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ORIGINAL ARTICLE

Phase 2a, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of a H_4R-antagonist (JNJ-39758979) in Japanese adults with moderate atopic dermatitis

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ABSTRACT

This trial was conducted to evaluate the safety and efficacy of the H_4R-antagonist JNJ-39758979 in adult Japanese patients with moderate atopic dermatitis (AD). Eligible patients were randomly assigned to JNJ-39758979 300 mg, 100 mg or placebo once daily for 6 weeks in this phase 2a, double-blind, multicenter, placebo-controlled study. Primary efficacy was assessed via week-6 Eczema Area and Severity Index (EASI) scores. Secondary efficacy assessments included Investigator's Global Assessment (IGA) and patient-reported outcome (PRO) pruritus assessments (Pruritus Categorical Response Scale [PCRS], Pruritus Numeric Rating Scales [PNRS], Pruritus Interference Numeric Rating Scale [PINRS] and Subject's Global Impressions of Change in Pruritus [SGICP]). Eighty-eight of 105 planned patients were randomized before the study was stopped and unblinded for safety reasons. The study did not meet the primary end-point. However, numerical improvements (i.e. decreases) in median EASI were observed with JNJ-39758979 100 mg (−3.7) and 300 mg (−3.0) versus placebo (−1.3) at week 6. Nominally significant improvements across PRO PCRS, PNRS and SGICP assessments were consistently observed, particularly with JNJ-39758979 300 mg. Safety, including adverse events (AE), was comparable between JNJ-39758979 and placebo with the exception of two patients (both receiving JNJ-39758979 300 mg) with serious AE of neutropenia, leading to premature study discontinuation. No deaths were reported. Except for neutropenia, no clinically relevant changes in laboratory values were observed. Although not conclusive, findings suggest H_4R-antagonism may be beneficial for AD, particularly in controlling pruritus. JNJ-39758979 appears to be associated with drug-induced agranulocytosis, likely an off-target effect.

Key words: **atopic dermatitis, H_4 receptor, itch, Japan.**

INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, inflammatory skin disease characterized by skin lesions, pruritus and dry skin[1–3] that is often predictive of subsequent atopic disorders such as allergic rhinitis and asthma. Atopic dermatitis has a worldwide lifetime prevalence of 10–20% in children and 1–3% in adults.[4] In Japan, the lifetime adult prevalence of AD is 3.3%[5] and the incidence of adult AD is reported to be increasing over time.[6] An increased incidence of severe/very severe AD has also been reported, with significantly higher incidences of AD in Japanese patients who are adolescents and adults than in infants and children.[6]

Atopic dermatitis is believed to be initially driven by type 2 T-helper (Th)2 cell responses, with Th1 cell responses playing more of a role in chronic lesions.[1–3] An increase in the inflammatory mediator histamine has been noted in the skin and plasma of patients with AD,[7,8] and histamine-releasing basophils and mast cells have been shown to be increased in AD lesions.[9,10] While antihistamines that target the histamine H_1

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receptor (H_1R) have frequently been used to treat AD-associated pruritus, their effectiveness has been reported to be limited.[1]

More recently, the histamine H_4 receptor (H_4R) has been identified to play a role in inflammatory responses.[11] The expression of H_4R by $CD4^+$ T cells tends to be higher in patients with AD versus non-afflicted individuals. Stimulation of the receptor leads to upregulation of interleukin (IL)-31 mRNA in Th2 cells, and IL-31 has been shown to correlate with AD severity.[12,13] Proliferation of keratinocytes from patients with AD has been shown to be increased upon activation of the H_4R.[14] Preclinical data also support a role for the H_4R in driving dermal inflammation. In several different mouse dermatitis models, treatment with an H_4R antagonist reduced the lesion, the infiltration of inflammatory cells and the production of inflammatory cytokines.[15–19] In addition, scratching was inhibited by H_4R antagonists in these models.[15,17,19]

JNJ-39758979, a potent, selective, orally active H_4R antagonist, has been evaluated in phase 1 studies assessing single and multiple ascending doses, and no significant safety issues were identified other than nausea.[20] In addition, JNJ-39758979 was able to inhibit the itch sensation induced by intradermal (i.d.) injection of histamine in healthy human subjects.[21] Given these findings, a phase 2a trial was conducted to evaluate the safety, tolerability and efficacy of two dose levels of JNJ-39758979 using an enteric-coated formulation, which is expected to reduce nausea, in adult Japanese patients with moderate AD. Additionally, because there were limited reliable patient-reporting tools available to measure itching in the clinical trial setting, the trial sponsor developed several pruritus rating scales that patients could self-administer electronically on a handheld device throughout the trial.

METHODS

This study was conducted in compliance with the principles set forth by the Declaration of Helsinki and current International Committee on Harmonization guidelines. The study protocol was approved by independent ethics committees, and all patients provided written informed consent prior to trial participation.

Patients

Adult (20–65 years of age) Japanese patients with moderate AD (10–50% body surface area [BSA] involved; Rajka–Langeland score of 4.5–7.5;[22] Investigator's Global Assessment [IGA] score of 3,[23] i.e. moderate disease) who had onset prior to age 13 years and were diagnosed according to the AD management guidelines issued by the Japanese Dermatological Association,[24] including the presence of pruritus, eczematous changes in a typical distribution and a chronic or chronically relapsing course, were eligible for study participation. Patients were also required to demonstrate acceptable compliance with using a hand-held electronic device to rate their pruritus and to have reported at least three instances of "moderate itching", "severe itching" or "extremely severe itching" either at night or during the day based on the Pruritus Categorical Response Scale (PCRS; see Study Evaluations section) within 7 days of randomization. Involvement of skin on body parts other than the hands and/or feet was also required.

Patients with any known malignancy (except non-recurrent basal cell carcinoma or squamous cell carcinoma) or any other skin condition that the investigator believed would interfere with AD assessment were excluded from participating. Use of non-steroid immunosuppressants or immunomodulators (e.g. cyclosporin A, azathioprine, mycophenolate mofetil, interferon-γ), systemic corticosteroids or daily high-dose inhaled corticosteroids was not permitted beginning 4 weeks prior to randomization. Use of topical therapy for AD (e.g. corticosteroids, calcineurin inhibitors, antihistamines, anesthetics, non-steroidal anti-inflammatory drugs, counter-irritants, medicated emollients) or topical/oral herbal preparations was not permitted beginning 1 week prior to randomization and continuing throughout study participation. Sponsor- or patient-provided non-medicated emollients were allowed; however, with the exception of white petroleum jelly, other patient-provided emollients required approval from the sponsor. Use of oral or parenteral antihistamines (including sleep medications with antihistaminic properties); other anti-allergy medications such as sodium cromoglicate, suplatast tosilate, tranilast; or soporifics was not permitted within 2 weeks of randomization.

