

Efficacy of increased dose of rupatadine up to 20 mg on itching in Japanese patients due to chronic spontaneous urticaria, dermatitis, or pruritus: A post hoc analysis of phase III clinical trial

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Abstract

Objectives: The effect of rupatadine, a novel H1 antihistamine with platelet-activating factor antagonist activity, had been demonstrated for itching in Japanese patients with chronic spontaneous urticaria, dermatitis, or pruritus in a 12-month, open-label clinical trial (JapicCTI-152787). However, patients could have received an updose at various timings due to distinct reasons in the study; timing of updose was not evaluated. This study aimed to elucidate the relationship between performance of rupatadine and timing of updose.

Methods: For 206 enrolled patients was evaluated the total pruritus score (TPS) to Week 2 with 10 mg rupatadine. From Week 3 to Week 52, rupatadine was updosed to 20 mg accordingly. Subpopulation was categorized by absence/presence of updosing and timing of updose (Week 3 or $\geq$ Week 5).

Results: Reduction of TPS from baseline to Week 2 in patients updosed at Week 3 was significantly lower than those given an updose at $\geq$ Week 5 and fixed dose. However, significant improvement in the change in mean TPS from 1 week pre-updose to the second week post-updose was achieved regardless of updose timing, scoring -0.903 for Week 3 and -0.983 for $\geq$ Week 5 ($P < 0.001$).

Conclusions: The results inferred the inclusivity of patients who either updosed during the earlier phase due to lack of efficacy, or later due to aggravation of symptoms. The results of this subgroup analysis produced evidence of appropriateness for using 10 mg rupatadine as the starting dose, and evaluating the necessity of updose to 20 mg during the first 2 weeks for nonresponsive patients.

KEYWORDS

antihistamine up dosing, chronic spontaneous urticaria, dermatitis, pruritus, Rupatadine

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1 | INTRODUCTION

Allergic skin disorders are mostly accompanied by pruritus, causing aggravation of dermal and emotional conditions in patients, appreciably reducing the QoL.¹ With the advancements in the studies on the pathophysiology of skin allergies, there are high demands for the translation of knowledge to future studies and improved treatment algorithms.² In the EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria, up dosing of second-generation antihistamines up to fourfold is recommended.³ In patients with pruritus, antihistamines are recommended in addition to appropriate skin care and other protective measures in Japan.⁴ However, not many studies have focused on the efficacy of updose and its association with baseline conditions and timing of response to the drug prior to updose.^{5,6}

Rupatadine is a second-generation antihistamine with minimal anticholinergic and sedative side effects due to its high selective antagonism.⁷ Rupatadine mechanism of action is characterized by its unique molecular structure: the lutidinyl group, which antagonizes platelet-activating factor (PAF) receptors, and the piperidinyl group, which antagonizes histamine H1 receptor. By its dual pharmacological activity, rupatadine effectively and safely alleviates pruritic skin diseases. Efficacious evidence of 10 and 20 mg rupatadine, as well as favorable safety profile in patients with cutaneous disorders, has been confirmed in several studies.^{8–10}

In our original 12-month long-term study with the starting dose of 10 mg rupatadine (updose to 20 mg after Week 2 was permitted for patients who fell under the criteria for dose increase), the results demonstrated that rupatadine significantly alleviates itch in adult and adolescent patients with eczema, dermatitis, pruritus, and chronic spontaneous urticaria in short- and long-term basis.¹¹ Statistically significant difference in total pruritus score (TPS) was achieved between baseline and Week 2 with 10 mg rupatadine. Efficacy beyond Week 2 in overall study population (inclusive of those administered with fixed dose of 10 mg and up dosed to 20 mg after Week 2) also remained throughout the study. Similar trend was achieved for each subgroup categorized by disease type. As in the above results, the former study analysis was conducted on the entire population without the consideration of differences in updose timing, and those between patients who experienced aggravation of symptoms and patients whose efficacy was not detected within the 2-week treatment period. The population also included patients whose dose was fixed at 10 mg for the entire study. The lack of segregation of such populations could have overlooked the association between the performance of rupatadine and characteristics of a potential effect factor. Such subgroup analysis could elucidate the effect of rupatadine up dosing in patients with disparate conditions. Here, we report the results on the additional subgroup analysis of TPS data from the former clinical trial.

