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Clinical effectiveness and safety of cetirizine versus rupatadine in chronic spontaneous urticaria: a randomized, double-blind, 6-week trial

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Abstract

Background Urticaria is a distressing condition associated with diverse clinical presentations. Chronic spontaneous urticaria (CsU) is characterized by wheals and angioedema. Its treatment requires an algorithmic approach to identify the optimum medication.

Objectives Cetirizine is commonly used in the treatment of urticaria. Rupatadine is a selective non-sedating H₁-antihistamine approved for the treatment of CsU. This trial was conducted to ascertain whether the properties of rupatadine offer advantages over cetirizine.

Methods Seventy patients with CsU were enrolled. Parameters assessed included: (i) mean number of wheals (MNW); (ii) pruritus; (iii) mean total symptom score (MTSS); (iv) size of wheal; (v) interference of wheals with sleep; and (vi) sedation. Patients with CsU were divided randomly into two groups. Routine investigations were performed at baseline and at the end of the study.

Results Evaluations of MTSS, MNW, and pruritus revealed statistically significant differences at week 3 compared with baseline in the cetirizine group. However, greater reductions in these parameters were obtained with rupatadine. In patients receiving rupatadine, reductions in the MNW, size of wheals, and intensity of erythema were also significant at six weeks ($P < 0.001$) and were significantly greater than those in the cetirizine group ($P < 0.05$).

Conclusions Improvements in MTSS, MNW, size of wheals, intensity of erythema, and differential eosinophil count imply that rupatadine is a particularly attractive therapeutic modality compared with cetirizine for the treatment of CsU.

Introduction

Allergic diseases are a global health problem; they remain under-diagnosed and are often inadequately treated. Urticaria is a particular example of a bothersome condition that can markedly impair the quality of life of affected individuals. Urticaria is associated with diverse clinical presentations and is characterized by the sudden appearance of wheals and/or angioedema¹ that resolve completely within hours or days. Urticaria is mainly classified into spontaneous, physical, and other types. Spontaneous urticaria is again subdivided into acute spontaneous urticaria, in which wheals and/or angioedema resolve in <6 weeks, and chronic spontaneous urticaria (CsU), which is characterized by the daily occurrence of itchy

wheals and/or angioedema that last for ≥ 6 weeks.² Physical urticaria is classified into cold contact, delayed pressure, heat contact, solar, demographic, and vibratory urticaria depending on the eliciting factors, whereas other urticaria types include aquagenic, cholinergic, contact, and exercise-induced urticaria.¹ The prevalence of urticaria in the world is 15–23%,^{3,4} and CsU accounts for nearly 80% of cases of chronic urticaria.⁵

Treatment of CsU is of the utmost importance as it has a great impact on quality of life and can impose negative effects on performance at school and in the workplace. Ultimately, this results in a high socioeconomic burden. Information about preventive measures, correct diagnosis, and the early and effective treatment of allergic disorders is required, especially in contexts in which it is not

possible to avoid the eliciting factors. The treatment of CsU requires an algorithmic approach to identify the medication or combination of medications that will completely prevent the occurrence of hives. This should begin with agents that have fewer side effects because treatment is often prolonged. The recommended first-line treatment consists of new-generation, non-sedating H_1 -antihistamines.⁶

Cetirizine is a well-known drug commonly used for the treatment of urticaria.⁷ Rupatadine is a newer selective long-acting non-sedating H_1 -antihistamine approved for the treatment of allergic rhinitis and CsU. In addition to its antihistaminic property, rupatadine antagonizes platelet activation factor (PAF) and inhibits the secretion of proinflammatory cytokines by mast cells and has shown effectiveness in the treatment of CsU at a dose of 10 mg/d.^{7–10} As the etiology of CsU is multifactorial, we conducted a trial to ascertain whether or not the additional properties of rupatadine offer advantages over cetirizine. Moreover, to the best of our knowledge, there is no literature comparing the efficacy and safety of rupatadine with those of cetirizine in the treatment of CsU. Therefore, we aimed to compare the efficacy and safety of rupatadine with those of cetirizine (a well-established drug) and to offer the best option for the treatment of CsU.

