Original Article

Comparative study of efficacy and safety of cetirizine and bilastine in patients of chronic spontaneous urticaria: Open-label, randomized, parallel-group study

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Abstract

Purpose: Bilastine is a novel second-generation antihistaminic. Very few studies in Indian population have compared the safety and efficacy of bilastine with other second-generation antihistaminic like cetirizine. Hence, the present study was planned.

Materials and Methods: This was a randomized, open-label comparative parallel group study conducted on 70 patients of chronic spontaneous urticaria (CSU). Patients either received cetirizine 10 mg or bilastine 20 mg once daily for 6 weeks. The primary endpoint was to find out the difference in the mean total symptom score (MTSS) at baseline and 6 weeks. The secondary endpoint was to find out changes in the scale of the number of wheals, change in pruritus scale, scale for size of wheal, change for interference of wheals with sleep, change in visual analog scale (VAS) for sedation, change in scale for intensity of erythema, and change in Scale for Extent of Skin Area Involvement (SESI).

Results: Bilastine and cetirizine offer a significant reduction in MTSS, mean number of wheals, and mean pruritus scale at baseline to 1, 3, and 6 weeks. The mean difference in MTSS was significantly more in bilastine. Cetirizine showed a significant increase in VAS score for sedation as compared to bilastine. Both the drugs were well tolerated and safe. Adverse events like headache, gastric irritation, dryness of mouth, and sedation were more reported in cetirizine group.

Conclusion: Bilastine was more efficacious than cetirizine in patients of CSU and the efficacy was seen earlier at 1 week, which was not seen in the cetirizine group.

Keywords: Bilastine, cetirizine, chronic spontaneous urticaria, urticaria

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INTRODUCTION

Chronic urticarial and chronic idiopathic urticaria now known as chronic spontaneous urticaria (CSU) is defined as daily or near-daily episodes of urticaria for more than 6 weeks.[1] CSU is known to be the most common form of urticaria (66% to 93% of cases).

Urticaria can be classified into spontaneous, physical, and other urticaria types. Spontaneous urticaria is further

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divided into acute and CSU, the lesions usually occur without an obvious stimulus and is considered idiopathic primarily.[2-4] Patients with urticaria report impaired quality of life which has a detrimental effect on patient's sleep and affect their daily activities.[5] It also has a large impact on society in terms of direct and indirect healthcare costs, resulting in a huge socioeconomic burden.

The pathogenesis of CSU is yet to be fully characterized. It is thought to be mediated by the aberrant release of histamine and other inflammatory mediators from mast cells and basophils.[1]

The mainstay of therapeutic options is aimed at symptomatic relief of urticaria by antagonizing the specific actions of H1-receptor-mediated histamine actions upon endothelial cells and on sensory nerves producing wheal and pruritus. The first-generation antihistamines have potent anticholinergic effects and sedative actions on the central nervous system (CNS) lasting longer than 12 h and are therefore not preferred. The recommended first-line treatment is second-generation, nonsedating H1-antihistamines[6] like cetirizine, loratadine, and fexofenadine which were extensively evaluated in the management of urticaria for safety and efficacy even up to a four-fold elevation of the standard doses.[1]

Bilastine is a novel second generation H1 antihistamine , used for the symptomatic treatment of CSU approved in 2019 by the Drugs Controller General of India. Bilastine has high specificity and affinity for the H1 receptor ,which is 3–6 times higher than cetirizine and fexofenadine.[7] It has a rapid onset of action (60 min) and a long duration (24 h) of effect. A study by Zuberbier *et al*. confirms that a therapeutic dose of bilastine 20 mg is a novel effective and safe treatment option for the management of symptomatic patients with CU.[8]

Bilastine is said to have a similar safety and tolerability profile as other new H1 antihistamines.[7]

To date, there are very few studies in the Indian population comparing the safety and efficacy of bilastine with second-generation antihistaminic[7] like cetirizine.

Hence, the present study was planned to assess and compare the efficacy and safety of bilastine and cetirizine in patients of CSU.

MATERIALS AND METHODS

Study design

The present study was a randomized, open-label comparative parallel-group study conducted on 70 patients of CSU after approval of the institutional ethics committee. This trial was registered with the Clinical Trial Registry of India (CTRI/2020/05/025031). Seventy patients were divided into two groups of 35 each to receive either cetirizine 10 mg or Bilastine 20 mg once daily for 6 weeks. Both the drugs were provided by the principle investigator and no financial burden was borne by the patients.

Patients attending the skin outpatient department (OPD) were screened and diagnosed by dermatologists. The patients fulfilling the inclusion criteria were briefed about the nature and purpose of the study. The patient's information sheet was given to all prospective participants and written informed consent was obtained.

