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Comparison of Efficacy, Safety and Cost-effectiveness of Rupatadine and Olopatadine in Patients of Chronic Spontaneous Urticaria: A Randomized, Double-blind, Comparative, Parallel Group Trial

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Abstract

Objective:

To compare efficacy, safety and cost-effectiveness of rupatadine and olopatadine in patients of chronic spontaneous urticaria.

Materials and Methods:

A 6-week, single-centered, randomized, double blind, parallel group comparative clinical study was conducted on patients with chronic spontaneous urticaria. Following inclusion and exclusion criteria, 60 patients were recruited and were randomized to two treatment groups and received the respective drugs for 6 weeks. At follow-up, parameters assessed were mean total symptom score (MTSS) calculated by adding the mean number of wheals (MNW) and the mean pruritus score (MPS), number of wheals, size of wheal, scale for interference of wheals with sleep (SIWS).

Results:

Both the drugs significantly reduced the MTSS, number of wheals, size of wheal, scale for interference of wheals with sleep, but olopatadine was found to be superior. In olopatadine group, there was significantly higher reduction in MTSS ($p = 0.01$), Number of wheals ($P < 0.05$), Size of wheals ($p < 0.05$), Scale for intensity of erythema ($p < 0.05$) and change in eosinophils count ($p = 0.015$) than that of rupatadine. Incidence of adverse effects was found to be less in olopatadine group when compared with rupatadine group. Cost effectiveness ratio was less in olopatadine group as compared to rupatadine group throughout the treatment.

Conclusions:

Olopatadine is a better choice in chronic spontaneous urticaria in comparison to rupatadine due to its better efficacy, safety and cost effectiveness profile.

Keywords: Chronic spontaneous urticaria, olopatadine, rupatadine

Introduction

What was known?

Rupatadine and olopatadine are the second generation H₁ receptor antagonist approved in treatment of chronic spontaneous urticaria (CsU). Olopatadine is recently approved for the treatment of chronic spontaneous urticaria. It has additional advantage over other drugs that it inhibits the release of inflammatory lipid mediators. Indian population is commonly affected by CsU. Patients have poor affordability for efficacious drug treatment of CsU. Hence, it was decided to provide better and improved cost effective treatment for CsU based on cost, efficacy and safety profile.

The prevalence of urticaria is estimated to occur in 15-23% of the population.[1,2] All types and subtypes of urticaria share a common distinctive skin reaction pattern like development of urticarial skin lesions and/or angioedema. Urticaria is mainly classified into spontaneous, physical and other urticarial types. Spontaneous urticaria is again subdivided in two types. Acute spontaneous urticaria having wheals and/or angioedema less than 6 weeks and chronic spontaneous urticaria (CsU) characterized by occurrence of daily itchy wheals and/or angioedema that last for at least 6 weeks.[3] CsU is a disease with a high burden for patients and high direct and indirect healthcare costs with large socio-economic implications.

CsU is evoked by release of histamine and other inflammatory mediators.[4] Second generation antihistaminics exhibit antiallergic activity by inhibiting late phase of allergic reaction by acting on leukotrienes (LTs) or by platelet activating factor(PAF) inhibition. Therefore, they do not have anticholinergic side effects and CNS depressant activity. Rupatadine is a novel selective long acting histamine H₁ receptor inverse agonist, currently approved in the treatment of CsU.[5,6] Rupatadine have a higher affinity for the H₁ receptor than fexofenadine and levocetirizine.[7] It has both antihistaminic and anti-platelet activating factor (PAF) property.[5] Olopatadine is selective histamine H₁ receptor-antagonist, recently approved for the treatment of CsU. It has additional advantage over other drugs that it inhibits the release of inflammatory lipid mediators.[8,9,10]

Indian population is commonly affected by CsU. As India is a developing country, patients have poor affordability for efficacious drug treatment of CsU. Hence, it was decided to provide better and improved cost effective treatment for CsU based on cost, efficacy and safety profile. Therefore, aim of present study was to study and compare rupatadine and the recently introduced olopatadine in the local population of Central India.

Materials and Methods

Sixty patients with CsU were enrolled in a prospective, double-blind, parallel, 6-week trial approved by the institutional ethics committee from February 2012 to October 2013. The trial procedure was designed in accordance with the ethical standards laid down by the Indian Council of Medical Research (ICMR) and Ethical Guidelines for Biomedical Research on Human Subjects. The trial is registered with CTRI under registration number CTRI/2014/04/004545. 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).