Materials and methods

Seventy patients with CsU were enrolled in a prospective, double-blind, parallel, 6-week trial approved by the institutional ethics committee of the Indira Gandhi Government Medical College and Hospital, Nagpur, from February 2010 to December 2011. The trial procedure was designed in accordance with the ethical standards laid down by the Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human Subjects. Informed consent was obtained from all patients prior to their inclusion in the study.

The parameters used to assess efficacy included: (i) number of wheals (scored as: 0 [none], 1 [1–5], 2 [6–15], 3 [16–25], 4 [>25]); (ii) pruritus (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe); (iii) mean total symptom score (MTSS) calculated by adding the mean number of wheals (MNW) and the mean pruritus score (MPS); (iv) size of wheal (scored as: 0 [no wheal], 1 [<0.5 cm], 2 [0.6–2.0 cm], 3 [2.1–4.0 cm], 4 [>4.0 cm]); (v) scale for interference of wheals with sleep (SIWS) (0 = none, 1 = mild, 2 = moderate, 3 = severe); and (vi) a visual analog scale (VAS) for sedation (scored on a scale of 0–100, where 0 = alert, 100 = very sleepy).

Patients with CsU were selected on the basis of their chief complaints and past history. The study inclusion criteria required participants to be attending the outpatient clinic in the Department of Dermatology, within the age group of

18–65 years, of either gender, with a history of urticarial wheal and/or angioedema for ≥ 3 days per week for six consecutive weeks for which no obvious cause had been established. Patients with an MTSS (24-hour reflective) of ≥ 3 , an MNW of ≥ 1 , and an MPS of ≥ 2 at screening and normal electrocardiogram (ECG) were included in the study. Only patients suffering CsU were included in the trial. Patients using any antihistamines other than rupatadine and cetirizine were included in the trial only after a washout period of seven days, irrespective of the doses of their previous drugs. Exclusion criteria denied the participation of subjects with acute spontaneous urticaria and all physical and other subtypes of urticaria, such as aquagenic, cholinergic, contact, and exercise-induced urticaria, a history of asthma or any other disease requiring the chronic use of inhaled or systemic corticosteroids, a history of failure to respond to previous antihistaminic drug treatment, a history of allergies to the study medication or an tolerance to antihistamines, use of a study drug or topical corticosteroids in the previous seven days, use of oral corticosteroids in the previous eight weeks, use of parenteral corticosteroids in the previous three months, and use of any other immune-modulating therapy. In addition, subjects with significant hematopoietic, cardiovascular, hepatic, renal, neurologic, psychiatric, or autoimmune disease were excluded from the study. Pregnant women and nursing mothers were also excluded from the trial.

A total of 104 patients were screened, 70 of whom were found to satisfy the inclusion and exclusion criteria and were recruited to the trial. Patients with CsU were divided randomly into two groups (groups A and B), with 35 patients in each group. The sample size was calculated with a standard deviation (SD) taken from a previous study and the level of significance set at 0.05 with power of 80%. A block randomization procedure was used for the random allocation of study drugs (i.e. cetirizine and rupatadine) with block sizes of four in equal proportions to ensure a uniform allocation ratio (1 : 1). Because this was a double-blind study, the drugs were presented in identical formats in terms of shape, size, texture, and packing. The randomized treatment allocation sequence was generated by a statistician using a random number table. The drugs (21 tablets of cetirizine or rupatadine) were handed over in identical plastic containers to a third person who was not directly involved in this study. This person labeled the containers according to the random allocation sequencing of patients. The codes used in this random allocation sequence were retained in a sealed envelope, which was opened only after the completion of the study. Both the patients and the investigators were unaware of the treatment administered. Drugs were issued to patients for a period of three weeks at a time. Patients were given a new supply of their drug at the end of the third week. Patients were asked to bring any unused drugs and containers to follow-up appointments at the completion of the study (6 weeks). Patient compliance was

determined by counting the numbers of unused tablets. Unused drugs were discarded later. Drugs were decoded at the end of the trial. Group A received cetirizine 10 mg and group B received rupatadine 10 mg, both once daily. The same dosages were maintained throughout the study. No comorbid conditions were observed in these patients during the study period. At the end of the study period, the subjects were assessed by dermatologists.

