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Original Article

Long-term safety and efficacy of rupatadine in Japanese patients with itching due to chronic spontaneous urticaria, dermatitis, or pruritus: A 12-month, multicenter, open-label clinical trial

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ABSTRACT

Background: Rupatadine is a novel H1 antihistamine with platelet-activating factor antagonist activity. Its efficacy and safety on pruritic skin diseases have been demonstrated by 10 mg/day rupatadine in a two weeks clinical trial.
Objective: To investigate the long-term efficacy and safety of rupatadine in the management of pruritus, and the clinical effect of updosing to 20 mg in Japanese adult and adolescent patients.
Methods: In this 52-week, multicenter, open-label clinical trial (JapicCTI-152787), 206 patients (132, eczema or dermatitis; 58, pruritus; and 16, chronic spontaneous urticaria) received the study medication. The primary efficacy endpoint was change from baseline in the total pruritus score to Week 2 by treatment with rupatadine 10 mg once daily. From Week 3 to Week 52, rupatadine updosing to 20 mg was allowed.
Results: The mean [95% CI] change from baseline to Week 2 in the total pruritus score was −1.241 [−1.450, −1.033] (paired *t* test, $P < 0.001$). The therapeutic effect persisted up to Week 52 (paired *t* test, $P < 0.001$). Adverse drug reactions (ADRs) were reported at an overall incidence of 18.0% (45 events in 37 patients). No serious or clinically significant ADRs were reported. Somnolence was the most common ADR (14.1%).
Conclusions: This clinical trial demonstrated the short- and long-term benefits of rupatadine in the management of patients with chronic spontaneous urticaria, dermatitis, and pruritus. Rupatadine 10 and 20 mg doses are effective for the treatment of itch in adults and adolescents, and can be used safely on a long-term basis.

1. Introduction

Eczema, atopic dermatitis, urticaria, and other inflammatory allergic cutaneous reactions cause itch. Itch often makes the patients scratch their skin, and persistent scratching can aggravate dermal conditions. Itch can even cause emotional disturbance and sleep loss. The management of itch is therefore a key component of the clinical treatment of patients with allergies.

A variety of stimuli induce the degranulation of skin mast cells, leading to the release of histamine, platelet-activating factor (PAF), and other chemical mediators. These mediators act on microvasculature and neural tissues, and cause capillary dilatation (erythema), plasma exudation (wheal), and itch sensation [1]. Histamine is a major biological modulator that triggers allergic reactions [2]. The binding of histamine to H1 receptors activates pruriceptors and transmits itch signals to the spinal cord [3]. Therefore, H1 antihistamines are the mainstay of pharmacotherapy in patients with allergic and pruritic skin diseases.

Second-generation nonsedating antihistamines are recommended as the first-line therapy for the treatment of chronic spontaneous urticaria (CSU) and other types of urticaria [1]. In Japan, second-generation nonsedating antihistamines have been proposed as an adjuvant therapy to topical antiinflammatory agents for the treatment of atopic dermatitis [4]. Recommendations on antihistamine treatment for atopic dermatitis are also applicable to the treatment of contact dermatitis, because both

Abbreviations: ADR, adverse drug reaction; AE, adverse event; CSU, chronic spontaneous urticaria; FAS, full analysis set; JapicCTI, Japan Pharmaceutical Information Center Clinical Trials Information; PAF, platelet-activating factor; SAS, safety analysis set; t_{max}, maximum drug concentration time; TPS, total pruritus score.

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types of dermatitis are characterized by eczematous skin reactions [5,6]. Antihistamines are also recommended in the treatment of generalized pruritus in addition to appropriate skin care and other protective measures [7]. A standard dose of non- or mildly sedating antihistamines is the first-line pharmacotherapy for generalized pruritus. Alternative or additional antihistamines may be needed depending on the development of adverse drug reactions (ADRs) and the strength of itch sensations.

Rupatadine is a second-generation antihistamine, first synthesized in the early 1990s. The structure of this agent has piperidinyl and lutidinyl components. Its piperidinyl moiety is structurally similar to loratadine, another second-generation antihistamine that has been marketed for treating allergic symptoms [8] its lutidinyl moiety has been shown to antagonize the receptor binding of PAF, a chemical mediator in inflammatory and other allergic responses [9,10]. The dual mechanism of action of rupatadine makes it a promising symptomatic therapy for patients with pruritic skin diseases.