Patients with CsU were selected on the basis of their chief complaints and past history. The study inclusion criteria required participants to attend 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-h reflective) of ≥ 3 , MNW of ≥ 1 and MPS of ≥ 2 at screening and normal electrocardiogram (ECG) were included in the study. Only patients suffering from CsU were included in the trial. Patients using any

antihistamines other than rupatadine and olopatadine were included in the trial only after a washout period of 7 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, history of asthma or any other disease requiring the chronic use of inhaled or systemic corticosteroids, history of failure to respond to previous antihistaminic drug treatment, history of allergies to the study medication or tolerance to antihistamines, use of a study drug or topical corticosteroids in the previous 7 days, use of oral corticosteroids in the previous 8 weeks, use of parenteral corticosteroids in the previous 3 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.

Total 60 patients were selected after screening. There were 2 groups. One group received either rupatadine 10 mg or olopatadine 10 mg once a day. By considering power as 80%, significance level of 0.05, standard deviation of 0.9 and expected difference of 0.7 unit in MTSS, the calculated sample size came to be 27 in each group. So, the study sample size was rounded to sixty (30 patients in each group) considering future rate of drop outs. GRAPH PAD PRISM version 5.00 software was used for calculation of sample size and statistician of the institution assisted in the analysis of the data. The study drugs were already marketed. All the drugs were purchased by the investigator. A block randomization procedure was used for the random allocation of study drugs (i.e. rupatadine and olopatadine) with block sizes of four in equal proportions to ensure a uniform allocation ratio (1:1). As 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 the statistician using computer generated random number table.

The drugs (7, 14 and 21 tablets of rupatadine or olopatadine) were handed over in identical plastic containers to a third person who was not directly involved in this study. This person labelled the containers according to the random allocation sequencing of the 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, patients and the investigators were unaware of the treatment administered. Drugs were issued to patients for a period of 1 week at 1st visit, for 2 weeks at 2nd visit and at the end of the third week. Patients were asked to bring any unused drug and empty containers at follow-up periods. Patient compliance was determined by counting the numbers of unused tablets.

Clinical assessment of patients was done by the principal investigator and the consultant dermatologist. Patients were instructed to count number of wheals at first visit and at the same time the crosschecking for the same was done by principal investigator and the consultant dermatologist. Measurement for size of wheal was done by principal investigator with measuring tape. For this measurement, the largest wheal on the body was chosen and the greatest diameter was considered for size of wheal and then categorized accordingly. Scale for intensity of erythema was noted according to colour of the wheal, the higher scale was taken when intensity of erythema varied between two wheals. Scale for extent of skin area involved (SESI) was calculated by the 'rule of 9' (used for calculation of burn percentage) and graded accordingly to the body surface area involved.

For cost-effectiveness analysis, only direct cost parameters were taken into consideration. Direct cost parameters were cost of medications used, medical procedures, and hospitalization charges, if any. Cost-effectiveness ratio of both treatment group was calculated based on formula as given below.

Cost-effectiveness ratio = Cost/outcome

Outcome was measured in terms of effectiveness. MTSS parameter was the main effectiveness parameter.

Laboratory investigations like total leukocyte count (TLC), differential leukocyte count (DLC), blood urea, serum creatinine, SGOT, SGPT, serum bilirubin and serum alkaline phosphate were carried out in the department of pathology and department of biochemistry. Laboratory investigations were carried out at 0 week for screening and at the end of study for assessment of safety of the investigational drugs.

Statistical analysis Statistical analysis was done in consultation with statistician of the institute. Results

were expressed as mean(SD). Analysis was done as “per-protocol analysis” group difference were ascertained by Mann-Whitney rank sum test or unpaired ‘t’ test. Difference within group were compared by Wilcoxon test or paired ‘t’ test or Friedman test with Dunn’s multiple comparison *post-hoc* test. Two-tailed *p* value of less than 0.05 was considered as statistically significant. GRAPH PAD PRISM version 5.00 software was used for statistical analysis.

Results

A total of sixty patients were randomized and allocated to the treatment, out of which fifty five patients completed the study according to the protocol [Figure 1]. Five patients lost to follow up at the end of 1st week of the study, three in rupatadine group and two in olopatadine group. The percentage of female patients was relatively more than male patients, 66.66 in rupatadine group and 57.14 in olopatadine group. Both the groups were comparable and there was no statistically significant difference between two groups at baseline [Table 1].