The clinical assessment of patients was performed by the principal investigator in consultation with the dermatologist. At the first visit, patients were instructed to count the number of wheals; this count was cross-checked by the principal investigator. Measuring tape was used to measure the size of wheal. This parameter considered the greatest diameter of the largest wheal on the body and categorized wheal size accordingly. The intensity of erythema was noted according to the color of the wheal; when the intensity of erythema varied between two wheals, the higher scale was used. The scale for the extent of skin area involved (SESI) was calculated using the "rule of 9s" (as for calculating the percentage of burn) and graded according to the body surface area involved. The patients were given a 6-week symptom diary to record parameters such as the number of wheals, pruritus scale, SIWS, and VAS for sedation. Numbers of wheals and the pruritus scale were recorded twice daily, whereas the SIWS was noted in the morning and the VAS for sedation in the evening.

Routine investigations, such as ECG, total leukocyte count (TLC), differential leukocyte count (DLC), liver function test, and kidney function test, were performed in each patient at baseline and at the end of the study. General clinical safety was monitored by the vigilant follow-up of patients in order to allow the treatment of any emergent adverse events and recorded in the case report form. Patients with any adverse drug reaction were treated appropriately.

Statistical analysis

Results were expressed as the mean $\pm$ SD. Between-group differences were ascertained using the Mann-Whitney rank sum test or unpaired *t*-test. Within-group differences were compared using the Wilcoxon test or paired *t*-test or Friedman's test with Dunn's multiple comparison post hoc test. A two-tailed *P*-value of <0.05 was considered to indicate statistical significance. GraphPad Prism Version 5.00 (GraphPad Software, Inc., La Jolla, CA, USA) was used for statistical analysis.

Results

A total of 70 patients were randomized and allocated to the treatment. Of these, 64 patients completed the trial according to the protocol. Five patients were lost to follow-up at the end of the first week of the study, including three in the cetirizine group and two in the rupatadine group. For reasons of non-response, one patient in the

cetirizine group was dropped from the study and shifted to another drug. Hence, data for these six patients were not integrated in the analysis. The two groups were homogeneous with respect to baseline demographic data (Table 1). Both groups included a higher percentage of female patients (61.29% in the rupatadine group and 64.51% in the cetirizine group).

Evaluations of MTSS, MNW, and MPS revealed statistically significant differences at week 3 compared with pretreatment levels in the cetirizine group. Reductions in these parameters first became apparent and were significant by the third week ($P < 0.05$); these improvements were maintained to the sixth week of treatment (Table 2). Similar results were obtained with rupatadine, but the reductions in these parameters were greater in this group. No significant differences in these parameters between the 3 and 6-week time-points were observed in either group.

To test whether treatment with rupatadine was more successful than that with cetirizine in resolving symptoms,

Table 1 Demographic characteristics of chronic spontaneous urticaria patients at baseline