Patients satisfying the following inclusion and exclusion criteria were included in the study.

Subjects aged 18–65 years, either gender, giving a history of urticarial wheal for at least 3 days a week for 6 consecutive weeks with no obvious cause prior to inclusion in the study, and a mean total symptom score (MTSS) (24 h reflective) ≥3 at screening were included in the study. This includes 1–5 number of wheal (score ≥1) at least a moderate severity of pruritus (score = 2).

Subjects with acute urticaria, history of asthma, hematopoietic, cardiovascular, hepatic, renal disorder, neurological and autoimmune diseases requiring chronic use of corticosteroids, or allergies to study medication, subjects on concomitant drug therapy like antihistamines, CNS depressants, and pregnant and nursing mothers were excluded from the study.

- Primary endpoints
  1. Difference in the MTSS at baseline and 6 weeks.
- Secondary endpoints
  1. Changes in scale of number of wheals
  2. Change in pruritus scale
  3. Change in scale for size of wheal
  4. Change for interference of wheals with sleep
  5. Change in visual analog scale (VAS) for sedation
  6. Change in scale for intensity of erythema
  7. Change in scale for extent of skin area involvement (SESI).

Calculation of the sample size

The sample size was calculated using the level of significance α = 5% and power 80%. A difference of 0.7 units in MTSS, assuming a standard deviation (SD) of 0.9 was taken from the previous study conducted. The calculated sample size was 31 in each group. Hence, the

total sample size was rounded to seventy (35 patients in each group) considering the future rate of dropouts.[9]

PS FOR SAMPLE SIZE software was used for the calculation of sample size.

Laboratory investigations like total leukocyte count (TLC), differential leukocyte count, blood urea, serum creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), serum bilirubin, and serum alkaline phosphatase were carried out at 0 weeks for screening and at the end of the study for assessment of safety of the investigational drugs. Patients were asked to come to the OPD for follow-up, subject diary assessment, and receive the medication 1, 3, 6 weeks after screening. Clinical assessment of the patients was done by the principal investigator and the consultant dermatologists for the number of wheals and other parameters at each visit.

Recording the parameters like scale for the number of wheals, pruritus scale, scale for the interference of wheals with sleep (SIWS), and VAS for sedation was done by the patient.[9]

Safety assessment

General clinical safety was monitored by vigilant follow-up of patients for the treatment of emergent adverse events, if any, and recorded in the case report form.

Statistical analysis

Results were expressed in mean (SD). Group difference was determined by the Mann–Whitney rank sum test or unpaired *t*-test. The difference within the group was compared by the Wilcoxon test or paired *t*-test or Friedman test with Dunn's multiple comparison *post hoc* test. A two-tailed $P < 0.05$ was considered statistically significant. GRAPH PAD PRISM VERSION 8.4.2 software (Glenmark Pharmaceuticals, Nagpur, Maharashtra, India) was used for statistical analysis.

RESULTS

A total of 70 patients were randomized and allocated to the treatment, out of which sixty-three completed the study (31 in cetirizine group and 32 in bilastine group). The data were analyzed in accordance with the per-protocol analysis. The mean duration of lesions of CSU patients in cetirizine group and bilastine group was 7.00 and 7.15, respectively, at the baseline.

The percentage of females in cetirizine group was 57.14%, and in bilastine, the group was 60%. Both groups were comparable and there was no statistically significant difference between the two groups at baseline. No significant difference between the groups, in parameters such as Mean Number Of Wheals (MNW), Mean Pruritus Scale (MPS), Mean Total Symptoms Score (MTSS), and Scale for Interference of Wheals with Sleep (SIWS), the number of wheals, size of wheals, the intensity of erythema and Scale for Extent Of Skin Area Involved (SESI) was seen at the baseline. When MNW score was compared at baseline, 1 week, 3 week and 6 week we found significant difference in cetirizine and bilastine group

When a comparison of the mean difference in MNW score in cetirizine and bilastine groups was done, MNW was reduced significantly in bilastine group as compared to cetirizine group at baseline, 3 weeks, and 6 weeks.

The MPS done at baseline, 1 week, 3 weeks, and 6 weeks, revealed significant differences within both the groups. When a comparison of the mean difference in MPS score in both the groups was done, no significant reduction was seen in both.

With the sum of scores of MNW and MPS, MTSS was calculated. A significant difference was revealed at baseline to 1, 3, and 6 weeks within cetirizine and bilastine group [Table 1]. The mean difference in MTSS in cetirizine and bilastine groups at baseline and 1 week, baseline and 3 weeks, and baseline and 6 weeks showed a significant reduction in bilastine group compared to cetirizine group at all the three intervals [Table 2].