Evaluations of MTSS, MNW and MPS revealed statistically significant differences at week 1, 3 and 6 weeks compared with pre-treatment levels in the rupatadine group. Reductions in these parameters first became apparent and were significant by the first and third week ($p < 0.05$); these improvements were maintained to the sixth week of treatment in rupatadine group [Table 2]. Similar results were obtained with olopatadine, but the reductions in these parameters were greater in this group compared to rupatadine group. No significant differences in these parameters between the 1, 3 and 6-week time-points were observed in either group.

To test whether treatment with olopatadine was more successful than that with rupatadine in resolving symptoms, we compared the effects of the drugs in both groups after 6 weeks of treatment, taking into consideration any change from baseline values in the study parameters. The reductions at 6 weeks in the MTSS, MNW and MPS were significantly ($p < 0.05$) greater in the olopatadine group compared with rupatadine group [Table 3]. It revealed no statistically significant difference in mean change of SIWS and SESI at baseline and 6th week in rupatadine group and olopatadine group. But the statistical difference was observed in mean change of number of wheals, size of wheals and scale for intensity of erythema at baseline and 6 week in rupatadine group and olopatadine group [Table 4].

A significant reduction in eosinophil count was observed with olopatadine in comparison with rupatadine [Table 4]. 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 olopatadine group. Overall incidences of adverse effects were 37% and 21% in the rupatadine and olopatadine groups, respectively. 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 was observed during the trial. Comparison of cost-effectiveness ratio of both rupatadine and olopatadine group was done at 1st, 3rd and 6th week. Table 5 shows the cost-effectiveness ratio in both groups at 1st, 3rd and 6th week. The treatment modality having less cost-effectiveness ratio is considered as superior. Thus, it was found that the olopatadine group remains cost-effective throughout the treatment despite having more cost per tablet than rupatadine.

Discussion

Chronic spontaneous urticaria is one of the most common skin diseases, defined as itchy hives that last for at least 6 weeks, with or without angioedema and that have no apparent external trigger. The condition generally has a prolonged duration of one to five years and has a detrimental effect on patients’ emotional, physical and health-related quality of life.[11] Approximately 50% of urticaria patients do not respond to treatment with standard doses of non-sedative antihistamines and require a heavier dose of antihistamines. Treating the symptoms of CsU and ensuring a better quality of life to the patients is challenging to the physicians. Increasing understanding of patho-physiologic mechanism in the last few decades has revealed the potential of the newer generation antihistaminic in the treatment of CsU.[12] Rupatadine and olopatadine have already proved the benefit of their better safety and efficacy profile individually in patient

of CsU. Our in-depth search and review of literature failed to retrieve any data comparing the efficacy, safety and cost effectiveness of these drugs. Thus, to the best of our knowledge, this is the first study in CsU to compare their efficacy, safety and cost effectiveness and thus to choose the best agent.

The baseline data shows no significant difference between the study groups with respect to the demographic and clinical parameters. This proves the homogeneity of our study subjects in the two groups. We found that CsU is more common in females. This observation is in correspondence with the previous studies.[13,14,15,16,17,18]

The mean total symptom score is a widely accepted and reliable tool to assess the efficacy of a drug in the treatment of urticaria and a decrease in the scoring suggests that there is an overall clinical improvement in the condition.[19] We observed significant difference in parameters such as MNW, MPS and MTSS after completion of the treatment in rupatadine as well as olopatadine group. No rescue medication was needed in any of the patient. In the present trial, progressive decrease in all the above scores were observed with the increase in duration of treatment. However, no significant difference was observed with rupatadine and olopatadine when these parameters were compared between one, three and six weeks within group. Significant decrease was observed in MNW and MPS after six weeks treatment with rupatadine[20,21] and olopatadine.