2 | METHODS

2.1 | Study design

Details on the design, methodology, and results for this study were published in other article.¹¹ The original study was a 12-month multicenter open-label phase III clinical trial conducted to investigate the long-term efficacy and safety of rupatadine 10 and 20 mg administered once daily for the management of itch associated with allergic cutaneous diseases, and plasma concentration in Japanese adults and adolescents with chronic spontaneous urticaria, dermatitis, or pruritus (Japan Pharmaceutical Information Center Clinical Trial Information [JapicCTI-152787]). Patients (i) were aged 12 to <65 years, (ii) had eczema, dermatitis, pruritus, or chronic spontaneous urticaria, (iii) had TPS (the sum of daytime and nighttime pruritus scores determined using the grading criteria shown in Table S1) not <2 for the last 3 days before the start of treatment, and (iv) had the ability to complete the patient diary. Ten milligram rupatadine was administered for 2 weeks and then permitted to updose to 20 mg once daily at Week 3 or later, if (i) the TPS averaged over the last 7 days before the study visit was >3 and (ii) the TPS was >4 on at least 3 of the 7 days (criteria for updose). Dose reduction from 20 to 10 mg was left to the discretion of the investigators. Patients who were enrolled in the full analysis set (FAS) were those who were treated with the study drug at least once and those who were evaluated for at least 1 efficacy variable after the treatment.

This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, reviewed, and approved by the designated institutional review boards for each study site.

3 | SUBGROUP ANALYSIS ON CHANGE IN TPS

The primary efficacy endpoint of this clinical trial was the change from baseline in the TPS to the 2 weeks of treatment. The effect of updose on TPS was assessed using the mean TPS value at the second week after updose when the blood concentration of rupatadine reached a steady state. For the secondary efficacy endpoint, TPS changes from baseline up to Week 52 were evaluated. In the current study, analyses focused on the comparison of subgroups classified by with or without up dosing; patients were divided into two groups who were categorized as up dosed (updose group, hereafter) and not up dosed (fixed-dose group, hereafter). Patients in the updose group were further divided into two groups by timing of the up dosing: (i) patients up dosed to 20 mg rupatadine at Week 3 (Week 3 group, hereafter) and (ii) patients up dosed to 20 mg rupatadine at Week 5 or later ($\geq$ Week 5 group, hereafter). No patients were up dosed at Week 4. In addition to the above, subgroup analysis was conducted with the aforementioned groups stratified by disease type (eczema/dermatitis, pruritus, and chronic spontaneous urticaria).

3.1 | Statistical analysis

Mean baseline TPS and change in mean TPS were described with 95% CI for each group. A two-tailed paired *t* test at a significance level of 0.05 was used for the analysis of significance of intragroup change in mean TPS. The intergroup comparison of TPS values and change in mean TPS between two subgroups of updose timing was performed using a two-tailed Student's *t* test at a significance level of 0.05, and comparison between three subgroups of updose timing was performed using the two-tailed Student's *t* test at a Bonferroni-adjusted significance level of 0.0167. Above analyses were repeated with the same methods in the subgroup analysis stratified by disease type.

4 | RESULTS

4.1 | Patients

Among the rupatadine-treated, 206 patients, consisting of 132 patients with eczema or dermatitis, 58 with pruritus, and 16 with chronic spontaneous urticaria, were included in the FAS. The demographic and baseline data of the FAS are provided in Table S2. Rupatadine was up-dosed from 10 to 20 mg in 130 patients (63.1%), including 13 (6.3%) whose dose was later reduced to 10 mg. There were 172 patients who received 12 or more weeks of study treatment. Of these patients, 129 patients remained in the study up to Week 52. The mean (SD) total exposure to rupatadine was 4188.6 (2367.6) mg. The mean (SD) drug adherence rate (defined as the percentage of days in which medication was taken as indicated) was 96.45% (6.92%). Due to the low sample size of patients, chronic spontaneous urticaria was not included in the subgroup analysis stratified by disease type.

5 | DISCREPANCIES IN THE BASELINE SCORES

Analysis on the baseline scores showed that the mean [95% CI] baseline TPS values were 4.761 [4.581, 4.940] in Week 3 group and 4.791 [4.524, 5.058] in $\geq$ Week 5 group (Table 1). Comparison with fixed-dose group (4.171 [3.923, 4.419]) by paired intergroup analysis yielded significantly higher scores at baseline for both Week 3 group and $\geq$ Week 5 group ($P < 0.001$). Conversely, the baseline scores were similar in Week 3 group and $\geq$ Week 5 group ($P = 0.846$).