Changes in SIWS and VAS for sedation were according to the patient's diary assessment, while the number of wheals, size of wheals, the scale of intensity of erythema, and SESI were according to the principal investigator assessment. We observed a significant reduction in SIWS, the number of wheals, size of wheals, and scales for the intensity of erythema and SESI at baseline and 6 weeks within cetirizine groups as well as within bilastine group.

Table 1: Comparison of mean total symptoms score in chronic idiopathic urticaria patients in cetirizine and bilastine group (*n*=63)

Interval (weeks)	Cetirizine group (*n*=31)	*P*	Bilastine group (*n*=32)	*P*
Baseline	6.44 (0.80)	-	6.43 (0.92)	-
1	5.21 (0.49)*	0.0137	4.68 (0.75)*	0.022
3	4.13 (0.61)****	<0.0001	3.28 (0.69)****	<0.0001
6	2.39 (0.71)****	<0.0001	1.83 (0.59)****	<0.0001

*$P<0.05$, ****$P<0.0001$. Values are expressed as mean (SD). Nonparametric Friedman test with Dunn's multiple comparison *post hoc* test. SD=Standard deviation. MTSS in the cetirizine group and bilastine group at baseline 1, 3, and 6 weeks. A significant difference was revealed at baseline to 1, 3, and 6 weeks within the cetirizine and bilastine groups

VAS score for sedation showed a significant increase at 6 weeks compared to baseline in cetirizine group [Table 3].

The mean difference in SIWS, the number of wheals, size of wheals, the scale for the intensity of erythema, SESI, and VAS for sedation in cetirizine group and bilastine group at baseline and 6 weeks revealed no statistically significant difference in mean change of size of the wheal, the intensity of erythema and SESI at baseline and 6 weeks in cetirizine group and bilastine group. However, the significant results were observed in mean change SIWS, the number of wheals, and VAS for sedation at baseline and 6 weeks in cetirizine group and bilastine group [Table 4].

There was a significant difference in total leukocyte counts and eosinophil counts from baseline to 6 weeks ($P \leq 0.0001$) in both groups. Basophil counts were reduced significantly in cetirizine group ($P \leq 0.0001$) from baseline to 6 weeks and monocytes were reduced significantly in bilastine group ($P = 0.0033$) from baseline to 6 weeks. When bilastine group was compared to cetirizine group for mean difference in monocytes and basophil count from baseline to 6 weeks, a significant reduction in monocytes ($P = 0.042$) and basophil ($P \leq 0.0001$) was seen in bilastine group.

An adverse event was noted in 13 patients taking cetirizine and four patients taking bilastine. The most common adverse event was sedation, found in eight patients in the cetirizine group and two patients in the bilastine group. Other adverse events were headache, gastric irritation, and dryness of mouth which was more in the cetirizine group. We revealed no change in electrocardiogram (ECG) of any patient between baseline to 6 weeks in both cetirizine group and bilastine group.

Table 2: Comparison of mean total symptoms score in chronic idiopathic urticaria patients in cetirizine and bilastine group (*n*=63)

Interval (weeks)	Cetirizine group (*n*=31)	Bilastine group (*n*=32)	*P*
Baseline and 1	−1.22 (0.74)	−1.74 (0.74)**	0.0021
Baseline and 3	−2.30 (0.96)	−3.14 (1.02)**	0.0020
Baseline and 6	−4.06 (0.94)	−4.59 (0.98)*	0.0344

*$P<0.05$, **$P<0.01$. The mean difference in MTSS in the cetirizine and bilastine group at baseline and 1 week, baseline and 3 weeks, baseline, and 6 weeks MTSS were reduced significantly in the bilastine group compared to the cetirizine group at all three intervals

DISCUSSION

The most common approach in treating CSU conditions is to prevent the release of histamine or to block its effect at the receptor sites on nerves and endothelial cells.

Therefore, the first line of management of CSU is the use of H1 antihistamines. The potential of newer generation antihistamines in the treatment of CSU is more so to be the mainstay of treatment of this condition.

Cetirizine and bilastine have proved to be more effective in CSU in several clinical trials. Very few studies have been done where cetirizine is compared to bilastine for CSU. Furthermore, bilastine got recently approved for allergic rhinitis and CSU in India (2019), so this study was taken up.