Characteristic	Cetirizine group (<i>n</i> = 31)	Rupatadine group (<i>n</i> = 33)	<i>P</i> -value
Patients recruited, <i>n</i>	35	35	
Patients at follow-up, <i>n</i>	31	33	
Age, years, mean $\pm$ SD	41.48 $\pm$ 11.49	43.81 $\pm$ 12.30	0.4354 ^a
Male : female ratio	1 : 1.86	1 : 1.56	
Height, cm, mean $\pm$ SD	160.71 $\pm$ 7.59	157.64 $\pm$ 8.63	0.1347 ^a
Weight, kg, mean $\pm$ SD	61.03 $\pm$ 9.81	62.81 $\pm$ 8.36	0.4355 ^a
Duration of lesions, months, mean $\pm$ SD	6.23 $\pm$ 3.17	6.57 $\pm$ 3.32	0.668 ^a
TLC, mean $\pm$ SD	8622.58 $\pm$ 1185.61	8445.46 $\pm$ 1029.29	0.7778 ^b
Neutrophils, %, mean $\pm$ SD	62.61 $\pm$ 5.30	62.70 $\pm$ 5.05	0.8560 ^b
Lymphocytes, %, mean $\pm$ SD	29.16 $\pm$ 6.14	29.09 $\pm$ 5.83	0.9946 ^b
Eosinophils, %, mean $\pm$ SD	6.93 $\pm$ 1.87	6.71 $\pm$ 1.53	0.7618 ^b
Monocytes, %, mean $\pm$ SD	0.77 $\pm$ 0.85	0.74 $\pm$ 1.00	0.8387 ^b
Basophils, %, mean $\pm$ SD	0.55 $\pm$ 0.72	0.51 $\pm$ 0.83	0.6873 ^b

^aUnpaired *t*-test.

^bMann-Whitney rank sum test.

SD, standard deviation; TLC, total leukocyte count.

Table 2 Mean total symptom score (MTSS), mean number of wheals (MNW) and mean pruritus score (MPS) at baseline and at 3 weeks and 6 weeks after the initiation of treatment with cetirizine or rupatadine in patients with chronic spontaneous urticaria

Parameter	Baseline, mean $\pm$ SD	At 3 weeks of treatment, mean $\pm$ SD	At 6 weeks of treatment, mean $\pm$ SD	d.f.	P-value
Cetirizine group (n = 31)					
MTSS	6.29 $\pm$ 1.19	3.14 $\pm$ 1.28 ^a	3.05 $\pm$ 1.26 ^a	2,90	<0.0001
MNW	3.13 $\pm$ 0.67	1.65 $\pm$ 0.73 ^a	1.56 $\pm$ 0.74 ^a	2,90	<0.0001
MPS	3.16 $\pm$ 0.73	1.5 $\pm$ 0.67 ^a	1.48 $\pm$ 0.7 ^a	2,90	<0.0001
Rupatadine group (n = 33)					
MTSS	6.24 $\pm$ 0.97	1.95 $\pm$ 1.19 ^a	1.80 $\pm$ 1.27 ^a	2,96	<0.0001
MNW	3.12 $\pm$ 0.74	1.02 $\pm$ 0.63 ^a	0.97 $\pm$ 0.74 ^a	2,96	<0.0001
MPS	3.12 $\pm$ 0.65	0.94 $\pm$ 0.65 ^a	0.83 $\pm$ 0.62 ^a	2,96	<0.0001

^aP < 0.05 compared with baseline, non-parametric Friedman's test with Dunn's post hoc test.
SD, standard deviation; df, degree of freedom.

Table 3 Comparison of effects of cetirizine and rupatadine on mean total symptom score (MTSS), mean number of wheals (MNW) and mean pruritus score (MPS) at 6 weeks in patients with chronic spontaneous urticaria with reference to the change from baseline

Parameter	Cetirizine group (n = 31), mean $\pm$ SD change from baseline	Rupatadine group (n = 33), mean $\pm$ SD change from baseline	P-value ^a
MTSS	-3.24 $\pm$ 1.79	-4.44 $\pm$ 1.78	<0.01
MNW	-1.56 $\pm$ 1.05	-2.15 $\pm$ 1.17	<0.05
MPS	-1.68 $\pm$ 1.05	-2.29 $\pm$ 0.96	<0.05

^aMann-Whitney rank sum test.
SD, standard deviation.

we compared the effects of the drugs in both groups after six weeks of treatment, taking into consideration any change from baseline values in the study parameters. The reductions at six weeks in the MTSS, MNW, and MPS were significantly ($P < 0.05$) greater in the rupatadine group compared with the cetirizine group (Table 3).