As of February 1, 2019, rupatadine has been licensed for the treatment of allergic rhinitis and urticaria in more than 80 countries worldwide including Japan. This article reports the results of a 12-month multicenter Phase 3 clinical trial conducted to investigate the long-term efficacy and safety of rupatadine in the management of itch associated with allergic cutaneous reactions in Japanese adult and adolescent populations (Japan Pharmaceutical Information Center Clinical Trials Information [JapicCTI] No. 152787). This clinical trial was designed on the basis of a previous 2-week clinical trial of rupatadine in Japanese patients with CSU (JapicCTI-152786), which underscored the need for a further study to characterize the clinical benefits and risk of long-term rupatadine use and updosing from 10 mg to 20 mg once daily [11]. This clinical trial was carried out taking note of the 1964 World Medical Association Declaration of Helsinki (revised in Fortaleza, Brazil, October 2013) [12] and related regulations and guidelines.

2. Methods

2.1. Patients

With the participation of 19 medical institutions across Japan, this open-label clinical trial investigated the effects of 10 mg and 20 mg rupatadine administered once daily for the management of itch associated with allergic cutaneous diseases. Before commencing this clinical trial, all medical institutions had the study protocol reviewed and approved by their local institutional review board. Supplementary Fig. 1 shows the outline of the study procedures.

The clinical trial enrolled patients (i) aged 12 to 64 years, (ii) who had eczema, dermatitis, pruritus, or CSU, (iii) whose total pruritus score (TPS, the sum of daytime and nighttime pruritus scores determined using the grading criteria shown in Supplementary Table 1) was ≥ 2 for the last 3 days before the study treatment. Written informed consent was obtained from adults and parents or guardians of adolescents, and written assent was obtained from minors aged < 20 years. Patient anonymity was preserved using methods approved by the institutional review board.

In principle, concomitant use of similar drugs to rupatadine were prohibited or restricted. Prohibited or restricted concomitant drugs and other exclusion criteria are summarized in Supplementary method 1.

This clinical trial was designed to enroll 180 patients (including 20 adolescents) for the evaluation of efficacy, consisting of 110 patients with eczema or dermatitis, 55 patients with pruritus, and 15 patients with CSU. For the evaluation of long-term safety, at least 100 patients (including 10 adolescents) were deemed necessary. Based on the results of similar H1 antihistamine clinical trials, these sample sizes were considered appropriate for ensuring valid and reliable long-term efficacy and safety evaluation.

After the first 2 weeks of treatment with 10 mg (at Visit 4 or later), investigators were permitted to updose to 20 mg once daily, if (i) the TPS score averaged over the last 7 days before the study visit was greater than 3, and if (ii) the TPS scores were greater than 4 on at least 3 of the 7 days (dose escalation criteria). Dose reduction from 20 mg to 10 mg was left to the discretion of the investigators.

Patients were asked to remain on study treatment for a minimum of 12 weeks (Visit 9). Patients who required further treatment remained on the study for a maximum of 52 weeks (Visit 29). The investigator was given the discretion to complete the study medication after 12 or more weeks of study treatment if the patient had a mean TPS score ≤ 1 for the last 7 days before the study visit (study completion criteria).

2.2. Efficacy

The primary efficacy outcome variable of this clinical trial was a change from baseline to Week 2 in TPS score (for patients remaining on the study treatment for 2 weeks, the scores were averaged over the 7 days preceding Visit 4; and for patients who prematurely withdrew from the study, scores were averaged over the last 7 days before discontinuation).

In the secondary efficacy analyses, TPS score changes from baseline up to Week 52 were evaluated. Furthermore, the patients and investigators rated their overall impression of improvement by using a 6-point grading scale and the results were summarized for Week 2, Week 12, and Week 52.

2.3. Safety

Patient safety was evaluated on the basis of clinical laboratory tests, vital signs, and adverse events (AEs). Treatment-emergent AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 [13]. Study-related AEs were classified as ADRs. Severity was rated using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [14].

2.4. Statistical analysis

All patients who received at least 1 dose of the study medication and provided at least 1 postbaseline efficacy measurement were included in the full analysis set (FAS). All patients who received at least 1 dose of the study medication were included in the safety analysis set (SAS).

The posttreatment changes from baseline of TPS were statistically assessed using the paired *t* test at a 2-tailed significance level of 0.05. No multiplicity adjustment was performed for exploratory efficacy analyses. Missing data were not imputed.