The duration of our study was 6 weeks following internationally accepted standards and guidelines for conducting efficacy studies in CSU. The baseline data show no significant difference between the study groups with respect to demographic and clinical parameters. This proves the homogeneity of our study subjects in the two groups. The number of women in our study was more as compared to men showing CSU is more common in females. Around 60% of the sample size in both groups was female. This same observation corresponds to various previous studies on CSU.[10]

The primary endpoint of our study was to observe differences in the MTSS at baseline and 6 weeks.

Table 3: Comparison in scale for the interference of wheals with sleep, number of wheals, size of wheals, the scale for the intensity of erythema, scale for extent of skin area involvement and visual analog scale for sedation at baseline and 6 weeks

Parameter	Cetirizine group (*n*=31)			Bilastine group (*n*=32)		
	Baseline	6 weeks	*P*	Baseline	6 week	*P*
SIWS	2.43 (0.49)	1.30 (0.60)****	<0.0001	2.62 (0.33)	0.95 (1.09)****	<0.0001
Numbers of wheals	3.16 (0.48)	1.42 (0.48)****	<0.0001	3.07 (0.57)	1.02 (0.41)****	<0.0001
Size of wheals	2.87 (0.80)	1.16 (0.45)****	<0.0001	2.62 (0.60)	0.93 (0.24)****	<0.0001
Scale for the intensity of erythema	2.41 (0.50)	1.00 (0.25)****	<0.0001	2.56 (0.50)	0.93 (0.24)****	<0.0001
SESI	2.41 (0.50)	1.00 (0.25)****	<0.0001	2.53 (0.50)	0.93 (0.24)****	<0.0001
VAS for sedation	18.07 (7.54)	21.93 (4.96)**	0.0012	17.79 (6.25)	17.23 (6.67)	0.0720

**$P<0.01$, ****$P<0.0001$. Values are expressed in mean (SD). Wilcoxon test. VAS=Visual analog scale, SIWS=Scale for the interference of wheals with sleep, SESI=Scale for extent of skin area involvement, SD=Standard deviation. There is a significant reduction in SIWS, the number of wheals, size of wheals, and scale for the intensity of erythema and SESI at baseline and 6 weeks within the cetirizine groups as well as within Bilastine group. VAS for sedation showing a significant increase at 6 weeks compared to baseline was observed only in the cetirizine group

Table 4: Comparison of mean difference in scale for the interference of wheals with sleep, number of wheals, size of wheals, the scale for the intensity of erythema, scale for extent of skin area involvement and visual analog scale for sedation at baseline and 6 weeks

Parameter	Cetirizine group	Bilastine group	*P*
SIWS	−1.13 (0.65)	−1.86 (0.61)****	<0.0001
Numbers of wheals	−1.73 (0.53)	−2.05 (0.57)*	0.0374
Size of wheals	−1.71 (0.69)	−1.62 (0.70)	0.7489
Scale for the intensity of erythema	−1.41 (0.56)	−1.62 (0.55)	0.1510
SESI	−1.41 (0.56)	−1.59 (0.61)	0.2719
VAS for sedation	+3.85 (6.28)	0.56 (1.94)****	<0.0001

*P value less than 0.05 ($P<0.05$) was considered as statistically significant. ****$P<0.0001$. Values are expressed as mean (SD). Mann–Whitney rank sum test. VAS=Visual analog scale, SIWS=Scale for the interference of wheals with sleep, SESI=Scale for extent of skin area involvement, SD=Standard deviation. There is no statistically significant difference in the mean change of size of the wheal, intensity of erythema, and SESI at baseline and 6 weeks in cetirizine group and bilastine group. But the significant results were observed in mean change SIWS, number of wheals, and VAS for sedation at baseline and 6 weeks in cetirizine group and bilastine group

It was observed that there was a significant difference from baseline to 1, 3, and 6 weeks in cetirizine as well as bilastine group, however when the two groups were compared for the mean difference of MTSS score there was a statistically significant difference seen at 1 week 3 week and 6 weeks in bilastine group as compared to cetirizine group. In week 1 itself, we observed a significant difference in MTSS in the bilastine group. This shows that the relief of symptoms was earlier in bilastine group as shown by the reduction in the number of wheal and pruritus scores at 1 week. The finding of our study was consistence with the study of Zuberbier *et al*. where bilastine reduced patients' mean reflective and instantaneous Total symptom score (TSS) from baseline to a significantly greater degree than placebo ($P < 0.001$); from day 2 onwards of treatment.[8]

In a study done by Patel and Danzig, cetirizine significantly reduced the number of wheals, size of the wheals, number of urticaria episodes, and severity of pruritus more effectively than placebo.[11]

The results of our study revealed a significant reduction in SIWS, number of wheals, size of wheals, the scale for the intensity of erythema, and SESI at baseline and 6 weeks within cetirizine group as well as in bilastine group. When bilastine group was compared to cetirizine group for SIWS and the number of wheal score significant reductions in the scores found in bilastine group ($P \leq 0.0001$). Despite extensive literature search, we could not find any study comparing cetirizine and bilastine in terms of the difference in SIWS and the number of wheal.