In the cetirizine group, the number of wheals, size of wheals, and intensity of erythema were significantly ($P < 0.01$) reduced after six weeks of treatment compared with baseline levels. In patients receiving rupatadine, reductions in the number of wheals, size of wheals, and intensity of erythema were also significant at six weeks ($P < 0.001$). When changes from baseline values in these parameters were compared between the groups, reductions in the rupatadine group were found to be significantly greater than those in the cetirizine group ($P < 0.05$) (Table 4). No significant differences in mean changes in the SIWS and SESI were observed in either group. A significant increase in the VAS for sedation was seen in the cetirizine group compared with the rupatadine group.

A significant reduction in eosinophil count was observed with rupatadine in comparison with cetirizine (Table 5). No significant differences between baseline and the 6-week time-point in serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum bilirubin, alkaline phosphatase, serum creatinine, and blood urea were observed in either the rupatadine or the cetirizine group. Overall incidences of adverse effects were 39 and 21% in the cetirizine and rupatadine groups, respectively (Table 6). Fisher's exact test was performed to compare the incidences of adverse effects between the two groups but was non-significant. No change in the ECG of any patient was observed during the trial.

Discussion

Understanding of the pathogenesis of acute and chronic pruritus has improved significantly in recent years. This has revealed the potential of non-sedating H₁-antihistamines in the treatment of CsU. The most common approach to managing chronic urticaria is to prevent the release of histamine or to block its effects at receptor sites on nerves and endothelial cells. Therefore, non-sedating H₁-antihistamines represent the keystone of urticaria treatment.¹¹ Treating the symptoms of CsU and ensuring a decent quality of life in patients is challenging to physicians. Our in-depth search and review of the literature failed to retrieve any data comparing the efficacy and safety of recently developed non-sedating antihistamines or of the PAF antagonist rupatadine with the well-established H₁-antihistamine cetirizine. Hence, a double-blind clinical trial was conducted to establish the optimal option for the treatment of CsU.

The baseline data show no significant difference between the study groups with respect to demographic

Table 4 Effects of cetirizine and rupatadine on the intensity of erythema, interference of wheals with sleep, number of wheals, size of wheals, extent of skin area involved and sedation in patients with chronic spontaneous urticaria at 6 weeks

Parameter	Cetirizine group (n = 31)			Rupatadine group (n = 33)			P-value ^a
	Baseline, mean ± SD	At 6 weeks, mean ± SD	P-value	Baseline, mean ± SD	At 6 weeks, mean ± SD	P-value	
SIE	2.23 ± 0.67	1.65 ± 0.88	<0.01	2.27 ± 0.67	1.09 ± 0.91	<0.001	<0.05
SIWS	2.1 ± 0.75	1.23 ± 0.62	<0.001	2.09 ± 0.77	0.97 ± 0.73	<0.001	0.24
Number of wheals	3.13 ± 0.67	1.52 ± 0.77	<0.0001	3.12 ± 0.74	0.85 ± 0.67	<0.0001	<0.05
Size of wheals, cm	2.32 ± 0.83	1.61 ± 0.84	<0.01	2.39 ± 0.75	1.09 ± 0.91	<0.0001	<0.05
SESI	2.29 ± 0.64	1.19 ± 0.65	<0.0001	2.33 ± 0.54	1.03 ± 0.88	<0.0001	0.46
VAS for sedation	20.65 ± 9.65	23.29 ± 9.27	0.0004	21.21 ± 9.37	21.79 ± 10.18	0.2179	<0.01

^aWilcoxon test, comparison of the mean difference between scores at baseline and at 6 weeks in the two groups.

SD, standard deviation; SIE, scale for intensity of erythema; SIWS, scale for interference of wheals with sleep; SESI, scale for extent of skin area involved; VAS, visual analog scale.