To investigate possible differences in the therapeutic effect of rupatadine, posttreatment changes from baseline of TPS were analyzed by disease type (eczema or dermatitis, pruritus, and CSU). Furthermore, to identify the subgroups of patients with possible concerns for drug safety, the incidence rates of AEs and ADRs were subject to stratification analysis by age (12–17 and 18–64 years), body weight (< 50, 50 to < 60, 60 to < 70, and ≥ 70 kg), sex, disease type, and complication (yes and no). In addition, the effect of rupatadine updosing to 20 mg once daily and possible variations in drug response among disease types were investigated in a posthoc manner.

3. Results

3.1. Patients

Fig. 1 shows the disposition of patients. This clinical trial enrolled 207 patients. Among them, 1 patient took no study medication, and the remaining 206 patients, consisting of 132 patients with eczema or dermatitis, 58 patients with pruritus, and 16 patients with CSU, received at least 1 dose of the study medication. In this clinical trial, the SAS was identical to the FAS.

The FAS included 183 adults (88.8%) and 82 males (39.8%). Supplementary Table 2 shows the demographic and baseline data of the FAS (= SAS). Rupatadine was updosed from 10 mg to 20 mg in 130 patients (63.1%), including 13 patients (6.3%) whose dose was later reduced to 10 mg. A total of 172 patients received 12 or more weeks of study treatment. Among these patients, 129 patients remained in the study up to Week 52.

3.2. Efficacy

Table 1 summarizes the results on the primary efficacy and secondary endpoints. The primary efficacy analysis showed that the mean [95% CI] change from baseline to Week 2 in TPS score was −1.241 [−1.450, −1.033], and this reduction was statistically significant ($P < 0.001$). The mean change in the primary efficacy endpoint was also statistically significant for both adolescents (−0.745, n = 23, $P = 0.008$) and adults (−1.304, n = 182, $P < 0.001$). By disease type, patients with eczema or dermatitis, patients with pruritus, and patients with CSU had a mean TPS reduction from baseline of −1.071, −1.183, and −2.971, respectively. These reductions were all statistically significant ($P < 0.001$). Among the 132 patients with eczema or dermatitis, atopic dermatitis accounted for the largest proportion (n = 66, Supplementary Table 2). In a posthoc analysis of patients with atopic dermatitis, the mean change from baseline in TPS score, the primary endpoint, was −0.827 ($P < 0.001$). The clinical advantage demonstrated in the FAS by the primary efficacy analysis remained throughout the study (Supplementary Fig. 2). Rupatadine effectively reduced both daytime and nighttime pruritus scores from baseline (Supplementary Table 3). Over time, an increasing proportion of patients and investigators rated that the conditions “extremely,” “very,” or “moderately” improved. At Week 52, 94.6% (122/129) of the patients and 92.2% (119/129) of the investigators judged that rupatadine therapy yielded “moderate” or better improvement (Fig. 2).

For the 130 patients updosed to 20 mg, the mean (SD) baseline TPS score was 4.774 (0.886). Their mean (SD) change from baseline in TPS score averaged over the 7-day period before and after dose escalation was −0.447 (0.919) and −1.386 (1.387), respectively. Furthermore, their mean (SD) change from baseline to Week 2 in TPS was −0.850 (1.315), which was significantly smaller ($P < 0.001$) than that (−1.920 [1.598]) of patients who did not undergo updosing (Table 2). Posthoc analyses showed that the patients who underwent rupatadine updosing to 20 mg once daily had a greater mean baseline TPS score and a smaller TPS change from baseline to Week 2 than those who did not, irrespective of their disease types (Supplementary Table 4). Fifty patients with atopic dermatitis had their dose escalated to 20 mg (Supplementary Table 5). The mean (SD) baseline TPS score of these patients was 4.867 (0.797). Their mean (SD) change from baseline in TPS score averaged over the 7-day period before and after dose escalation was −0.495 (0.908) and −1.250 (1.331), respectively. These reductions were statistically significant ($P < 0.001$).

3.3. Safety

Supplementary Table 6 and Table 3 show the AEs and ADRs reported at an incidence ≥ 1.0%, respectively. The frequencies of ADRs are summarized in Table 4 by dose and duration of treatment: Week 1 to Week 2 (*Period 1*), Week 3 to Week 12 (*Period 2*), and Week 13 to Week 52 (*Period 3*).