Study design

Eligible patients enrolled into this randomized, phase 2a, double-blind, multicenter, placebo-controlled, parallel-group study were randomly assigned (1:1:1) to receive placebo, JNJ-39758979 100 mg or JNJ-39758979 300 mg once daily for up to 6 weeks. Randomization, based on a computer-generated randomization schedule, was balanced using randomly permuted blocks and stratified by investigational centers. All patients were to receive three identically appearing tablets (JNJ-39758979 100 mg or placebo) daily, in the morning with a meal or within 30 min after a meal. Patients were permitted to use triamcinolone acetonide (TCA) 0.1% ointment twice daily for a maximum of 7 days per episode as needed for the treatment of AD flares if protocol-specified flare criteria (IGA increase from 0 to ≥2 or IGA increase of 1 if most recent IGA ≥1) were met and it was determined appropriate by the investigator. For each patient, use of TCA for treatment of AD flares was limited to one course in each of the screening, first 3-week (days 1–22) and second 3-week (day 23 through the end of treatment) study periods.

Study evaluations

The Eczema Area and Severity Index (EASI), a validated scoring system,[25] was employed to assess AD severity. Four body regions (head/neck, trunk, upper limbs, lower limbs) were assessed separately for erythema, infiltration/papulation, excoriation and lichenification.

The IGA of AD was performed by the investigator to measure disease severity based on morphology, without reference back to the baseline state. The IGA utilizes a 6-point scale (0 = "clear" to 5 = "very severe disease") and has been used in other AD studies to assess overall disease severity.[23]

The Pruritus Categorical Response Scale (PCRS), Pruritus Numeric Rating Scales (PNRS) and Pruritus Interference Numeric Rating Scale (PINRS) are instruments developed by the sponsor to evaluate both the severity and the duration of pruritus associated with AD and the impact of pruritus on daily activity and sleep. The scales were translated to Japanese through a 2-forward/1-backward translation process and were administered twice daily electronically on a handheld device (once in the morning and once in the evening). The PCRS allows patients to rate their worst itching at night and during the day on a 5-point categorical response scale ranging from "no itching" to "extremely severe itching". The PNRS assesses severity of worst itching using an 11-point (range, 0–10) numeric rating scale (NRS), whereby 0 = "no itching" and 10 = "worst possible itching". The PINRS assesses pruritus interference with sleep and daily activities on an 11-point NRS (range, 0–10), whereby 0 = "did not interfere" and 10 = "completely interfered". In addition, the Subject's Global Impressions of Change in Pruritus (SGICP) was administered on paper at site visits to document the perceived change (improvement or deterioration) from baseline in severity/duration of itching using a 7-point scale (ranging from "a lot better/more now" to "a lot worse/less now" with a neutral center point ("neither better/more nor worse/less"). In addition to serving as indicators of efficacy, data collected from these scales were intended to be used for psychometric performance tests to inform the selection of response scale (categorical vs numeric) and attributions (intensity, duration and impact) of the final scale for future trials.

Adverse events (AE) and concomitant medications were documented from the time of informed consent signing until study termination. Samples for clinical laboratory and pharmacokinetic evaluation testing were collected at predefined time points. JNJ-39758979 plasma and whole blood concentrations were determined using a validated, specific and sensitive liquid chromatography/mass spectrometry/mass spectrometry method. Five known metabolites of JNJ-39758979 (Fig. S2) were also measured.

Data analysis and sample size determination

Because the study was unblinded and terminated early due to safety reasons before the database was locked and the statistical analysis plan was finalized, the efficacy analysis was performed post-hoc and included available data for all randomized patients who received at least one dose of study medication and had at least one post-baseline measurement. As planned in the protocol, each JNJ-39758979 group was compared against placebo using a two-sided test at an α-level of 0.05. All significance tests should be considered nominal and interpreted with caution.

Patients who met one or more of the treatment failure criteria (used TCA during the previous 3-week treatment period, used prohibited medications and/or discontinued due to worsened underlying AD) had the last observation before failure carried forward from the date of treatment failure onward throughout the treatment period. Because most patients were withdrawn from the study before the week-6 assessment due to the premature termination of the study, missing data were not imputed. Changes from baseline in weekly averages were calculated for patient-reported outcome (PRO) assessments; the weekly average was calculated for time periods defined as follows: the visit date of the EASI assessment was used for weeks 1, 2, 4 and 6, while for weeks 3 and 5, which had no EASI visit date, week 4 minus 7 days and week 6 minus 7 days, respectively, were employed as PRO visit dates. The weekly average score was then calculated as the average score during −7 to −1 days before the visit date.

Comparison of each treatment group versus placebo was to be conducted using an ANCOVA model, with treatment group as a factor and baseline value as a covariate, for continuous data or Fisher's exact test for dichotomous data. Note that a non-parametric analysis was actually used due to non-normal distribution for changes in EASI scores from baseline to week 6.

All safety analyses performed included all randomized patients who received at least one dose of study agent. All reported AE with onset during the treatment phase were included in the analysis. Laboratory data were summarized by type of laboratory test. Reference ranges and predefined markedly abnormal criteria were used in the summary of laboratory data.

The sample size calculation was based on the primary end-point, namely, the change from baseline in EASI score at week 6. Assuming a standard deviation (SD) of approximately 5.9, 35 patients per treatment group would have provided 95% power to detect a treatment difference of 5.2 or more when using a two-sided Student's t-test at $\alpha = 0.05$.

RESULTS

Patient disposition

One hundred and five patients were screened across 22 sites at the time of early termination of the study. Eighty-eight of these patients were randomized, and 87 received at least one dose of study agent, including 33 with placebo, 27 with JNJ-39758979 100 mg and 27 with JNJ-39758979 300 mg. Thirty-eight (43.2%) patients were withdrawn early from the trial, most commonly due to the sponsor's decision to stop the study, and 50 (56.8%) patients completed the week-6 visit and had evaluable EASI data (Table 1).

Baseline patient and disease characteristics

Patients entered the study with AD involvement of approximately 30% of their BSA and that was generally considered to be moderate in intensity. Baseline characteristics were generally similar across randomized treatment groups (Table 2).

Efficacy results

Primary end-point. The changes in EASI scores from baseline to week 6 (primary efficacy end-point) were numerically, but not significantly, greater with JNJ-39758979 100 mg (median, −3.70) and 300 mg (median, −3.00) versus placebo (median, −1.30; $P = 0.1672$ and 0.1992, respectively; Fig. 1) based on

Table 1. Summary of patient disposition (all randomized patients)

	Placebo	JNJ-39758979 100 mg QD	JNJ-39758979 300 mg QD
No. of randomized patients	33	28	27
Early withdrawal, *n* (%)	11 (33.3)	15 (53.6)	12 (44.4)
Withdrawal of consent	1	0	1
>1 AD flare requiring TCA from day 1–22 or day 23–end of treatment	0	0	1
Adverse event	0	1	1
Physician decision	1	2	0
Other	9	12	9
No. of treated patients	33	27	27
Patients who completed			
Week 1 visit	33	27	27
Week 2 visit	32	21	22
Week 4 visit	28	17	18
Week 6 visit	21	13	16
Patients who discontinued study agent before week 6, *n* (%)	11 (33.0)	14 (50.0)	12 (44.4)
Safety population	33	27	27
Modified intention-to-treat population	33	27	27

AD, atopic dermatitis; QD, once daily; TCA, triamcinolone acetate.

the non-parametric ranked ANCOVA analysis comparing the distribution of the changes in EASI scores.