6 | SUBGROUP ANALYSIS ON TPS OVER TIME BY TIMING OF UPDOSE

The effect of 10 mg rupatadine up to Week 2 was analyzed between fixed-dose group, Week 3 group, and $\geq$ Week 5 group (Table 2), respectively. The change in mean TPS [95% CI] from baseline showed statistically significant reduction in the fixed-dose group at Day 3 (−1.237 [−1.600, −0.874]), Week 1 (−1.455 [−1.810, −1.101]), and Week 2 (−1.920 [−2.287, −1.552]) compared to baseline. Similar trend in efficacy of 10 mg rupatadine compared to that of the fixed-dose group was observed for $\geq$ Week 5 group; the change in mean TPS [95% CI] from baseline at Day 3 (−1.023 [−1.385, −0.660]), Week 1 (−1.198 [−1.570, −0.825]), and Week 2 (−1.525 [−1.917, −1.132]) was statistically significant. The changes in mean TPS [95% CI] from baseline for Week 3 group at Day 3 (−0.376 [−0.600, −0.152]), Week 1 (−0.338 [−0.536, −0.140]), and Week 2 (−0.290 [−0.473, −0.106]) were also statistically significant, but were smaller compared with those for the fixed-dose group ($P < 0.001$ for all time points) and for $\geq$ Week 5 group ($P < 0.001$ for all time points). This is evident in Figure 1A), showing the change in TPS over time up to Week 2.

Nevertheless, the changes in mean TPS [95% CI] from 1 week prior to updose to the second week post-updose in both Week 3 group (−0.903 [−1.168, −0.638]) and $\geq$ Week 5 group (−0.983 [−1.271, −0.695]) were statistically significant ($P < 0.001$; Table S3) and the magnitudes of score reduction in the two groups were similar when the effect on TPS was compared within the same time window around the updose timing (Figure 1B).

7 | SUBGROUP ANALYSIS ON TPS OVER TIME BY DISEASE TYPE

Changes in TPS from baseline in the updose group and fixed-dose group in each disease type at Week 2 are as shown in Table S4. The change over time in the mean TPS [95% CI] was significantly smaller in the updose group (−0.850 [−1.078, −0.622]) compared with the fixed-dose group (−1.920 [−2.287, −1.552]; $P < 0.001$). Similar trend was observed when both groups were categorized by patients with eczema/dermatitis (−0.746 [−0.977, −0.516] vs −1.742 [−2.117, −1.366]) and patients with pruritus (−0.794 [−1.320, −0.267] vs −1.697 [−2.434, −0.961]); $P < 0.001$ and $P = 0.040$, respectively).

TABLE 1 Comparison of the baseline mean total pruritus score for Week 3 group, $\geq$ Week 5 group, and fixed-dose group

	N	Mean	SD	Min	Median	Max	95% CI for the Mean	P-value ^a		
								a	b	c
Week 3 group	71	4.761	0.758	3.00	4.667	6.33	4.581, 4.940	$P < 0.001$	$P < 0.001$	$P = 0.846$
$\geq$ Week 5 group	59	4.791	1.024	2.00	4.667	8.00	4.524, 5.058			
Fixed-dose group	76	4.171	1.085	2.00	4.000	8.00	3.923, 4.419			

a: Week 3 group vs fixed-dose group, b: $\geq$ Week 5 group vs fixed-dose group, c: Week 3 group vs $\geq$ Week 5 group.

^aA two-tailed Student's *t* test with a Bonferroni-adjusted significance level of 0.0167 was used for intergroup analyses.

TABLE 2 Mean and change in total pruritus score from baseline for Week 3 group, ≥Week 5 group, and fixed-dose group for each time point up to Week 2