AEs occurred at an incidence rate of 18.9% in Period 1, 38.6% in Period 2, and 67.8% in Period 3, with an overall rate of 78.6% (430 events in 162 patients). ADRs were reported at a rate of 9.7% in Period 1, 7.9% in Period 2, and 1.7% in Period 3, with an overall incidence of 18.0% (45 events in 37 patients). By severity, Grade 1 and Grade 2 ADRs were documented at an incidence rate of 14.6% and 3.4%, respectively. The Grade 2 ADRs were somnolence, constipation, dry mouth, increased liver function test values, and hypoesthesia. No Grade 3 or higher ADRs were reported. Moreover, No serious or clinically significant ADRs were reported.

Somnolence was the most common ADR (14.1%) and the only ADR documented in adolescents. Its incidence rate (13.0%) was comparable to that in adults (14.2%). No noteworthy trends in the occurrence of ADRs were revealed by stratification analyses by age, body weight, sex, disease type, or complication. Furthermore, the pharmacokinetic data of this clinical trial showed that the plasma concentration profiles of rupatadine and desloratadine were comparable between adults and adolescents (Supplementary method 2 and Supplementary Figure 3).

In the treatment periods, somnolence was the only ADR reported at a rate ≥ 1.0% in Period 1. In Period 2, somnolence (5.0%) and thirst (2.0%) occurred at a rate ≥ 1.0%. In Period 3, somnolence (1.1%) was the only ADR that developed at a rate ≥ 1.0%. All ADRs that were documented in Period 3 had been reported in Period 1 or Period 2.

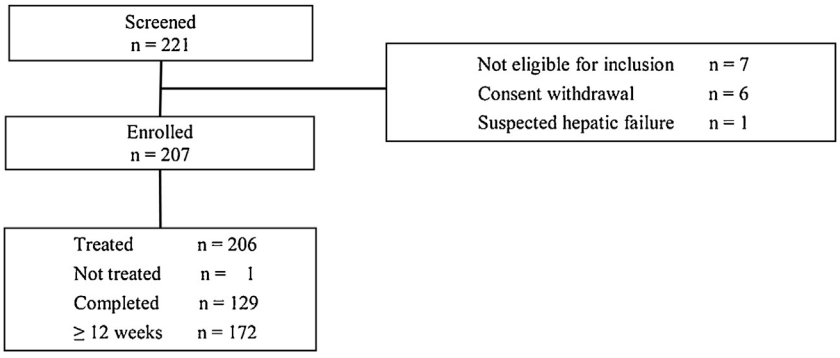

Fig. 1. Disposition of patients. Reasons for premature discontinuation: consent withdrawal (n = 13), violation of eligibility criteria (n = 17), nonmedical reasons (n = 7), disease aggravation (n = 6), AEs (n = 14), other (n = 10).

Table 1
Change over time in total pruritus score: full analysis set.

Disease Type	Baseline TPS	TPS Change From Baseline†				
		First 7 Days	Week 2	Week 12	Week 26	Week 52
Total						
No. of patients	206	206	205	181	153	129
Mean (SD)	4.552 (1.005)	−0.996 (1.392)	−1.241 (1.512)	−2.109 (1.512)	−2.415 (1.453)	−2.738 (1.643)
95% CI for mean difference	NA	−1.188, −0.805	−1.450, −1.033	−2.331, −1.887	−2.647, −2.183	−3.024, −2.452
Median	4.667	−0.619	−0.857	−2.000	−2.196	−2.714
Min., max.	2.00, 8.00	−7.00, 1.71	−6.57, 1.86	−7.50, 1.38	−7.25, 1.14	−7.57, 1.00
Paired *t* test *P*- value	NA	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Eczema or dermatitis						
No. of patients	132	NE	132	113	NE	79
Mean (SD)	4.477 (0.977)		−1.071 (1.226)	−1.933 (1.222)		−2.631 (1.447)
Median	4.667		−0.786	−1.867		−2.714
Min., max.	2.00, 6.33		−6.00, 1.86	−5.83, 0.24		−5.67, 0.37
Paired *t* test *P*- value	NA		< 0.001	NE		NE
Pruritus						
No. of patients	58	NE	58	54	NE	36
Mean (SD)	4.575 (0.957)		−1.183 (1.667)	−2.203 (1.813)		−2.502 (1.865)
Median	4.667		−0.571	−2.000		−1.967
Min., max.	2.33, 7.00		−6.14, 1.10	−6.60, 1.38		−6.71, 1.00
Paired *t* test *P*- value	NA		< 0.001	NE		NE
Chronic spontaneous urticaria						
No. of patients	16	NE	15	14	NE	14
Mean (SD)	5.083 (1.274)		−2.971 (2.105)	−3.166 (1.970)		−3.952 (1.685)
Median	5.000		−3.381	−3.128		−4.000
Min., max.	3.33, 8.00		−6.57, −0.14	−7.50, 0.44		−7.57, −0.86
Paired *t* test *P*- value	NA		< 0.001	NE		NE
Atopic dermatitis						
No. of patients	66	NE	66	NE	NE	NE
Mean (SD)	4.682 (0.925)		−0.827 (0.985)			
Median	4.667		−0.690			
Min., max.	2.00, 6.33		−3.57, 1.86			
Paired *t* test *P*- value	NA		< 0.001			