Table 5 Comparison of changes in laboratory parameters from baseline to 6 weeks after the initiation of treatment with cetirizine and rupatadine in patients with chronic spontaneous urticaria

Parameter	Cetirizine group (n = 31)		Rupatadine group (n = 33)		P-value ^a
	Baseline	At 6 weeks	Baseline	At 6 weeks	
TLC, mean ± SD	8622.58 ± 1185.61	8003.23 ± 1290.09 ^b	8445.46 ± 1029.29	7748.49 ± 959.86 ^c	0.3609
Neutrophils,%, mean ± SD	62.61 ± 5.30	61.42 ± 5.71	62.70 ± 5.05	59.58 ± 4.39 ^c	0.1448
Lymphocytes,%, mean ± SD	29.16 ± 6.14	31.9 ± 6.15 ^b	29.09 ± 5.83	34.42 ± 4.49 ^d	0.124
Eosinophils,%, mean ± SD	6.93 ± 1.87	5.81 ± 1.85 ^c	6.71 ± 1.53	4.61 ± 1.94 ^d	<0.05 ^b
Monocytes,%, mean ± SD	0.77 ± 0.85	0.81 ± 0.79	0.74 ± 1.00	0.76 ± 0.97	0.7197
Basophils,%, mean ± SD	0.55 ± 0.72	0.52 ± 0.77	0.51 ± 0.83	0.64 ± 0.90	0.6899

^aWilcoxon test, comparison of the mean difference in data from baseline to 6 weeks in the two groups.

^bP < 0.05.

^cP < 0.01.

^dP < 0.0001.

TLC, total leukocyte count; SD, standard deviation.

Table 6 Adverse drug reactions in patients with chronic spontaneous urticaria treated with cetirizine or rupatadine

Adverse event	Cetirizine group (n = 31)	Rupatadine group (n = 33)
Headache, n	2	2
Gastric irritation, n	1	0
Dryness of mouth, n	1	1
Sedation, n	8	4
Total, n (%)	12 (38.71%)	7 (21.21%)

and laboratory parameters. This proves the homogeneity of the study subjects in the two groups. We found that CsU is more common in females. This observation corresponds with data reported by previous studies.^{12,13}

A widely accepted and reliable tool to assess the efficacy of a drug in the treatment of urticaria is total symptom score. A decrease in the total score suggests there is an overall clinical improvement in the condition.⁵ We found significant decreases in the MTSS, MNW, and MPS, a finding that concurs with those of previous studies of cetirizine^{14–16} and rupatadine.^{8,17} Another comparative trial of rupatadine found a linear trend for a time-dependent decrease in MTSS at weeks 3 and 4.¹⁷ In the present trial, progressive decreases in all these parameters were observed with increasing duration of treatment.

Other major findings of this study were reductions in the SIWS, size of wheals, intensity of erythema, and extent of skin area involved with both cetirizine and rupatadine. In the cetirizine group, only the reductions in the size of wheals and intensity of erythema were comparable with

the findings of previous studies,¹⁸ whereas in the rupatadine group, outcomes in the SIWS were comparable with those of previous research.¹⁷ Even after an extensive search, we were unable to find any study comparing changes in the extent of interference of wheals with sleep or extent of skin area involved in relation to cetirizine treatment, or changes in the size of wheals, intensity of erythema, and extent of skin area involved in relation to rupatadine treatment. Therefore, it was not possible to compare the results of the present study with previous findings. Hence, the present study is unique in comparing outcomes in these parameters for both drugs. A significant increase in sedation was observed with cetirizine, which is similar to that of a previous study analyzing VAS for sedation.¹⁹ No significant change in VAS for sedation was found with rupatadine, which also supports the finding of a previous study.²⁰ Rupatadine has a marked selectivity for peripheral over central H₁ receptors, which results in fewer side effects.⁹ This effect may be responsible for the greater efficacy of rupatadine with fewer side effects. This property may be more beneficial in patients who are engaged actively throughout the day in their respective fields.