Timing	N	Mean	SD	Min	Median	Max	95% CI for the Mean	P-value ^a	P-value [†]		
									a	b	c
Baseline											
Week 3 group	71	4.761	0.758	3.00	4.667	6.33	4.581, 4.940	-	P < 0.001	P < 0.001	P = 0.846
≥Week 5 group	59	4.791	1.024	2.00	4.667	8.00	4.524, 5.058	-			
Fixed-dose group	76	4.171	1.085	2.00	4.000	8.00	3.923, 4.419	-			
Day 3											
Week 3 group	71	4.385	0.966	0.33	4.333	7.00	4.156, 4.614	-	P < 0.001	P < 0.001	P = 0.001
≥Week 5 group	59	3.768	1.197	0.00	4.000	5.67	3.456, 4.080	-			
Fixed-dose group	76	2.934	1.379	0.00	3.000	6.33	2.619, 3.249	-			
Week 1											
Week 3 group	71	4.423	0.847	1.86	4.429	7.00	4.222, 4.623	-	P < 0.001	P < 0.001	P < 0.001
≥Week 5 group	59	3.593	1.209	0.57	4.000	5.57	3.278, 3.908	-			
Fixed-dose group	76	2.716	1.326	0.00	2.714	5.86	2.413, 3.019	-			
Week 2											
Week 3 group	71	4.471	0.756	3.29	4.286	6.86	4.292, 4.650	-	P < 0.001	P < 0.001	P < 0.001
≥Week 5 group	59	3.266	1.227	0.00	3.143	5.29	2.947, 3.586	-			
Fixed-dose group	75	2.262	1.338	0.00	2.429	4.86	1.955, 2.570	-			
Change in TPS from baseline at Day 3											
Week 3 group	71	-0.376	0.946	-3.00	0.000	1.67	-0.600, -0.152	P = 0.001	P < 0.001	P = 0.413	P = 0.002
≥Week 5 group	59	-1.023	1.391	-6.00	-0.667	1.00	-1.385, -0.660	P < 0.001			
Fixed-dose group	76	-1.237	1.588	-7.00	-1.000	1.33	-1.600, -0.874	P < 0.001			
Change in TPS from baseline at Week 1											
Week 3 group	71	-0.338	0.836	-2.52	-0.190	1.71	-0.536, -0.140	P = 0.001	P < 0.001	P = 0.324	P < 0.001
≥Week 5 group	59	-1.198	1.430	-5.57	-0.714	0.67	-1.570, -0.825	P < 0.001			
Fixed-dose group	76	-1.455	1.552	-7.00	-1.095	0.86	-1.810, -1.101	P < 0.001			
Change in TPS from baseline at Week 2											
Week 3 group	71	-0.290	0.776	-2.43	-0.286	1.86	-0.473, -0.106	P = 0.002	P < 0.001	P = 0.148	P < 0.001
≥Week 5 group	59	-1.525	1.507	-6.14	-1.333	0.81	-1.917, -1.132	P < 0.001			
Fixed-dose group	75	-1.920	1.598	-6.57	-1.762	1.10	-2.287, -1.552	P < 0.001			

a: Week 3 group vs fixed-dose group, b: ≥Week 5 group vs fixed-dose group, and c: Week 3 group vs ≥Week 5 group.
 TPS, total pruritus score.
^aA two-tailed paired t test with a significance level of 0.05 was used for the analysis on the significance of mean change in total pruritus score from baseline.
[†]A two-tailed Student's t test with a Bonferroni-adjusted significance level of 0.0167 was used for intergroup analyses.