Major secondary end-points. One of 15 (6.7%) patients receiving JNJ-39758979 100 mg and one of 17 (5.9%) patients receiving 300 mg had IGA scores of "Clear" (0) or "almost clear" (1) at week 6, compared with two of 22 (9.1%) patients in the placebo group ($P = 1.000$ for both comparisons).

At week 6, mean changes from baseline in PCRS Daytime and Night-time Pruritus Severity were numerically greater for patients receiving JNJ-39758979 100 mg (−0.58 and −0.56, respectively) and nominally significant for 300 mg (−0.87 and −0.86, respectively) than in patients receiving placebo (−0.26 and −0.17, respectively). Improvements in daytime and night-time pruritus intensity appeared to be dose-dependent (Figs 2a; S1A,B).

Mean changes from baseline to week 6 in PNRS Daytime Pruritus Severity and Daytime Pruritus Duration were numerically greater for patients receiving JNJ-39758979 100 mg (−1.87 and −1.94, respectively) and nominally significant for 300 mg (−2.28 and −2.26, respectively; both $P < 0.05$ vs placebo) than in patients receiving placebo (−0.57 and −0.91, respectively). Similar findings were observed for mean changes in PNRS Night-time Pruritus Severity and Duration, and improvements in Daytime and Night-time pruritus intensity and duration appeared to be dose-dependent (Figs 2b,c; S1C,D).

Mean changes from baseline to week 6 in PINRS Impact of Pruritus on Daily Activity and Sleep showed numerically (with a

Table 2. Summary of baseline patient and disease characteristics (safety population)

	Placebo	JNJ-39758979 100 mg QD	JNJ-39758979 300 mg QD
No. of patients	33	27	27
Male patients, *n* (%)	23 (69.7)	17 (63.0)	19 (70.4)
Age (years), mean (SD)	31.6 (10.0)	30.2 (8.9)	30.4 (9.5)
Body mass index (kg/m^2), mean (SD)	22.7 (3.8)	23.5 (3.7)	22.8 (3.1)
Age of onset of atopic dermatitis, *n* (%)			
<2 years	2 (6.1)	4 (14.8)	6 (22.2)
2 to <6 years	16 (48.5)	16 (59.3)	12 (44.4)
6 to <12 years	12 (36.4)	7 (25.9)	9 (33.3)
≥12 years	3 (9.1)	0 (0.0)	0 (0.0)
Percent body surface area, mean (SD)	30.1 (11.4)	27.0 (10.2)	31.7 (13.1)
Atopic dermatitis severity† (3–9), mean (SD)	7.0 (0.6)	6.8 (0.7)	6.9 (0.6)
PCRS			
Daytime severity, mean (SD)	2.3 (0.7)	2.5 (0.6)	2.4 (0.7)
Night-time severity, mean (SD)	2.2 (0.7)	2.2 (0.6)	2.4 (0.6)
PNRS			
Daytime severity, mean (SD)	5.9 (1.6)	6.2 (1.5)	6.2 (1.6)
Daytime duration, mean (SD)	5.6 (1.7)	5.8 (1.5)	5.7 (1.5)
Night-time severity, mean (SD)	5.7 (1.7)	5.7 (1.6)	5.9 (1.7)
Night-time duration, mean (SD)	5.1 (1.5)	5.1 (1.7)	5.5 (1.7)
PINRS			
Daily activity, mean (SD)	5.1 (1.7)	5.1 (1.7)	4.8 (1.8)
Sleep, mean (SD)	4.9 (1.7)	4.6 (1.7)	4.7 (2.0)
EASI, mean (SD)/median	13.3 (5.6)/12.0	13.3 (6.1)/11.6	15.2 (6.7)/13.4

†Rajka and Langeland T (1989).[22] EASI, Eczema Area and Severity Index; PCRS, Pruritus Categorical Response Scale (weekly average); PINRS, Pruritus Interference Numeric Rating Scale; PNRS, Pruritus Numeric Rating Scale (weekly average); QD, once daily; SD, standard deviation.

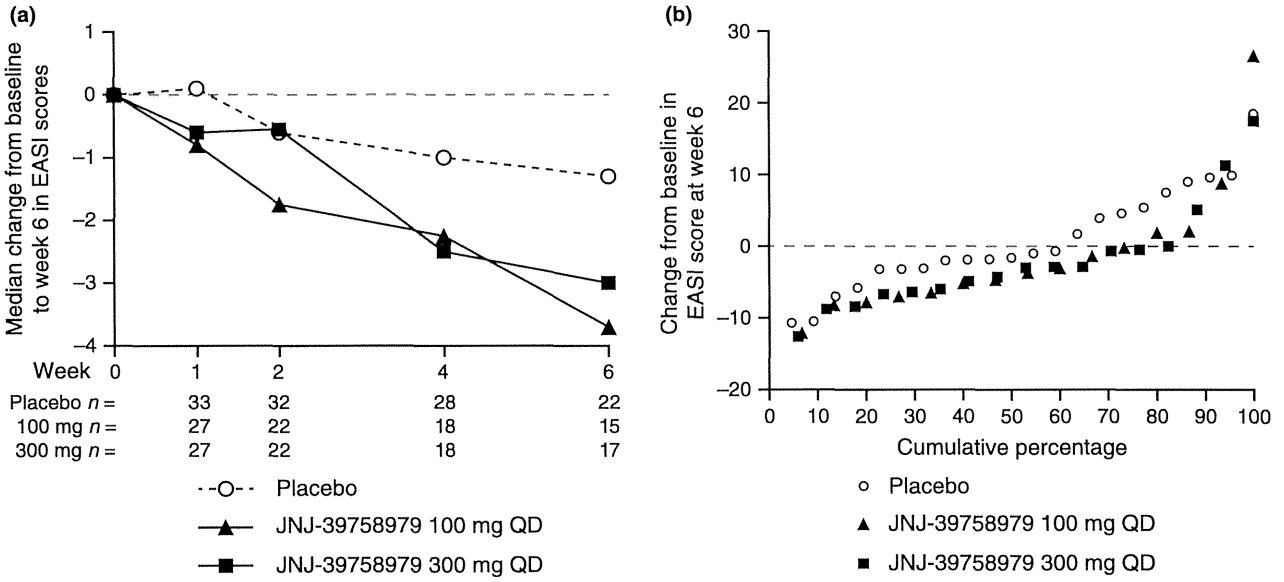


Figure 1. Changes from baseline to week 6 in EASI scores, shown as median changes (a) and cumulative percentage of patients (b) by treatment group. EASI, Eczema Area and Severity Index, QD, once daily.

trend toward nominal significance) greater reduction in patients receiving JNJ-39758979 100 mg (−1.01 and −0.86, respectively) and 300 mg (−1.71 and −1.64, respectively; both $P < 0.10$ vs placebo) than in patients receiving placebo (−0.66 and −0.65, respectively). These numerical improvements in the impact of pruritus on daily activity and sleep appeared to be dose dependent (Figs 2d; S1E,F).