† Daily total pruritus scores were averaged over 1 week for Week 2 and over 2 weeks for Week 12, Week 26, and Week 52 evaluation time points. Data on patients with atopic dermatitis were obtained from a posthoc analysis. TPS indicates total pruritus score, min., minimum; max., maximum; CI, confidence interval; NA, not applicable; and NE, not evaluated.

For different rupatadine doses, ADRs were reported in Period 1 at a rate of 9.2% with 10 mg and 5.9% with 20 mg. In Period 2 and Period 3 combined, ADRs were documented at a rate of 3.3% with 10 mg and 10.8% with 20 mg. In Period 1, somnolence was the only ADR with an incidence $\geq$ 1.0% and had a rate of 7.8% with 10 mg and 5.9% with 20 mg. In Period 2 and Period 3 combined, somnolence (1.3%) and thirst (1.3%) occurred at an incidence rate $\geq$ 1.0% in patients receiving 10 mg, and patients receiving 20 mg reported somnolence more frequently (7.7%).

4. Discussion

4.1. Efficacy

This 52-week clinical trial evaluated the long-term efficacy and safety of rupatadine in the management of pruritic skin diseases. The primary efficacy endpoint showed that 2-week rupatadine 10 mg treatment effectively reduced TPS from baseline. The secondary efficacy analyses showed consistent reduction from baseline up to Week 52. Furthermore, the analyses of the primary efficacy outcome by skin disease type (eczema or dermatitis, pruritus, and CSU) showed a statistically significant decrease from baselines in all disease types. These results demonstrate that rupatadine is effective for the short- and long-term management of itching in daytime and nighttime in a variety of pruritic allergic skin diseases.

The clinical benefit of rupatadine in the management of itch was consistent with the subjective and objective overall impression ratings by the patients and their physicians. Over time, the increasing numbers of patients and investigators assessed that the clinical conditions “extremely” or “very” improved with rupatadine. At Week 52, most of the patients and investigators judged that rupatadine therapy achieved “moderate” or better improvement (94.6% and 92.2%, respectively).

This clinical trial also assessed the therapeutic effect of rupatadine updosing from 10 to 20 mg. Rupatadine was updosed in 130 patients. In these patients, the mean change from baseline in TPS score over the 1-week period preceding the updosing was −0.447. The difference from baseline further decreased to −1.386 during the second week following the updosing, thus exhibiting the greater potency of rupatadine 20 mg in alleviating itch. However, when their mean TPS change from baseline to Week 2 was retrospectively analyzed posthoc, the results showed that these patients made significantly less improvements over the first 2 weeks of rupatadine 10 mg treatment than patients who did not undergo updosing throughout the study. A further analysis of these results may provide clues to optimizing the therapeutic benefits of rupatadine, and it may be helpful to examine the timing of rupatadine updosing (i.e., immediately after Week 2 or later) and its cause (e.g., insufficient response or disease aggravation).