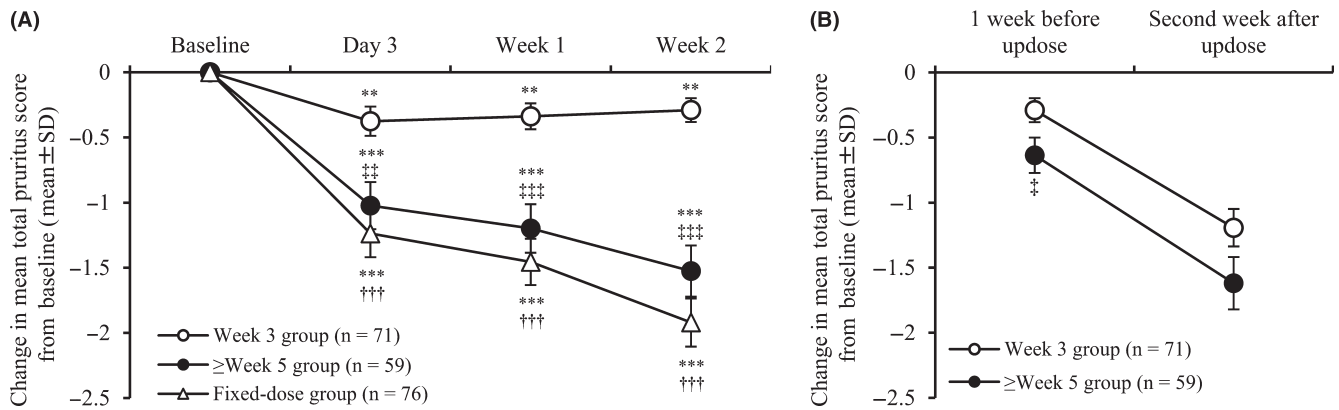


FIGURE 1 A, Change in mean total pruritus score from baseline up to Week 2 in the updose group and fixed-dose group in all subjects. B, Change in mean total pruritus score from 1 week prior to updose to 2 week after updose. ††† P < 0.001 for Week 3 group vs fixed-dose group (Student's t test). † P < 0.05, †† P < 0.01, and ††† P < 0.001 for Week 3 group vs $\geq$ Week 5 group (Student's t test). ** P < 0.01 and *** P < 0.001 for comparison with baseline value (paired t test)

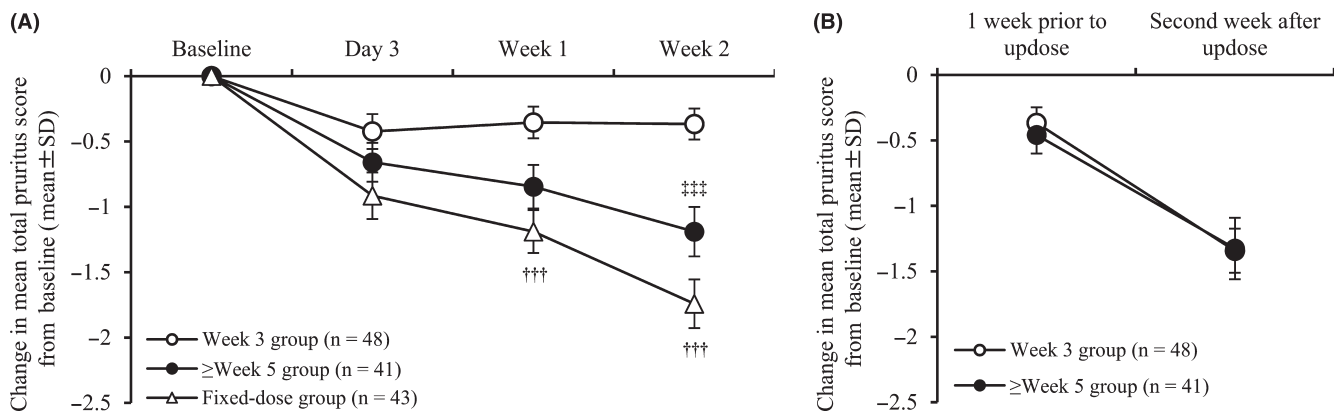


FIGURE 2 A, Change in mean total pruritus score from baseline up to Week 2 in the updose group and fixed-dose group in patients with eczema/dermatitis. B, Change in mean total pruritus score from 1 week prior to updose to 2 week after updose in patients with eczema/dermatitis. ††† P < 0.001 for Week 3 group vs fixed-dose group (Student's t test). ††† P < 0.001 for Week 3 group vs $\geq$ Week 5 group (Student's t test)

Similar trend as the above results was observed for the analysis using disease subgroups with categorized updose timing (Week 3 group and $\geq$ Week 5 group), as seen in the patients with eczema/dermatitis and pruritus (Figures 2 and 3).

8 | DISCUSSION

Oral antihistamines such as rupatadine, a dual-acting selective oral H1 antagonist, are used for alleviating pruritus associated with cutaneous diseases safely and promptly.¹² However, studies on the efficacy of antihistamine up dosing for pruritus-targeting patients other than urticaria are scarce.^{5,6} The current additional subgroup analysis focused on the effect of rupatadine on patients with heterogeneous characteristics such as varied baseline cutaneous conditions and updose timing to 20 mg for the purpose of interpreting the possible influence of the said factors on the improvement of symptoms for patients suffering from itch.