The probable superiority of olopatadine over rupatadine may be attributed to the following findings. Olopatadine can reduce the amount of cell-associated PAF by 52.8%, which is more than rupatadine.[8] PAF is known to increase vascular permeability and is increasingly recognized as an important mediator in inflammation. It also suppresses LTs and TXA₂ release and PAF formation by reducing arachidonic acid release from membrane phospholipids, probably through interference with phospholipase A₂ (PLA₂).[22] Olopatadine has shown to suppress the activity of S100A12 which is a member of the S100 family of calcium-binding proteins and exerts multiple pro-inflammatory activities including chemotaxis for monocytes and neutrophils.[23] All these actions inhibit the inflammatory mediators which are the main contributors for vasodilation, vascular leakage, wheal formation, pruritus and eosinophil chemotaxis. Thus, olopatadine decreases the symptoms of urticaria by reducing number of wheals, pruritus scale etc., more significantly as compared to rupatadine. Other major findings of this study are reduction in SIWS, size of wheals, scale for intensity of erythema and scale for extent of skin area involved between baseline and six weeks within rupatadine and olopatadine group. We revealed significant change in size of wheals, scale for intensity of erythema and scale for extent of skin area involved with rupatadine supporting the previous study.[20] Difficulty occurred with olopatadine, as there is no study comparing parameters like size of wheals, scale for intensity of erythema and scale for extent of skin area involved. Therefore, it was not possible to compare the result of present study with previous study. Hence, the present study is unique in comparing outcomes in these parameters for both drugs.

We found no difference between differential basophil count, differential monocyte count, biochemical parameters (SGOT, SGPT, serum bilirubin, alkaline phosphatase, serum creatinine and blood urea) with rupatadine and olopatadine both. Our study with rupatadine and olopatadine support the finding of decrease in TLC, differential neutrophil count, differential eosinophil count and revealed no significant difference in differential monocyte count and differential basophil count.[24] We did not find any significant change in biochemical parameters. This observation supports previous study on safety analysis of rupatadine and olopatadine.[24,25]

Sedation was the most frequently occurring adverse event with rupatadine, which supports previous studies conducted on rupatadine for its safety profile. Other adverse events noted were headache, gastric irritation and dryness of mouth. Most frequently occurring adverse event with olopatadine was sedation, which supports this finding with previous study, but number of events was less than rupatadine.[25,26] Our study did not find any change in ECG, supporting the previous studies which also showed no change in ECG findings.

To compare the cost-effectiveness of two drugs, we have taken into consideration the direct health cost of the drug treatment only. When we compare the cost-effectiveness ratio of the treatment i.e. rupatadine and olopatadine, we found that cost-effectiveness ratio was less in olopatadine throughout the treatment of CsU

i.e. from baseline to 1st week, 3rd week and 6th week. For pharmacoeconomic analysis, treatment modality having less cost-effectiveness ratio is considered as superior. Although, the cost of per tablet of olopatadine is more than rupatadine, difference in outcome/effectiveness i.e. MTSS, was more in olopatadine as compared to rupatadine from baseline to 6th week treatment. Thus, it suggests that olopatadine is cost-effective over rupatadine for the treatment of CsU. However, after in-depth search, we couldn't find any studies related to our finding, as there were no cost-effective studies done before between rupatadine and olopatadine group in patients of CsU. Hence, our results could not be compared with other studies. Although the present study was double-blind with small sample size and was of short duration, the value of its result cannot be ignored. However, studies with larger sample size and longer follow-up periods, along with measurement of absolute eosinophil count, may yield more meaningful data to compare rupatadine and olopatadine.

Conclusion

Treatment with olopatadine 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 olopatadine is a particularly attractive cost effective therapeutic modality compared with rupatadine for the treatment of CsU.

What is new?

The data of comparison of rupatadine and olopatadine in CsU based on cost, efficacy and safety profile is not available. Therefore, the present study was undertaken to compare the rupatadine and the recently introduced olopatadine in the local population of Central India and to find the most cost effective treatment in patients having poor affordability. Treatment with olopatadine was well tolerated with minimum side-effects. Olopatadine is a particularly attractive cost effective therapeutic modality compared with rupatadine for the treatment of CsU.

Footnotes

Source of Support: Nil

Conflict of Interest: Nil.