A time course for the PNRS Night-time severity and duration indicated that there was no difference between the placebo and active arms during the first 3 weeks of the study (Fig. 3a, b). However, starting at approximately week 4, patients receiving either dose level of JNJ-39758979 showed greater numerical improvements compared with placebo, suggesting that the onset of antipruritic action of the compound took several weeks. In general, similar time courses were observed with the other pruritus assessments (Fig. S1).

Additional efficacy assessments. When patient-reported changes in pruritus intensity and duration from baseline to week 6 were assessed using the SGICP, treatment with JNJ-39758979 100 mg and 300 mg yielded nominally significant improvements relative to placebo for both change in pruritus severity (P vs placebo = 0.0352 and =0.0112, respectively) and change in amount of time itching (P vs placebo = 0.0005 and =0.0053, respectively; Fig. 4a,b).

Patients were permitted to use TCA 0.1% ointment for the treatment of AD flares (see Study design). More patients in the placebo group used TCA during the week-0–3 and week-3–6 treatment periods (eight [24.2%] and seven [21.2%] placebo patients, respectively) than in the JNJ-39758979 100-mg (five [18.5%] and two [7.4%]) patients, respectively) and 300-mg (three [11.1%] and two [7.4%] patients, respectively) groups.

Safety

The proportions of patients reporting AE were comparable across the JNJ-39758979 100-mg and 300-mg groups and the placebo group (40.7%, 51.9% and 54.5% respectively), with the most common reported events being AD, nasopharyngitis, gingivitis and abdominal discomfort (Table 3). Most of the AE were mild or moderate in intensity in all treatment groups, except the two serious AE reported below in the JNJ-39758979 300-mg group. These two serious cases of neutropenia led to the sponsor's decision to prematurely stop the trial. An additional three patients prematurely discontinued study agent, including two patients due to underlying AD (one each 100 mg and 300 mg) and one patient with asthma and pharyngitis (300 mg) (Table 3).

Two serious AE of neutropenia, both in the 300-mg group, were reported. The first patient, a 31-year-old woman, reported urticaria approximately 24–28 days following randomization and treatment. Subsequently, she was found to have worsening asthma and cervical/axillary lymphadenopathy with fever. At the patient's scheduled week-4 visit, she was withdrawn from the study because of worsening asthma. Laboratory test results showed a white blood cell (WBC) count of 1.2×10^9/L and an absolute neutrophil count (ANC) of 0.01×10^9/L. The patient was admitted to the hospital and underwent a bone marrow biopsy, which revealed a mildly hypoplastic marrow with decreased myeloid cells, but preserved erythroid and megakaryocytic cells. She received treatment with intravenous (i.v.) cefepime and recombinant granulocyte colony-stimulating factor. Following an uneventful 8-day hospital stay, the patient was discharged with a WBC count of 12.5×10^9/L and an ANC of 5.43×10^9/L. A second patient, a 48-year-old woman who received JNJ-39758979 300 mg, reported fever and chills

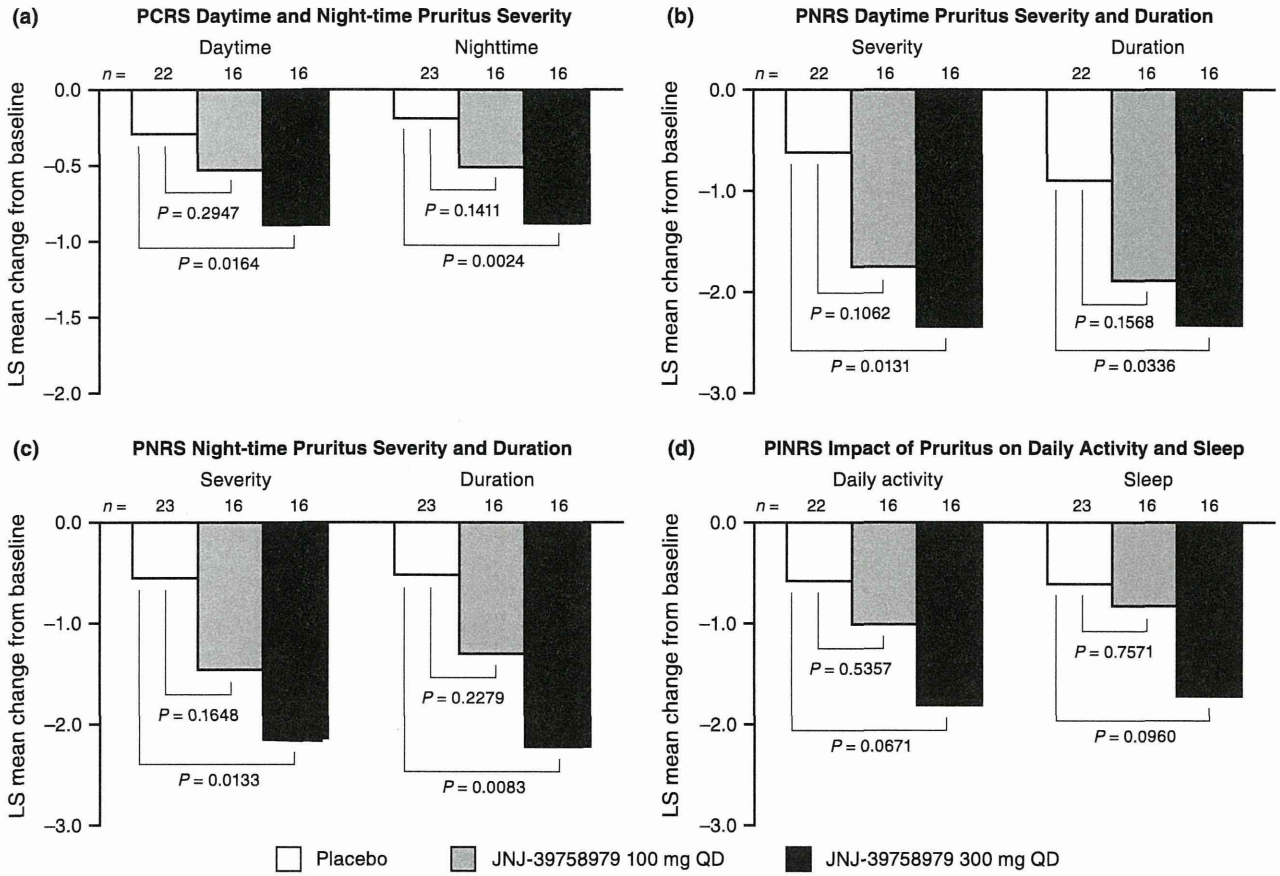
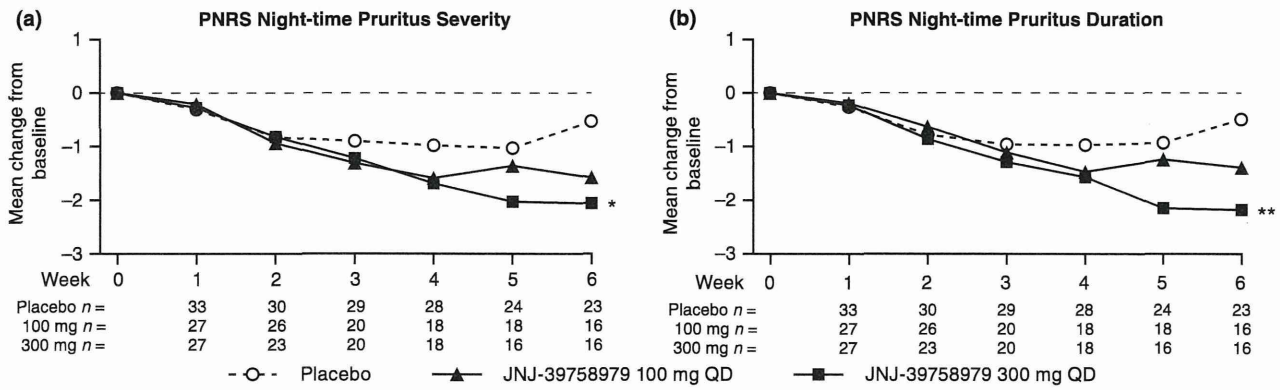