In the current subgroup analysis, the intergroup difference in the baseline TPS values was evaluated in order to interpret the potential

impact on the performance of 10 mg rupatadine up to Week 2. The results show that the baseline value of the fixed-dose group is significantly lower, regardless of disease type, compared to Week 3 group and $\geq$ Week 5 group which scored similar baseline values. Concurrently, the comparison of change in mean TPS of the three groups showed that fixed-dose group and $\geq$ Week 5 group, with statistically dissimilar baseline values, had similar patterns in the rate of TPS reduction up to Week 2. This finding implicated that baseline values of TPS do not necessarily indicate whether treatment with 10 mg rupatadine will be effective, evident from the lack of consistency in the relationship between reduction in TPS and the level of baseline TPS. Alternatively, the similarity of the change in TPS from baseline after up dosing in Week 3 group and $\geq$ Week 5 group (P = 0.846) suggests the efficacy of rupatadine up dosing to 20 mg, regardless of timing, and baseline TPS. On the other hand, the result that the lower CI limits of the mean baseline TPS values for the two up dosed groups (4.581, 4.524) were higher than the upper CI limits of fixed-dose group (4.419) suggests that 20 mg may not be required if the baseline score is <4.5 (Table 1). This finding suggests the potential use of the baseline TPS as a pretreatment predictive marker

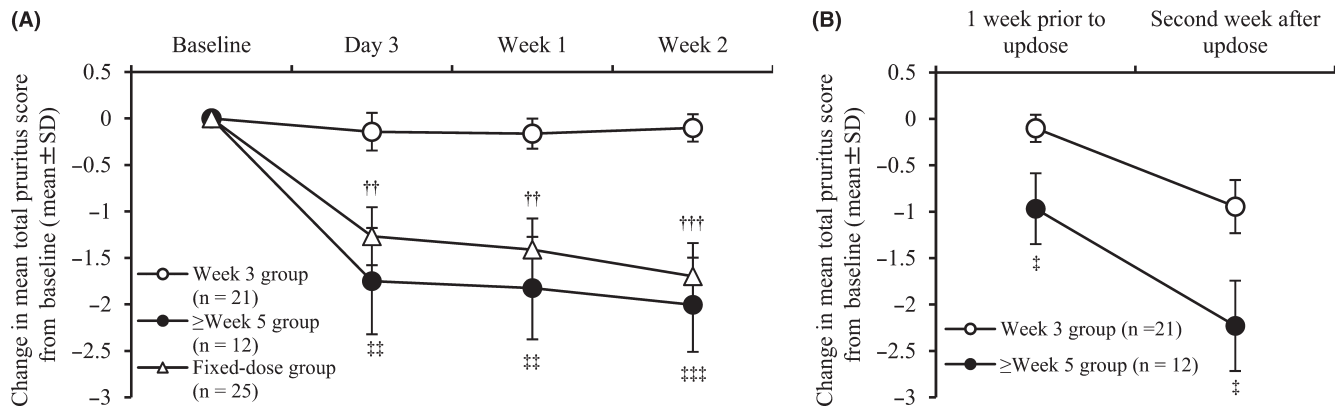


FIGURE 3 A, Change in mean total pruritus score from baseline up to Week 2 in the updose group and fixed-dose group in patients with pruritus. B, Change in mean total pruritus score from 1 week prior to updose to 2 week after updose in patients with pruritus. $^{††}P < 0.01$ and $^{†††}P < 0.001$ for Week 3 group vs fixed-dose group (Student's *t* test). $^{‡}P < 0.05$, $^{‡‡}P < 0.01$, and $^{‡‡‡}P < 0.001$ for Week 3 group vs $\geq$ Week 5 group (Student's *t* test)

for the necessity of updose to 20 mg. Further investigation on this matter is worth conducting.

In a subgroup analysis with population stratified by disease type, similar pattern was observed in the comparison of fixed-dose group, Week 3 group, and $\geq$ Week 5 group.

A recent open study on the effect of rupatadine for chronic spontaneous urticarial symptoms provided some evidence on higher efficacy of 20 mg rupatadine compared to the standard 10 mg dose.¹¹ In the current study, the group of patients updosed to 20 mg rupatadine was categorized into two groups to investigate potential difference in the efficacy by timing for updose. Results showed that, regardless of the efficacy observed during the 10-mg dose period and timing of updose, updose to 20 mg improved TPS in a similar manner and magnitude (reduction of approximately 0.9 in both groups). Such evidence could imply that the results of the subgroup analysis further revealed the efficacy in using 20 mg rupatadine in patients exhibiting insufficient response to 10 mg rupatadine or experiencing aggravation of symptoms.