The mean difference in MNW was found as early as week 1 in the bilastine group when compared to cetirizine group. A phase 1, double-blind, randomized, placebo-controlled, single oral dose, cross-over study compared the antihistaminic effects of bilastine, cetirizine, and placebo against histamine-induced wheal and flare responses, over periods of 24 h, in 21 healthy male volunteers. The authors found no significant differences between overall inhibitions of wheal or flare in bilastine and cetirizine group but bilastine was faster in the onset of action than cetirizine. At 1.5 h, both wheals and flares were inhibited by 70% in 11/12 volunteers taking bilastine and 3/11 taking cetirizine ($P = 0.003$).[12]

The findings of our study show that sedation was more in the cetirizine group as compared to bilastine at week 6 and the difference was statistically significant. We used a VAS for sedation. It showed a significant increase in sedation at 6 weeks when compared to baseline only in cetirizine group. Systemic administration of antihistamines may more frequently associate with their well-known side-effect, sedation, which is more common with first-generation antihistamines.[13]

This finding was in line with a study by Reményi *et al*. which was a comparative study of the effect of bilastine and cetirizine on cognitive functions. Concerning somnolence, in our study, we observed only 2 subjects had an adverse event of excessive sedation in bilastine group whereas in cetirizine group 8 subjects reported excessive sedation.[13]

The adverse effects of antihistamines on the CNS depend upon their capacity to cross the blood-brain barrier (BBB) and bind to the central RH1. This in turn depends on the lipophilicity of the drug molecule, its molecular weight (MW), and affinity for P-glycoprotein (P-gp) (CNS xenobiotic substances extractor protein). The second-generation molecules which are regarded as P-gp substrates are therefore considered nonsedating antihistaminic.[14] The MW of bilastine is 463.61 g/mol and is greater than cetirizine (388.8), the molecule is larger which in principle complicates its capacity to cross the BBB.[15-17]

We found no differences in biochemical parameters (SGOT, SGPT, serum bilirubin, alkaline phosphatase, serum creatinine, and blood urea) with cetirizine and bilastine both. The previous study showed no significant difference in biochemical parameters observed between baseline and 4 weeks with cetirizine as well as bilastine.[8]

One important finding of our study was a significant reduction in TLC and eosinophil count in both groups for 6 weeks. Eosinophils may enhance urticaria in three ways: First, eosinophil-derived stem cell factor promotes the recruitment and local maturation of mast cells in the tissues. Second, eosinophil proteins, such as major basic protein, eosinophil cationic protein, and eosinophil peroxidase can provoke mast cell degranulation. And third, activated eosinophils also express tissue factor, the main initiator of the coagulation cascade leading to thrombin formation. Eosinophil infiltration may contribute to tissue edema of the skin in urticaria but can also, together with increased mast cells**,** prime the skin for further healing. Histological studies have shown the presence of eosinophils and eosinophil granules in urticaria lesions.[18] We could not find any study comparing cetirizine and bilastine in terms of differences in monophil count and basophil count.

In our study, the incidence of adverse events like headache gastric irritation and sedation was more with cetirizine as compared to bilastine. Our study did not find any change in ECG in both of the groups and these finding of our study is similar to, previous studies.[8]

Thus, the findings of our study in terms of Mean TSS, suggest that bilastine was more efficacious than cetirizine and the efficacy was earlier at 1 week which was not seen in the cetirizine group. We also found a significant difference in SIWS, number of wheal, in bilastine as compared to cetirizine. Thus, bilastine is a highly effective H1-antihistamine even when used at the basic dose of 20 mg daily.

Although bilastine is more expensive than cetirizine, it is more efficacious and safe and further cost-effectiveness studies should be done to find out which drug is more cost-effective.

CONCLUSION

Thus, the findings of our study suggest that bilastine was more safe and efficacious than cetirizine in patients of CSU. The efficacy with bilastine was seen earlier at 1 week which was not seen in the cetirizine group. There was a significant reduction in SIWS, number of Wheals, and VAS for sedation with bilastine when compared to cetirizine. The incidence of adverse events like headache, gastric irritation, and sedation was more with cetirizine as compared to bilastine. Our study did not find any change in ECG in both of the groups. The favorable tolerability profile of may make it a highly effective H1-antihistamine at the basic dose of 20 mg daily.

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Conflicts of interest

There are no conflicts of interest.

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