Figure 2. Least square (LS) mean changes from baseline to week 6 in PCRS Daytime and Night-time Pruritus Severity (a), PNRS Daytime Pruritus Severity and Duration (b), PNRS Night-time Pruritus Severity and Duration (c), PINRS Impact of Pruritus on Daily Activity and Sleep (d). PCRS, Pruritus Categorical Response Scale (weekly average, 0 = no itching, 1 = mild itching, 2 = moderate itching, 3 = severe itching, 4 = extremely severe itching); PINRS, Pruritus Interference Numeric Rating Scale (impact on activity/sleep, 0 = did not interfere to 10 = completely interfered); PNRS, Pruritus Numeric Rating Scale (weekly average, severity 0 = no itching to 10 = worst possible itching, duration 0 = none of the time to 10 = all of the time); QD, once daily.



*, ** p vs. placebo < 0.05 and 0.01, respectively, based on a baseline-adjusted analysis of covariance model of the least squares mean difference.

Figure 3. Mean changes from baseline over time to week 6 in PNRS Night-time Pruritus Severity (a) and PNRS Night-time Pruritus Duration (b). PNRS, Pruritus Numeric Rating Scale (weekly average, severity 0 = no itching to 10 = worst possible itching; duration 0 = none of the time to 10 = all of the time); QD, once daily.

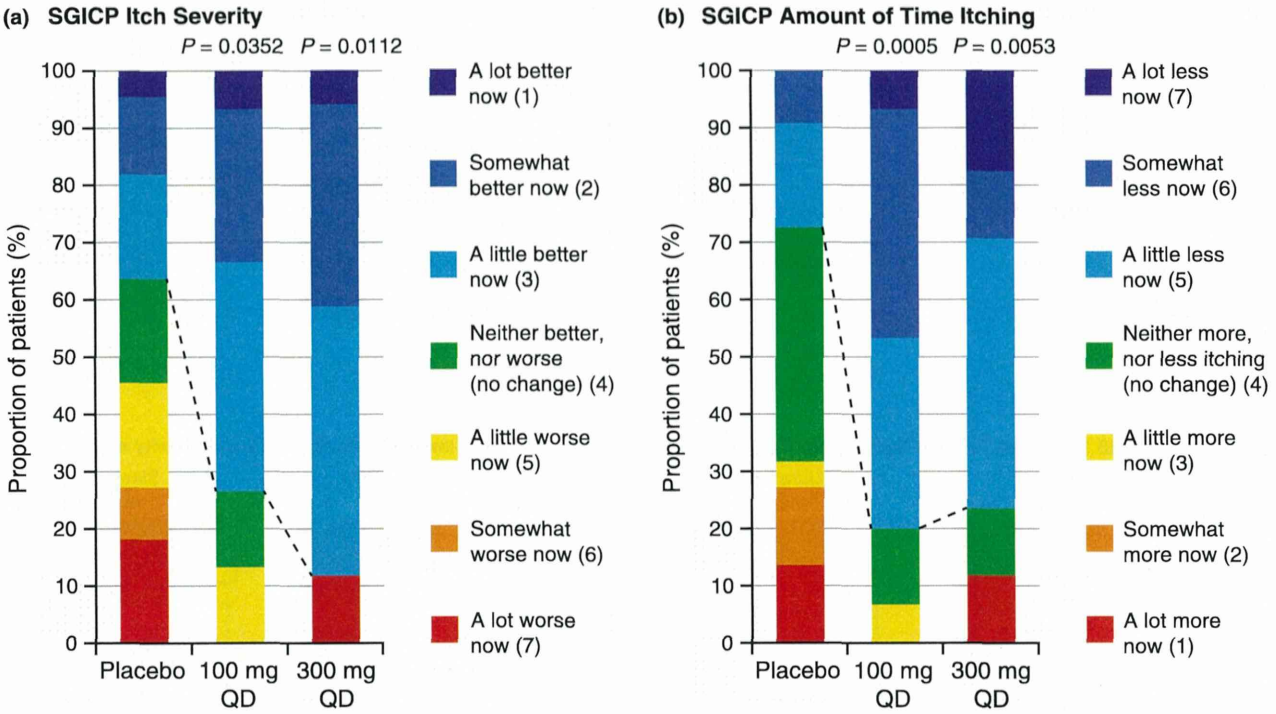


Figure 4. Change in itch severity from baseline to week 6 according to SGICP Pruritus/Itch Severity (a) and SGICP Amount of Time Itching (b). QD, once daily; SGICP, Subject's Global Impressions of Change in Pruritus (1 = a lot better now, 2 = somewhat better now, 3 = a little better now, 4 = no change, 5 = a little worse now, 6 = somewhat worse now, 7 = a lot worse now).

at her planned week-6 visit; laboratory test results included a WBC count of 0.83 × 10^9/L, an ANC of 0.01 × 10^9/L and mildly elevated liver function tests. The patient was admitted to the hospital and received i.v. cefepime. A bone marrow biopsy was performed, revealing a normoplastic marrow with decreased mature myeloid cells, but preserved erythroid, megakaryocytic and megaloblastic cells. The patient's hospital course was uneventful; her liver function test results returned to normal and neutrophil count recovered without treatment.