Evidence from previous studies suggests that common time to change in symptoms after the start of treatment with rupatadine is less than 1 week,¹² and similar tendency is observed as well in other H1 antagonists.¹³ In the present analysis, approximately 1 point improvement of mean TPS in the patients who experienced improvement with 10 mg rupatadine was observed between 3 days and 1 week of treatment, which is in line with the past studies. Hence, a 2-week period of treatment with the standard recommended dose of 10 mg, and an observational period of Day 3 through Week 2, is a reasonable time frame for deciding whether updose should take place, allowing enough time for adequate evaluation on the performance.

There were potential limitations of this analysis. The categorization of the updose group patients into Week 3 group and $\geq$ Week 5 group were specified by the premise that patients updosed at Week 3 were done so due to a lack of efficacy, and patients updosed at Week 5 due to the aggravation of symptoms, and this could be considered to result in a potential bias. The statistical methods used in our analysis did not include adjustments by demographic factors. The current study also had limited sample size of patients from each

disease type categories and could have had an impact on statistical power; the method used for analysis in the current study, as well as other methods, could be debatable depending on the initial condition of the population.^{14,15} Furthermore, the incorporation of the Bonferroni correction for intergroup analysis between the three groups could have increased the possibility of type II error despite the reduction of type I error.¹⁶ Lastly, this study was a post hoc study analysis¹⁷; the patients were not recruited based on, and designed upon this analysis. Similarly, this study was an open-labeled study, which could have caused bias in the results.

The current analysis illustrated similarity in the pattern of improvement for fixed-dose group and $\geq$ Week 5 group, reflected by the similarity in the change in TPS from baseline with 10 mg rupatadine at Day 3, Week 1, and Week 2 (no significant difference between the two groups). On the other hand, Week 3 group showed limited improvement, with significantly lower change in TPS compared with the other groups. In conclusion, the results of this subgroup analysis produced evidence that it is appropriate in clinical practice for medical institutions to set 10 mg rupatadine as the starting dose, as prescribed in the package insert, and evaluate whether an updose is necessary through Week 1 to Week 2.

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CONFLICT OF INTERESTS

Dr Michihiro Hide is a member of the Journal of Cutaneous Immunology and Allergy Editorial Board. Management of the peer review process, and all editorial decision-making, for this article was undertaken by Editor in Chief, Yoshiki Tokura who managed this article.

[Correction added on 6 September 2019, after first online publication: Conflict of Interest statement has been updated]

APPROVAL OF THE RESEARCH PROTOCOL

The research protocol was approved by Pharmaceuticals and Medical Devices Agency (PMDA).

INFORMED CONSENT (ESPECIALLY FOR CASE)

Written informed consent from all study subjects was obtained.

REGISTRY AND THE REGISTRATION NO

JapicCTI-152787.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supplementary Table 1. Daytime and nighttime pruritus rating criteria

Score	Pruritus	
	Daytime	Nighttime
0	No or just slight itch	No or just slight itch
1	Occasionally feels itch but not strong enough to start scratching	Feels a slight itch, but able to fall asleep without scratching
2	Occasional itch and scratching	Some itch, but disappears by scratching. No waking up due to itch
3	Considerable itch and scratch in the public	Sometimes wakes up owing to itch
4	Cannot relax because of constant itching	Cannot sleep because of itch

Supplementary Table 2. Demographic and baseline characteristics of study patients

Variable	Statistics/Subgroups	N = 206
Sex	Male	82 (39.8%)
	Female	124 (60.2%)
Age, years	No. of patients	206
	Mean (SD)	35.7 (13.9)
	Median	35.0
	Minimum–Maximum	12–64
Age distribution 1, years	12–17	23 (11.2%)
	18–64	183 (88.8%)
Age distribution 2, years	12–19	33 (16.0%)
	20–29	43 (20.9%)
	30–39	43 (20.9%)
	40–49	47 (22.8%)
	50–59	32 (15.5%)
	60–64	8 (3.9%)
Height, cm	No. of patients	206
	Mean (SD)	162.60 (7.89)
	Median	163.00
	Minimum–Maximum	141.2–185.6
Weight, kg	No. of patients	206
	Mean (SD)	58.39 (11.41)
	Median	55.70
	Minimum–Maximum	33.0–109.7
Weight distribution, kg	< 50	46 (22.3%)
	50 to < 60	79 (38.3%)
	60 to < 70	52 (25.2%)
	≥ 70	29 (14.1%)
Complications	No	53 (25.7%)
	Yes	153 (74.3%)
Previous therapy, pharmacological	No	66 (32.0%)
	Yes	140 (68.0%)
Previous therapy, nonpharmacological	No	191 (92.7%)
	Yes	15 (7.3%)
Duration of disease, months	No. of patients	206
	Mean (SD)	101.8 (120.2)
	Median	51.5
	Minimum–Maximum	0–602
Baseline total pruritus score	< 5	121 (58.7%)
	≥ 5	85 (41.3%)
Type of pruritic skin disease	Eczema or dermatitis	132 (64.1%)
	Acute eczema	3 (1.5%)
	Chronic eczema	29 (14.1%)
	Contact dermatitis	12 (5.8%)
	Atopic dermatitis	66 (32.0%)
	Nummular eczema	3 (1.5%)
	Seborrheic dermatitis	3 (1.5%)
	Asteatotic eczema	10 (4.9%)
	Other†	6 (2.9%)
	Skin pruritus	58 (28.2%)
	Generalized	44 (21.4%)
	Localized	14 (6.8%)