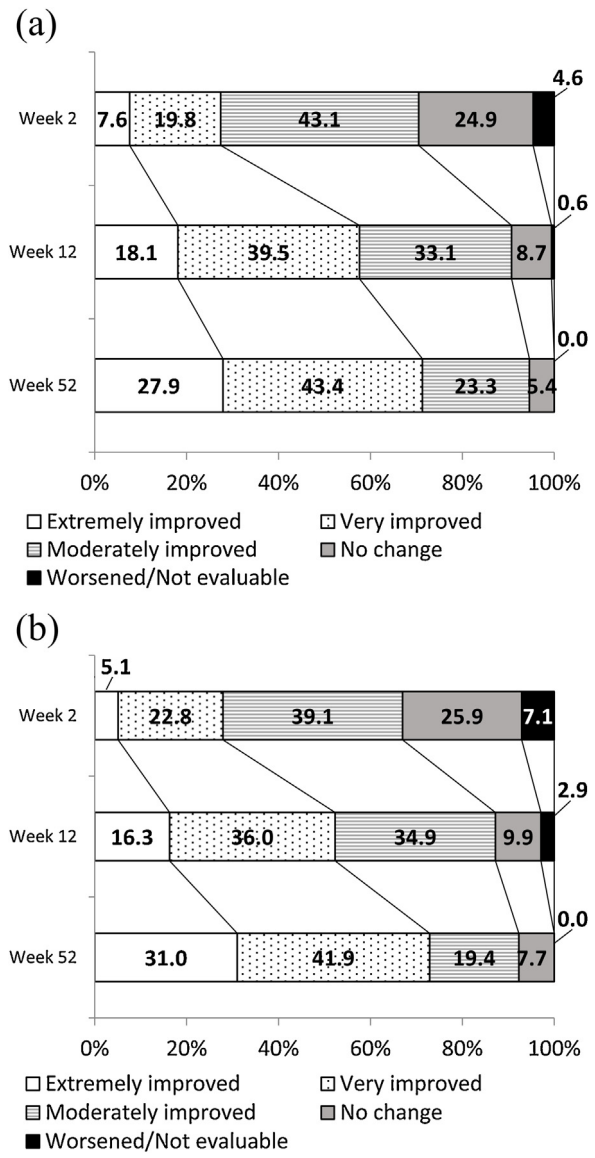

Fig. 2. Patient and physician overall impression: full analysis set. (a) Patient overall impression. (b) Physician overall impression. The numbers in the graph indicate the percentage of relevant responses.

Given the safety findings from clinical studies of rupatadine up to 40 mg, rupatadine 20 mg can be a viable option for treating refractory and persistent itch [15–18].

This clinical trial exhibited the clinical benefit of rupatadine in the management of itch in patients with atopic dermatitis. These results are consistent with several previous randomized clinical trials that demonstrated the clinical efficacy of H1 antihistamines for the treatment of pruritus associated with atopic dermatitis [19,20]. Furthermore, loratadine, which produces the same active metabolite desloratadine as rupatadine, significantly reduced the pruritus visual analog scale score in patients with atopic dermatitis when loratadine was added to the corticosteroid therapy compared with when the corticosteroid therapy was administered alone [21]. Since the involvement of PAF in the mechanism underlying itch in atopic dermatitis is clinically suggested [22], the PAF-antagonist action of rupatadine may have a positive effect on the management of itch in atopic dermatitis. Future studies are needed to explore the role of PAF in the pathogenesis of itch and help clarify the therapeutic benefits of rupatadine.

4.2. Safety

The excellent drug adherence (e.g., median number of treatment days of 362.0) and the ADR profile of rupatadine reported in this clinical trial underpins the long-term tolerability and safety of rupatadine. No Grade 3 or higher ADRs to rupatadine were reported, and most ADRs were Grade 1.

4.3. Use in adolescents

This clinical trial showed the clinical benefit and the absence of noteworthy safety signals in the use of rupatadine in adolescents. A statistically significant TPS score decrease from baseline to Week 2 was noted in both adolescent and adult patients. No noteworthy trends were detected in the frequency or profile of ADRs in these age subgroups.

4.4. Study implications

The moderately common occurrence of mild somnolence documented in this clinical trial suggests that rupatadine has the potential to depress the central nervous system. Täubel et al. investigated the effects of rupatadine on sustained attention, psychomotor reaction time, and spatial working memory in a

Table 2
Change in total pruritus score in patients with and without rupatadine updosing to 20 mg: full analysis set.