Aside from the two serious events of neutropenia, no markedly abnormal neutrophil counts were observed over time. Among JNJ-39758979-treated patients, 3.7% had more than one markedly abnormal increase in eosinophil counts and 5.6% had more than one markedly abnormal decrease in lymphocytes; no patient receiving placebo had either of these abnormalities (Table 3).

Pharmacokinetic analyses

Following administration of daily JNJ-39758979 doses for up to 6 weeks, the mean trough concentrations were generally consistent across sampling time points, ranging 80.4–106 ng/mL in plasma and 327–367 ng/mL in whole blood of patients receiving the 100-mg dose and ranging 159–187 ng/mL in plasma and 681–698 ng/mL in whole blood of patients receiving the 300-mg dose (with exclusion of two patients with agranulocytosis). In the two patients with agranulocytosis, both of whom received JNJ-39758979 300 mg, individual JNJ-39758979 trough concentrations ranged 86.6–194 ng/mL in plasma and 308–717 ng/mL in whole blood across sampling time points, which are within the range observed in other patients with the same duration of treatment (Table S1). Similarly, concentrations of several known JNJ-39758979 metabolites (Fig. S2) in the patients with agranulocytosis were all within the range observed in other patients over the course of the study (Table S1). A potential reactive known human metabolite, M11, was not detected in any patient in this study.

DISCUSSION

Atopic dermatitis is a common, chronic, inflammatory skin disease for which limited efficacy has been demonstrated by antihistamines targeting the H_1R.[1] The lack of efficacy of H_1R antihistamines has been used as evidence that histamine is not a major mediator of the disease. However, it may be that the effects of histamine are mediated by another receptor such as the H_4R because preclinical models of this receptor have been shown to mediate both pruritus and inflammation in dermal inflammation models.[26] In addition, a phase 1 study in healthy normal volunteers also demonstrated that JNJ-39758979 can inhibit the itch induced by i.d. injection of histamine.[21] Based on these data, we evaluated JNJ-39758979, a potent, selective, orally active H_4R antagonist, in this phase 2a trial of adult Japanese patients with moderate AD. While the trial was stopped early (see below) and did not meet the primary endpoint of change from baseline to week 6 in the EASI assessment, numerical improvements (i.e. decreases) in median

Table 3. Summary of key safety assessments among treated patients

	Placebo *n* (%)	JNJ-39758979 100 mg QD *n* (%)	JNJ-39758979 300 mg QD *n* (%)	Combined *n* (%)
No. of treated patients	33	27	27	54
No. (%) of patients with ≥1:				
Adverse events	18 (54.5)	11 (40.7)	14 (51.9)	25 (46.3)
Common adverse events (>5%)				
Atopic dermatitis	14 (42.4)	7 (25.9)	8 (29.6)	15 (27.8)
Nasopharyngitis	2 (6.1)	0	4 (14.8)	4 (7.4)
Gingivitis	0	0	2 (7.4)	2 (3.7)
Abdominal discomfort	2 (6.1)	1 (3.7)	0	1 (1.9)
Serious adverse events	0	0	2 (7.4)	2 (3.7)
Febrile neutropenia	0	0	1 (3.7)	1 (1.9)
Neutropenia	0	0	1 (3.7)	1 (1.9)
Adverse events leading to permanent stop of study medication	0	1 (3.7)	2 (7.4)	3 (5.6)
Atopic dermatitis	0	1 (3.7)	1 (3.7)	2 (3.7)
Asthma	0	0	1 (3.7)	1 (1.9)
Pharyngitis	0	0	1 (3.7)	1 (1.9)
No. (%) of patients with markedly abnormal post-baseline laboratory measurement				
Neutrophils (decrease)				
Any abnormal value	0	0	2 (7.4)	2 (3.7)
>1 abnormal value	0	0	0	0
Eosinophils (increase)				
Any abnormal value	3 (9.1)	1 (3.7)	3 (11.1)	4 (7.4)
>1 abnormal value	0	1 (3.7)	1 (3.7)	2 (3.7)
Lymphocytes (decrease)				
Any abnormal value	3 (9.1)	0	8 (29.6)	8 (14.8)
>1 abnormal value	0	0	3 (11.1)	3 (5.6)

QD, once daily.

changes from baseline in the EASI score were observed with JNJ-39758979 100 mg (−3.7) and 300 mg (−3.0) versus placebo (−1.3). In addition, nominally significant improvements in pruritus across the PRO of PCRS, PNRS and SGICP assessments were consistently observed, particularly with JNJ-39758979 300 mg. While a variety of assessment tools were employed to assess itching, changes from baseline to week 6 in all PRO measures except the two PINRS impact assessments were consistently greater than a commonly employed, distribution-based, "minimally important difference" threshold, namely, one-half of the baseline standard deviation,[27,28] and SGICP results demonstrated a similar trend. Thus, taken together, the efficacy data collected suggest that H_4R antagonism may be beneficial for AD, particularly in controlling pruritus.

Patients participating in this trial entered the study with AD generally considered moderate in intensity, involving approximately 30% of their BSA. The disease presentation in the trial cohort was thus generally consistent with that of the overall Japanese AD population.[6]

Changes in the EASI scores from baseline to week 6 (primary efficacy end-point) were not normally distributed and were thus subjected to non-parametric ranked ANCOVA analysis comparing the distribution of the changes in EASI scores. While median changes in the EASI scores were not significantly larger with JNJ-39758979 100 or 300 mg (−3.70 and −3.00, respectively) versus placebo (−1.30) at week 6, possibly due to the small sample size and/or insufficient length of evaluation that resulted from stopping the trial early, improvement with active therapy did exceed the clinically relevant change of 2.75 identified in a recent evaluation of the responsiveness and minimal clinically important differences of several outcome measures, including the EASI, used in AD.[29] The improvements in EASI scores were consistent with patterns observed for use of TCA 0.1% ointment for the treatment of AD flare, with more patients in the placebo than active treatments groups using TCA during both the week-0–3 and week-3–6 study periods. Evaluation of changes in EASI scores over time generally indicated that numerical improvement was evident, on average, by 4 weeks following the start of treatment.

Few published clinical trials specifically measure the change in pruritus score from baseline to the end of the study.[30] Given that pruritus can be the predominant symptom of AD, verifying itch reduction is an important part of establishing the efficacy of investigative agents for AD. As such, because few reliable patient-reporting tools were available to measure itching in the clinical trial setting, the trial sponsor developed several pruritus rating scales that patients could self-administer electronically twice daily on a handheld device throughout the trial. Using the

sponsor-developed pruritus PRO ratings, and as noted above, clinically meaningful improvement was assessed using a threshold of one-half of the baseline standard deviation.[27,28] In the case of the PNRS and PCRS PRO tools we employed, mean changes from baseline generally far exceeded one-half of the baseline standard deviation for both of the JNJ-39758979 doses, but not placebo, beginning at week 3 (Table 2). It is important to note that PRO tools are distinguished from measurement of physiological phenomena by the incorporation of patient values, judgments and preferences into the assessment.[27] As such, the meaning of a discrete change in PRO scores can be unclear. In such instances, distribution-based methods such as statistical significance, sample variability and measurement precision can be utilized. In addition to evaluating efficacy, data collected from these scales were intended to inform the selection of outcome measures for future trials.