	Chronic spontaneous urticaria	16 (7.8%)
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†Other skin diseases include rosacea-like dermatitis (n = 3), dyshidrotic eczema (n = 1), nodular prurigo (n = 1), and pleomorphic chronic prurigo (n = 1).

Supplementary Table 3. Mean Total Pruritus Score Before and After Updose in Week 3 group and ≥Week 5 group

Timing		N	Mean	SD	Min	Median	Max	95%CI for the Mean	P-value†	P-value††
1 week prior to updose	Week 3 group	71	4.471	0.756	3.29	4.286	6.86	(4.292,4.650)	-	p=0.013
	≥Week 5 group	59	4.155	0.659	3.14	4.143	6.86	(3.983,4.327)	-	
Second week after updose	Week 3 group	71	3.567	1.306	0.29	3.857	5.57	(3.258,3.876)	-	p=0.084
	≥Week 5 group	59	3.172	1.269	0.00	3.429	5.57	(2.841,3.503)	-	
Change in TPS from baseline to 1 week prior to updose	Week 3 group	71	-0.290	0.776	-2.43	-0.286	1.86	(-0.473,-0.106)	p=0.002	p=0.032
	≥Week 5 group	59	-0.636	1.042	-3.29	-0.667	1.71	(-0.908,-0.364)	p<0.001	
Change in TPS from baseline to second week after updose	Week 3 group	71	-1.193	1.217	-4.43	-1.000	1.57	(-1.481,-0.905)	p<0.001	p=0.081
	≥Week 5 group	59	-1.619	1.546	-5.67	-1.524	1.43	(-2.022,-1.216)	p<0.001	
Change in TPS from 1 week prior to updose to second week after updose	Week 3 group	71	-0.903	1.119	-3.57	-0.714	1.14	(-1.168,-0.638)	p<0.001	p=0.685
	≥Week 5 group	59	-0.983	1.104	-3.71	-0.714	0.71	(-1.271,-0.695)	p<0.001	

TPS: total pruritus score

†A two-tailed paired t-test with a significance level of 0.05 was used for the analysis on the significance of mean change of total pruritus score from baseline

††A two-tailed student's t-test with a significance level of 0.05 was used for intergroup analysis between Week 3 group and ≥Week 5 group

Supplementary Table 4. Subgroup Analysis of the Change in Mean Total Pruritus Score from Baseline to Week 2 in Updose group and Fixed dose group by Disease Type

Disease type		N	Mean	SD	Min	Median	Max	95%CI for the Mean	P-value†
Overall	Updose group	130	-0.850	1.315	-6.14	-0.571	1.86	(-1.078,-0.622)	p<0.001
	Fixed dose group	75	-1.920	1.598	-6.57	-1.762	1.10	(-2.287,-1.552)	
Eczema/dermatitis	Updose group	89	-0.746	1.096	-6.00	-0.571	1.86	(-0.977,-0.516)	p<0.001
	Fixed dose group	43	-1.742	1.221	-4.00	-1.762	0.43	(-2.117,-1.366)	
Skin pruritus	Updose group	33	-0.794	1.484	-6.14	-0.333	1.05	(-1.320,-0.267)	p=0.040
	Fixed dose group	25	-1.697	1.784	-4.71	-1.429	1.10	(-2.434,-0.961)	

†A two-tailed student's t-test with a significance level of 0.05 was used for intergroup analyses