Evaluation Time Point	Subgroup	No. of Patients	Total Pruritus Score			*P* Value[†]
			Mean	SD	95% CI for the Mean	
Baseline (BL)	10 mg	76	4.171	1.085	3.923, 4.419	< 0.001
	Updosed	130	4.774	0.886	4.621, 4.928	
Week 2 (W_2)	10 mg	75	2.262	1.338	1.955, 2.570	< 0.001
	Updosed	130	3.924	1.162	3.723, 4.126	
Change from BL to W_2	10 mg	75	−1.920	1.598	−2.287, −1.552	< 0.001
	Updosed	130	−0.850	1.315	−1.078, −0.622	
One week before updosing (BU)	Updosed	130	4.327	0.728	–	–
Second week after updosing (AU)	Updosed	130	3.388	1.299	–	–
Change from BL to BU	Updosed	130	−0.447	0.919	−0.606, −0.287	< 0.001
Change from BL to AU	Updosed	130	−1.386	1.387	−1.627, −1.146	< 0.001
Change from BU to AU	Updosed	130	−0.940	1.109	−1.132, −0.747	< 0.001

[†] Statistical comparisons between the 10 mg and updosed subgroups were conducted using the *t* test, and changes from BL to BU, BL to AU, and BU to AU of the updosed subgroup were statistically analyzed using the paired *t* test. The 10 mg subgroup comprises patients who did not undergo rupatadine updosing to 20 mg throughout the study, whereas the updosed subgroup includes patients who underwent updosing after the 2-week fixed dose period.

Table 3
Adverse drug reactions reported at incidence ≥ 1.0%.

MedDRA Version 19.0		Adverse Drug Reactions	
SOC	PT	No. of Events	No. of Patients (n = 206)
General disorders and administration site conditions			
	Thirst	5	5 (2.4%)
Investigations			
	Liver function test increased	2	2 (1.0%)
Nervous system disorders			
	Somnolence	29	29 (14.1%)

SOC indicates system organ class; and PT, preferred term.

small-scale clinical trial [23]. Their results showed that rupatadine 10 mg was not associated with apparent cognitive impairment. However, the study parameters were worsened by higher doses, thus suggesting that the effects of rupatadine were dose dependent. These findings are contrary to the results of our previous study of rupatadine administered for 2 weeks in patients with CSU, which revealed no noteworthy difference in the rate of somnolence between the rupatadine 10 mg and 20 mg groups [11]. In a separate study, the influence of rupatadine, hydroxyzine (active control), and placebo on car driving was investigated in a randomized, double-blind, three-way crossover design [24]. In this study, healthy volunteers operated the test instrument at 2 h postdose, and no significant difference was noted between rupatadine and placebo in the primary outcome measure of vehicle control (standard deviation of lateral position). These seemingly contradicting results warrant further research to investigate the effect of rupatadine on cognitive, psychomotor, and memory performance and ensure its optimal usage.

In our study, the incidence rate of somnolence from Week 3 to the end of the treatment was higher in patients who updosed rupatadine to 20 mg (10/130, 7.7%) than those who continued rupatadine at 10 mg (2/151, 1.3%). In interpreting these results, the following points should be considered: (1) patients experience somnolence commonly in the early stages of treatment (incidence of somnolence with rupatadine 10 mg within 2 weeks of treatment: 16/206, 7.8%) and (2) a small proportion of patients underwent updosing to 20 mg before Week 3 because of the time window of ± 2 days of the scheduled visit date (n = 17). Unlike our previous clinical trial that employed the parallel-group design [11], the present clinical trial does not allow for a reliable determination of the frequency of somnolence with 20 mg rupatadine or a direct comparison of the incidence between doses.

A major limitation of this clinical trial was its open-label design, and its results may have been influenced by a positive expectation bias. Another limitation of this clinical trial was the small number of patients with CSU, and this limitation may have obscured the effect of rupatadine updosing to 20 mg in this subgroup. The limitations of this clinical trial suggest that a further investigation of the effect of rupatadine updosing and the role of PAF in the pathogenesis of itch, as mentioned in the Discussion section, is necessary. Despite these limitations, this clinical trial demonstrated the short- and long-term benefits of rupatadine in the management of itch in patients with eczema, dermatitis, pruritus, and CSU. Rupatadine is an effective H1 antihistamine medication for the treatment of itch in adults and adolescents, and it can be used safely on a long-term basis.

Table 4
Onset of adverse drug reactions classified by treatment duration and rupatadine dose.