The reduction in the EASI score may reflect anti-inflammatory properties of JNJ-39758979. Indeed, this is suggested by preclinical data, wherein H_4R antagonists have been shown to reduce inflammation in a number of preclinical dermatitis models.[15–19] In one model induced by the application of fluorescein isothiocyanate, dermal inflammation was reduced in H_4R-deficient mice or with treatment with H_4R antagonist.[15] In this model, the numbers of eosinophils and mast cells in the inflamed skin were reduced with compound treatment, as was the migration of dendritic cells. Increases in these cell types have been associated with AD.[2,3] In addition, the tissue levels of the cytokines IL-4, IL-6, IL-1β and tumor necrosis factor, as well as chemokine ligand (CCL)-2, CCL-3, CCL-5, granulocyte-macrophage colony-stimulating factor and IL-8, were reduced with H_4R antagonist treatment.[15] All of these cytokines and chemokines have been linked to the development of AD.[2,3] Some of these effects may be a result of a reduction in T-cell activation upon treatment with the H_4R antagonist, as the antigen-specific proliferation and cytokine production by T cells was shown to be impacted.[15] An impact on T-cell activation has been observed in mouse asthma and arthritis models and with human T cells *in vitro*.[31–33]

Along with a role in inflammation, the H_4R has also been implicated in directly mediating pruritic responses.[26] The scratching observed in acute and chronic dermatitis models can be blocked by H_4R antagonism.[15,17,19,34] The antipruritic properties of H_4R antagonists may be a result of directly inhibiting pruritic signals, because scratching induced by histamine in mice is reduced upon treatment with H_4R or in mice that lack the receptor.[35–37] The same is true in humans. In a clinical study, itch was induced in healthy volunteers by i.d. injection of histamine after subjects received a single oral dose of JNJ-39758979, cetirizine or placebo. JNJ-39758979 significantly reduced the pruritus score when compared with placebo and to a similar extent as seen with cetirizine.[21] These results, combined with the preclinical data, suggest that the H_4R can directly mediate neuronal pruritic signaling.

However, the inhibition of itch noted in the current AD study may not represent a direct inhibition of pruritic signals. If it did, then it may be expected that the antipruritic effects would be noted very soon after treatment initiation. However, the effects on itch, as measured by the various scales, were not observed until 3–4 weeks after the start of dosing. A more likely explanation is that the inhibition of the H_4R reduces inflammation or the production of another mediator of pruritus that then leads to a reduction in itch. One candidate for this would be the production of IL-31, because it has been shown that production of IL-31 from T cells can be mediated via the H_4R.[12] IL-31 is an important cytokine produced by activated Th2 cells and is thought to be involved in both inflammation and pruritus in AD.[38]

In our study, safety events, such as AE rates, were comparable between JNJ-39758979 and placebo, with the exception of two patients (both receiving JNJ-39758979 300 mg) with serious AE of neutropenia, leading to premature study discontinuation. No deaths were reported, and while markedly abnormal low lymphocyte levels were reported in three JNJ-39758979-treated patients (including the two patients with serious neutropenia), no other clinically relevant changes in laboratory values were observed.

Drug-induced agranulocytosis is an idiosyncratic adverse drug reaction that has been described for almost all classes of drugs.[39] The pathogenesis is a heterogeneous process that is not yet fully understood; however, immune and toxic mechanisms have been most commonly implicated in mediating this rare disorder. Reactive drug metabolites rather than the drug itself may cause agranulocytosis. Clozapine, a drug which induces agranulocytosis in almost 1% of treated patients, is an example of a drug that is metabolized to a reactive intermediate (nitrenium ion) through oxidation by hypochlorous acid.[40] This intermediate has been hypothesized to deplete the adenosine triphosphate supply of neutrophils leading to apoptosis. Genetic susceptibilities have also been suggested as conferring risk for agranulocytosis; several studies implicate single nucleotide polymorphisms in genes belonging to the human leukocyte antigens in the development of agranulocytosis.[41–43] Thus, the agranulocytosis observed in this trial is expected to be related to a possible unknown reactive intermediate(s) of JNJ-39758979 resulting in a toxic or immune-mediated effect on neutrophil homeostasis, which is consistent with the prevailing hypothesis for the mechanism by which most drugs cause agranulocytosis. There were generally no differences in the concentrations of measured JNJ-39758979 metabolites between the overall population and the two patients with agranulocytosis, but the causative reactive intermediates may be too transient to be detectable in the blood, or may only be present in the tissues. It is known that a potentially reactive metabolite of JNJ-39758979 (M11, Fig. S2) can be formed, but it was not detected in any patient in this study. For drugs (e.g. clozapine) that are associated with reactive intermediate- and/or metabolite-mediated idiopathic agranulocytosis, safety signals are often not observed in preclinical toxicity studies.[44] This also appears to be the case for JNJ-39758979, for which no evidence of effects on neutrophils or bone marrow was observed in toxicity studies in rat and monkey or in H_4R-deficient mice.[20] Furthermore, there is neither preclinical nor clinical evidence suggesting a causal relationship between H_4R antagonism and agranulocytosis.

In summary, although not conclusive due to early study termination, findings suggest H_4R-antagonism may be beneficial for AD, particularly in controlling pruritus. JNJ-39758979 appears to be associated with drug-induced agranulocytosis, most likely an off-target effect.

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CONFLICT OF INTEREST: Y. Murata, H. Kikuchi, M. Kato and T. Kato are employees of Janssen Pharmaceutical KK; K. Hisamichi was an employee of Janssen Pharmaceutical at the time of study conduct and the initial stages of manuscript preparation. M. Song, X. L. Xu, and R. Thurmond are employees of Janssen Research & Development, LLC. C.-F. Chiou, C. Guzzo and A. Greenspan are employees of Janssen Scientific Affairs, LLC. M. Ohtsuki and M. Furue have received support from Janssen Pharmaceutical KK for their advisory role in the conduct of this trial.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Mean changes from baseline to week 6 in Pruritus Categorical Response Scale (PCRS) Daytime Pruritus Severity (A), PCRS Night-time Pruritus Severity (B), Pruritus Numeric Rating Scales (PNRS) Daytime Pruritus Severity (C), PNRS Daytime Pruritus Duration (D), Pruritus Interference Numeric Rating Scale (PINRS) Impact of Pruritus on Daily Activity (E) and PINRS Impact of Pruritus on Sleep (F).

Figure S2. Structures of known JNJ-39758979 metabolites assessed in the study.