An increase in eosinophil count is the hallmark of late phases of allergic diseases. The scrupulous control of this parameter is an important therapeutic aim.²¹ Previous research found a greater reduction in eosinophil count with rupatadine compared with cetirizine, which suggests the superiority of rupatadine.²² Decreases in differential eosinophil count, TLC, and differential neutrophil count were revealed, whereas no significant differences in differential monocyte and basophil counts were seen in the rupatadine group.²² We also observed an increase in differential lymphocyte count. We did not find any significant change in biochemical parameters with either drug. This observation supports the findings of a previous study on the safety of rupatadine.²³

The incidence of adverse events with cetirizine (38.71%) in the present study was high in comparison with previous studies.^{14,15} In our trial, patients were actively asked at follow-up visits to report any adverse symptom or event they had experienced during the trial period. Thus, this increase in the incidence of adverse events may be attributable to the more thorough reporting of adverse events in comparison with that in studies in which patients have reported adverse events spontaneously. We found no changes in ECG, in line with previous studies that have reported similar ECG findings.^{23–25}

The plausible superiority of rupatadine in this study can be explained by its additional properties. The etiology of CsU is multifactorial and refers mainly to histamine, PAF, and various cytokines. Platelet activation factor is

known to increase vascular permeability and is increasingly recognized as an important mediator in inflammation.²⁶ Both PAF and histamine are known to complement and promote the secretion of one another.²⁴ Rupatadine inhibits both histamine and PAF, resulting in a more inhibitory effect on the vasodilatation, vascular leakage, edema, wheal formation, pruritus, and eosinophil chemotaxis produced by these inflammatory mediators.¹⁵ Rupatadine has shown potent antiallergic activity *in vitro* (i.e. mast cell degranulation inhibition) and *in vivo* in several type I hypersensitivity models. Rupatadine, in addition, has anti-inflammatory effects that act directly on H₁ receptors. It has a high H₁ receptor-binding affinity, which allows the molecule to inhibit histamine-induced interleukin-6 and interleukin-8 production using concentrations that are below plasma levels at the therapeutic dose.^{11,22}

Although the present study used a small sample size and was of short duration, the value of its results cannot be ignored. However, studies with larger sample sizes and longer follow-up periods, along with measurements of absolute eosinophil counts, may yield more meaningful data to compare rupatadine with cetirizine.

Conclusions

Treatment with rupatadine was well tolerated with minimum side effects. Improvements in MTSS, size of wheals, intensity of erythema, and differential eosinophil count with a new dual-blocking property of the inflammatory mediators imply that rupatadine is a particularly attractive therapeutic modality compared with cetirizine for the treatment of CsU.

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References

- 1 Zuberbier T, Asero R, Bindslev-Jensen C, *et al.* EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009; **64**: 1417–1426.
- 2 Mete N, Gulbahar O, Aydin A, *et al.* Low B12 levels in chronic spontaneous urticaria. *J Investig Allergol Clin Immunol* 2004; **14**: 292–299.