MedDRA Version 19.0		Adverse Drug Reactions													
SOC	PT	≤ Week 2 (Period 1, n = 206)		Week 3 to Week 12 (Period 2, n = 202)		≥ Week 13 (Period 3, n = 174)		≤ Week 2 (Period 1)				≥ Week 3 (Period 2 + Period 3)			
								10 mg† (n = 206)		20 mg† (n = 17)		10 mg† (n = 151)		20 mg† (n = 130)	
		E	P (%)	E	P (%)	E	P (%)	E	P (%)	E	P (%)	E	P (%)	E	P (%)
Gastrointestinal disorders		2	2 (1.0%)	1	1 (0.5%)	3	1 (0.6%)	2	2(1.0%)	0	0(0.0%)	1	1(0.7%)	3	1(0.8%)
	Abdominal discomfort	1	1 (0.5%)	0	0 (0.0%)	0	0 (0.0%)	1	1(0.5%)	0	0(0.0%)	0	0(0.0%)	0	0(0.0%)
	Constipation	0	0 (0.0%)	1	1 (0.5%)	3	1 (0.6%)	0	0(0.0%)	0	0(0.0%)	1	1(0.7%)	3	1(0.8%)
	Dry mouth	1	1 (0.5%)	0	0 (0.0%)	0	0 (0.0%)	1	1(0.5%)	0	0(0.0%)	0	0(0.0%)	0	0(0.0%)
General disorders and administration site conditions		2	2 (1.0%)	4	4 (2.0%)	0	0 (0.0%)	2	2(1.0%)	0	0(0.0%)	2	2(1.3%)	2	2(1.5%)
	Malaise	1	1 (0.5%)	0	0 (0.0%)	0	0 (0.0%)	1	1(0.5%)	0	0(0.0%)	0	0(0.0%)	0	0(0.0%)
	Thirst	1	1 (0.5%)	4	4 (2.0%)	0	0 (0.0%)	1	1(0.5%)	0	0(0.0%)	2	2(1.3%)	2	2(1.5%)
Hepatobiliary disorders		0	0 (0.0%)	1	1 (0.5%)	0	0 (0.0%)	0	0(0.0%)	0	0(0.0%)	1	1(0.7%)	0	0(0.0%)
	Hepatic function abnormal	0	0 (0.0%)	1	1 (0.5%)	0	0 (0.0%)	0	0(0.0%)	0	0(0.0%)	1	1(0.7%)	0	0(0.0%)
Investigations		0	0 (0.0%)	1	1 (0.5%)	1	1 (0.6%)	0	0(0.0%)	0	0(0.0%)	0	0(0.0%)	2	2(1.5%)
	Liver function test increased	0	0 (0.0%)	1	1 (0.5%)	1	1 (0.6%)	0	0(0.0%)	0	0(0.0%)	0	0(0.0%)	2	2(1.5%)
Nervous system disorders		17	17 (8.3%)	11	11 (5.4%)	2	2 (1.1%)	16	16(7.8%)	1	1(5.9%)	2	2(1.3%)	11	11(8.5%)
	Hypoaesthesia	0	0 (0.0%)	1	1 (0.5%)	0	0 (0.0%)	0	0(0.0%)	0	0(0.0%)	0	0(0.0%)	1	1(0.8%)
	Somnolence	17	17 (8.3%)	10	10 (5.0%)	2	2 (1.1%)	16	16(7.8%)	1	1(5.9%)	2	2(1.3%)	10	10(7.7%)
Total		21	20 (9.7%)	18	16 (7.9%)	6	3 (1.7%)	20	19(9.2%)	1	1(5.9%)	6	5(3.3%)	18	14(10.8%)

MedDRA indicates Medical Dictionary for Regulatory Activities; SOC, system organ class; PT, preferred term; E, number of events; and P, number of affected patients. The figures in parentheses show the proportion of patients in percentage.
† Patients are grouped according to their dose at the time of adverse drug reactions.

Author contributions

MH served as the medical advisor of this clinical trial and contributed to literature search, study design, data analysis, and manuscript preparation. TS, AT, and HA engaged in the study design, data collection and interpretation, and manuscript review.

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Conflict of interest

MH received lecture and/or consultation fees from Teikoku Seiyaku, the sponsor of this study, TAIHO Pharmaceutical Co., Novartis, MSD, Mitsubishi Tanabe Pharma Co. and Kyowahakko-Kirin Co.. The sponsor has borne the costs for the preparation and submission of this manuscript, including third-party writing assistance. TS, AT, and HA are employees of Teikoku Seiyaku.

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Appendix A. Supplementary data

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