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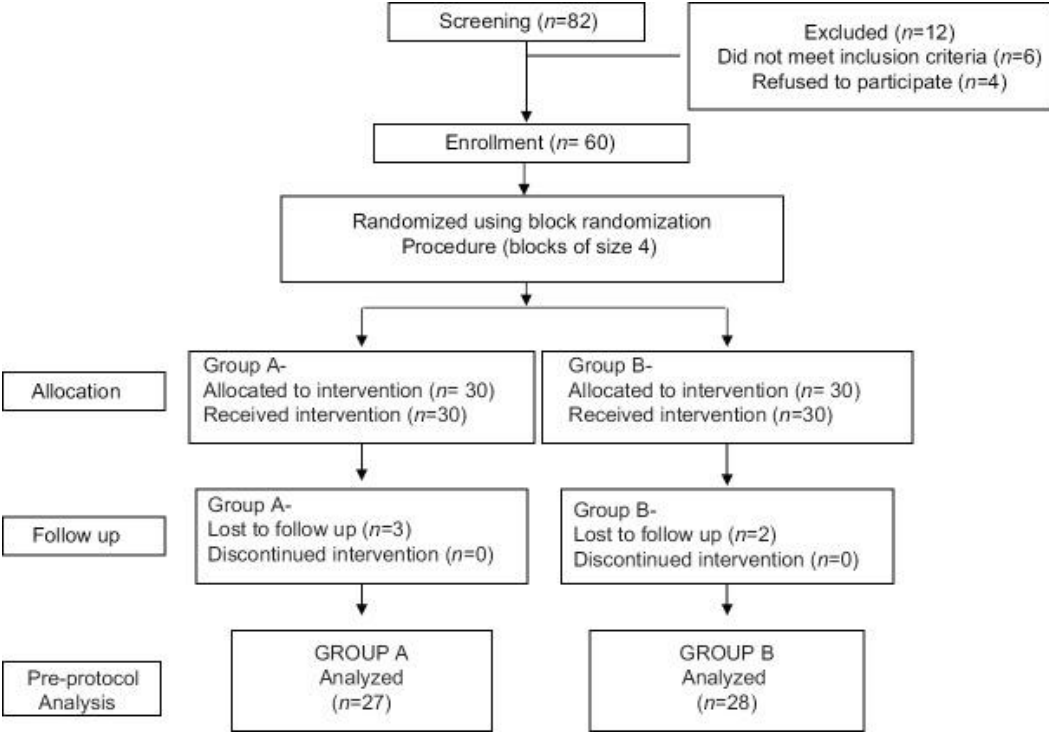
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Figures and Tables

Figure 1



Flowchart of the study

Table 1

Characteristic	Rupatadine group	Olopatadine group	p value
patients recruited, <i>n</i>	30	30	
patients at follow-up, <i>n</i>	27	28	
Age (years)	39.44 (6.65)	38.78 (8.04)	0.74 [‡]
Male: Female ratio	33.33:66.65	42.86:57.14	
Height (centimeters)	159.93 (4.98)	157.45 (4.83)	0.079 [‡]
Weight (kilogram)	62.55 (4.71)	61.21 (5.84)	0.35 [‡]
Duration of lesion (months)	5.52 (2.54)	5 (1.83)	0.34 [‡]
TLC	8422 (1325.4)	8232.1 (952)	0.73 [#]
Neutrophils (%)	62.18 (5.3)	62.857 (4.90)	0.49 [#]
Lymphocytes (%)	29.63 (5.90)	29.75 (5.70)	0.87 [#]
Eosinophils (%)	6.88 (1.76)	6.75 (1.55)	0.58 [#]
Monocytes (%)	0.74 (0.85)	0.85 (1)	0.79 [#]
Basophils (%)	0.55 (0.72)	0.53 (0.79)	0.81 [#]

Values are expressed as mean (SD), [‡](Unpaired 't' test), [#](Mann-Whitney rank sum test), SD: Standard deviation, TLC: Total leukocyte count, CsU: Chronic spontaneous urticaria

Baseline demographic data and clinical characteristics of CsU patients

Table 2

Parameter	Baseline	Mean±SD			d.f	P value
		At 1st weeks of treatment	At 3 weeks of treatment	At 6 weeks of treatment		
Rupatadine group (n=27)						
MTSS	6.33 (0.96)	3 (0.61)*	2.64 (0.76)*	2.38 (0.48)*	3,105	<0.001
MNW	3.26 (0.65)	1.68 (0.55)*	1.31 (0.51)*	1.20 (0.40)*	3,105	<0.001
MPS	3.07 (0.67)	1.33 (0.66)*	1.33 (0.42)*	1.18 (0.31)*	3,105	<0.001
Olopatadine (n=28)						
MTSS	6.60 (0.92)	2.05 (0.96)*	1.94 (0.91)*	1.5 (0.76)*	3,109	<0.001
MNW	3.28 (0.66)	1.03 (0.56)*	0.85 (0.32)*	0.69 (0.61)*	3,109	<0.001
MPS	3.32 (0.55)	1.01 (0.67)*	1.08 (0.75)*	0.80 (0.43)*	3,109	<0.001