Table S1. Whole blood and plasma concentrations of JNJ-39758979 and known metabolites (M3, M5, M12 and M13)

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Pruritus of patients with atopic dermatitis in daily life and therapeutic effects experienced by them: Results of a web-based questionnaire survey

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Running head: Pruritus and treatment efficacy of atopic dermatitis: a web-based survey

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Conflict of interest: None declared

What's known/what's new statements: The status of pruritus in patients with atopic dermatitis has been examined in several web-based studies.

In this web-based survey with 1180 participants, we visualized pruritus-causing conditions/occasions in patient daily life and found that topical corticosteroids were overall effective in soothing pruritus and somewhat immediate potency of moisturizes among effective uses. Severer patients used more types of first-line treatments, but efficacy of each therapeutic agent became lower as the disease got severer.

Dear Editor,

It is important to recognize pruritic occasions/conditions and how their treatment is effective in soothing pruritus in patients with atopic dermatitis (AD) to facilitate patient communication and improve patient instructions in a typical clinical setting. For this purpose, we conducted a web-based questionnaire survey.

Patients and methods

A total of 1190 self-declared patients with AD visited our educational websites for AD (http://www.kyudai-derm.org/atopy/index.html or

http://www.kyudai-derm.org/kayumi/index.html) and agreed to answer a questionnaire from October 2007 to April 2008 (n=682) and from July 2011 to June 2012 (n=508), and 1180 completed it (99.2%). Subjects aged <10 were excluded from treatment efficacy analyses due to its limited reliability. The questionnaire was based on our previous study.[1]

More females (67.1%) participated in this study than males (32.9%), and their ages were distributed as follows: <10 years old, 4.1%; 10 to <20, 21.7%; 20s, 40.6%; 30s, 24.0%; 40s, 7.6%; and 50+ (2.1%) (Suppl. Table S1). They were also categorized into in employment (50.9%), students (34.2%), housewives (8.0%) and others (6.9%). The study was approved by the ethics committee of Kyushu University.

Results

Over the last seven days, 98.4% and 94.1% of answerers felt a daytime- and nocturnal pruritus, respectively (Suppl. Table S2). On itch-causing activities, the responses in decreasing order of frequency were perspiration, bathing/after bathing, wearing tingling-inducing clothes, lying under bedclothes, along with other rarer factors (Figure 1A). Clothing made of wool, artificial chemical fibers, fur or hemp causes pruritus often

(Figure 1B). Regarding mental factors, exacerbation of pruritus occurs when subjects were irritable/tense, unoccupied, angry, busy, nervous or sad, in decreasing order of frequency (Figure 1C).

Moisturizers were used most frequently (88.1%), followed by corticosteroids (78.4%), oral antihistamines (64.3%) and tacrolimus (38.1%), with significant difference among all these different frequencies (Figure 2A). Among the active users, the overall antipruritic efficacy of corticosteroids was highest (56.4%), followed by oral antihistamines (44.4%), tacrolimus (36.4%) and moisturizers (26.0%), with significant difference (Figure 2B). Among the treatment-responders, immediate potency ("effective within one hour") was highest with moisturizers (65.1%), followed by corticosteroids (39.8%), tacrolimus (29.4%) and oral antihistamines (18.4%), with statistical significance (Figure 2C). We further extended this study by classifying the subjects according to the degree of pruritus as itching scores correlate well with the disease severity of AD.[2,3] Subjects were categorized into mild (6.5% of the total), moderate (62.6%) and severe groups (30.8%), respectively by cross-tabulation of daytime and nocturnal itch scores (Suppl. Table S3). The use rates of therapeutic agents were higher as degree of pruritus gets severer (Suppl. table S4). In accordance with this, patients with severer pruritus used significantly more types of therapeutic agent than those with

milder severity (Suppl. FigureS1). Fundamentally, the efficacy of therapeutic agents were lower as degree of pruritus gets severer (Table 1).

Discussion

Abnormal sensation to acetylcholine,[4] *Malassezia* antigen in sweat[5] or hypersensitivity to warm sensation by artemin[6] may trigger perception-induced pruritus in AD. Infrequent responses of "sea bathing" or "pool swimming" as pruritogenic situations might also correspond with this hypothesis. Clothing made of cotton or silk may be recommended for AD patients. Patients experience more pruritus in association with negative feelings. In agreement with this, depression in AD[7] is known to exacerbate pruritus.

The low usage of a topical tacrolimus might be due to transient sensation of stimulation and/or the warning of a possible risk of skin malignancy by the United States Food and Drug Administration (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051760.htm) that might discourage both patients' usage and doctors' prescriptions.

Corticosteroids were the best in overall antipruritic efficacy, and good in immediate potency, compared to tacrolimus. However, tacrolimus have a unique antipruritic mechanism,[8] and may be worth administering even in those under topical corticosteroid treatment.[9] Lowest antipruritic efficacy by moisturizers may be due to lack of anti-inflammatory properties since severity of disease, rather than dry skin, correlates well with pruritus of AD.[10] As for the highest immediate potency by moisturizers, we speculate that a kind of placebo effect due to sense of security associated with moisturizer usage might explain in some patients who have had obscure concerns about the usage of corticosteroids.[11] The antipruritic efficacy of oral antihistamines that could come through either its sedative- or non-sedative effects was unexpectedly high, although multiple use of other agents might possibly confound the efficacy judgment.

Patients with severer diseases may desperately seek more effective antipruritic treatments as they used significantly more types of therapeutic agent than those with milder disease. More aggressive treatments such as ultraviolet radiation or oral cyclosporine, might thus be recommended for treating such patients. Alternatively,

patients with severer pruritus might be fallen into undertreatment condition, since many patients with AD have poor treatment adherence.[1 2]

The potential limitations and biases of this study were lack of physician-based disease diagnosis and severity assessment and influence of placebo effects. Patients without internet access and those who did not know our websites were excluded.

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Figure legends

Figure 1. Daily activities, clothing fabric and mental conditions that affect pruritus in AD patients

Patients were asked to select daily activities from a panel (multiple choices allowed), and a total of 5115 responses were obtained and arranged in order of frequency (A). Patients were also asked to select types of clothing fabric that caused pruritus from a

panel (multiple choices allowed), and a total of 2355 responses were obtained and arranged in order of frequency (B). In addition, patients were asked to select mental conditions that worsened their pruritus from a panel (multiple choices allowed), and a total of 2551 responses were obtained and arranged in order of frequency (C).

Figure 2. Antipruritic efficacy and immediate potency of treatments for AD

The frequency of usage of each medication was examined by the number of users of each medication divided by the total number of patients (A). The antipruritic efficacy was examined by the number of "effective" answers divided by the number of users of each medication (B). The immediate potency was examined by the number of "effective within one hour" answers divided by the number of "effective" answers for each medication (C). Fisher's exact test was used for statistical analysis and a p-value of <0.05 was considered to be statistically significant.

Suppl. Figure S1. The numbers of types of therapeutic agent that patients use

The numbers of types of therapeutic agent that patients used according to the severity of pruritus. Test of independence with Bonferroni correction were used $*p<0.05$, $**p<0.01$