- 3 Fernando S, Broadfoot A. Chronic urticaria: assessment and treatment. *Aust Fam Physician* 2010; 39: 135–139.
- 4 Bernstein JA. Chronic urticaria: an evolving story. *Isr Med Assoc J* 2005; 7: 774–777.
- 5 Anuradha P, Maiti R, Jyothirmai J, *et al.* Loratadine versus levocetirizine in chronic spontaneous urticaria: a comparative study of efficacy and safety. *Indian J Pharmacol* 2010; 42: 12–16.
- 6 Zuberbier T, Asero R, Bindslev-Jensen C, *et al.* EAACI/GA(2)LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; 64: 1427–1443.
- 7 Rath SK. Comparison of levocetirizine and cetirizine in chronic spontaneous urticaria. *Indian J Dermatol* 2004; 49: 130–131.
- 8 Gemenez-Arnau A, Pujol M, Lanosi S, *et al.* Rupatadine in the treatment of chronic spontaneous urticaria: a double-blind, randomized, placebo-controlled multicenter study. *Allergy* 2007; 62: 539–546.
- 9 Metz M, Maurer M. Rupatadine for the treatment of allergic rhinitis and urticaria. *Expert Rev Clin Immunol* 2011; 7: 15–20.
- 10 Keam SJ, Plosker GL. Rupatadine: a review of its use in the management of allergic disorders. *Drugs* 2007; 67: 457–474.
- 11 Kim H, Lynde C. Impact of desloratadine on symptoms and quality of life in subjects with chronic spontaneous urticaria: a multicenter, practice-based study. *Arch Drug Inf* 2008; 1: 63–69.
- 12 Yadav S, Upadhyay A, Bajaj AK. Chronic urticaria: an overview. *Indian J Dermatol* 2006; 51: 171–177.
- 13 Godse KV, Zawar V, Krupashankar D, *et al.* Consensus statement on the management of urticaria. *Indian J Dermatol* 2011; 56: 485–489.
- 14 Sugiura K, Hirai S, Suzuki T, *et al.* Evaluation of cetirizine hydrochloride-based therapeutic strategy for chronic urticaria. *Nagoya J Med Sci* 2008; 70: 97–106.
- 15 Curran MP, Scott LJ, Perry CM. Cetirizine: a review of its use in allergic disorders. *Drugs* 2004; 64: 523–561.
- 16 Patel P, Danzig M. Comparative efficacy and safety of loratadine and cetirizine in patients with chronic spontaneous urticaria. *Adv Ther* 1997; 14: 318–322.
- 17 Dubertret L, Zalupca L, Cristodoulo T, *et al.* Once-daily rupatadine improves the symptoms of chronic spontaneous urticaria: a randomized, double-blind, placebo-controlled study. *Eur J Dermatol* 2007; 17: 223–228.
- 18 Guerra L, Vincenzi C, Marchesi E, *et al.* Loratadine and cetirizine in the treatment of chronic urticaria. *J Eur Acad Dermatol Venereol* 2006; 3: 148–152.
- 19 David VK, Badyal DK, Varghese A, *et al.* Comparative effect of newer antihistamines on psychomotor functions in Indian population. *JK Science* 2010; 12: 15–18.
- 20 Vuurman E, Theunissen E, Oers A, *et al.* Lack of effects between rupatadine 10 mg and placebo on actual driving performance of healthy volunteers. *Hum Psychopharmacol* 2007; 22: 289–297.
- 21 Maiti R, Jaida J, Rahman J, *et al.* Olopatadine hydrochloride and rupatadine fumarate in seasonal allergic rhinitis: a comparative study of efficacy and safety. *J Pharmacol Pharmacother* 2011; 2: 270–276.
- 22 Maiti R, Rahman J, Jaida J, *et al.* Rupatadine and levocetirizine for seasonal allergic rhinitis a comparative study of efficacy and safety. *Arch Otolaryngol Head Neck Surg* 2010; 136: 796–800.
- 23 Mion OG, Campos RA, Antila M, *et al.* Futura Study. Evaluation of efficacy and safety of rupatadine fumarate in the treatment of persistent allergic rhinitis. *Braz J Otorhinolaryngol* 2009; 75: 673–679.
- 24 Katiyar S, Prakash S. Pharmacological profile, efficacy and safety of rupatadine in allergic rhinitis. *Prim Care Respir J* 2009; 18: 57–68.
- 25 Marmouz F, Giralt J, Izquierdo I. Morning and evening efficacy evaluation of rupatadine (10 and 20 mg), compared with cetirizine 10 mg in perennial allergic rhinitis: a randomized, double-blind, placebo-controlled trial. *J Asthma Allergy* 2011; 4: 27–35.
- 26 Church MK, Maspero JF, Maurer M, *et al.* The scope of pharmacological and clinical effects of modern antihistamines, with a special focus on rupatadine. Proceedings from a satellite symposium held at the 21st World Allergy Congress, Buenos Aires, December 8, 2009. *World Allergy Organ J* 2010; 3(Suppl. 4): S1–S16. doi:10.1097/WOX.0b013e31818dcf5d.