4 receptor α monoclonal antibody[27] and a systemic Janus kinase (JAK) inhibitor[28] were launched as treatments for severe AD. Furthermore, other biologics (e.g., nemolizumab) and JAK inhibitors (e.g., abrocitinib) are under development.[4] In line with the availability of new treatment options for severe cases, the treatment strategy and goals in AD are expected to change in the future,[29] which is expected to also change the willingness of patients to adhere to AD treatment. Our findings will also be valuable as comparative data for the results of future patient surveys performed after the introduction of new therapeutic options because differences between our results and those of new surveys can show the change in patients' perspectives as a result of the advances in treatment.

Our study has some limitations. Survey respondents comprised a self-selected sample, which may not reflect the entire population. Patient-reported outcome is subjective, and some outcomes might not be valid from a medical perspective. Data on children and younger adolescents were lacking. Finally, controls were defined as people who had no history of visiting a hospital for any disease in the past year. Therefore, if patients with AD had not visited any hospital in the past year and they participated in the survey, they may have been included in the control group.

In conclusion, we showed that medication adherence in patients with AD was positively associated with patients' health literacy level and their level of satisfaction with communication with health-care providers. Considering the health literacy level, health-care providers are expected to explain AD to their patients and ensure that they understand the disease, prognosis, importance of treatment, and treatment options.

ORCID

Kazumasa Kamei https://orcid.org/0000-0001-7220-5142
Tomohiro Hirose https://orcid.org/0000-0002-9569-6834
Akio Tanaka https://orcid.org/0000-0002-5354-7064

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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