Values are expressed as mean (SD), Non parametric Friedman test with Dunn's multiple comparison post hoc test. *P <0.001 compared to baseline, d.f: Degree of freedom, MTSS: Mean total symptom score, MNW: Mean number of wheals, MPS: Mean pruritus score, SD: Standard deviation

Mean total symptom score, mean number of wheals and mean pruritus score at baseline and at 1 week, 3 weeks and 6 weeks after the initiation of treatment with rupatadine or olopatadine in patients with chronic spontaneous urticaria

Table 3

Parameter	Change from baseline at 6 th weeks	
	Rupatadine	Olopatadine
MNW	−2.07 (0.76)	−2.66 (0.80)*
MPS	−1.88 (0.71)	−2.51 (0.68)**
MTSS	−3.94 (0.96)	−5.10 (1.25)**

Values are expressed as mean (SD), Mann-Whitney rank sum test.
P* <0.05 compared to rupatadine group, *P* <0.01 compared to rupatadine group, MTSS: Mean total symptom score, MNW: Mean number of wheals, MPS: Mean pruritus score, CsU: Chronic spontaneous urticaria

Comparison of effects of rupatadine and olopatadine on mean difference in MNW, MPS and MTSS at 6th weeks in CsU patients taking into account the change from baseline

Table 4

Parameter	Rupatadine group (n=27)		Olopatadine group (n=28)		P value ^a
	Baseline	6 th week	Baseline	6 th week	
SIWS	3.03 (0.59)	1.03 (0.93)***	3 (0.67)	0.53 (0.63)***	>0.05
Number of wheals	2.92 (0.72)	1.29 (0.91)***	3.03 (0.79)	0.64 (0.62)***	<0.05
Size of wheals	3.14 (0.36)	1.25 (0.83)**	3.07 (0.60)	0.75 (0.75)***	<0.05
Scale for intensity of erythema	3 (0.62)	1.51 (0.7)**	2.96 (0.57)	0.92 (0.76)***	<0.05
SESI	2.29 (0.64)	2.03 (0.65)***	2.96 (0.57)	0.89 (0.78)***	>0.05
TLC	8422.06 (1325.71)	8174.23 (1017.09)*	8232.1 (786.29)	7892.49 (920.86)**	>0.05
N (%)	62.18 (5.3)	61.11 (5.86)	62.85 (4.90)	60.89 (4.54)**	>0.05
L (%)	29.63 (5.90)	31.88 (6.51)*	29.75 (5.70)	33.59 (4.44)***	>0.05
E (%)	6.9 (1.87)	5.81 (1.85)*	6.75 (1.55)	4.03 (1.34)***	<0.05
M (%)	0.74 (0.85)	0.85 (0.81)	0.857 (1.00)	0.92 (0.97)	>0.05
B (%)	0.55 (0.72)	0.55 (0.80)	0.53 (0.79)	0.60 (0.73)	>0.05

Values are expressed as mean (SD), Wilcoxon test. * $P < 0.05$ compared to baseline. ** $P < 0.01$ compared to baseline. *** $P < 0.001$ compared to baseline. ^aWilcoxon test, comparison of the mean difference between scores at baseline and at 6 weeks in the two groups, TLC: Total leukocyte count, CsU: Chronic spontaneous urticaria, SIWS: Scale for interference of wheals with sleep, SESI: Scale for extent of skin area involved

Comparison of effects of rupatadine and olopatadine on SIWS, number of wheals, size of wheals, scale for intensity of erythema, SESI and on laboratory parameters in CsU patients taking into account the change from baseline

Table 5

	Rupatadine	Olopatadine
Cost-effectiveness ratio at 1 st week	11.08	9.53
Cost-effectiveness ratio at 3 rd week	29.91	28.38
Cost-effectiveness ratio at 6 th week	55.78	50.98

Comparison between cost-effectiveness of both rupatadine and olopatadine group at the end of 1st, 3rd and 6th week

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