

A Comparative, Three-Arm, Randomized Clinical Trial to Evaluate the Effectiveness and Tolerability of Bilastine vs Fexofenadine vs Levocetirizine at the Standard Dose and Bilastine vs Fexofenadine at Higher Than the Standard Dose (Up-Dosing) vs Levocetirizine and Hydroxyzine (in Combination) in Patients with Chronic Spontaneous Urticaria

Bela Shah¹, Dhiraj Dhoot², Ankita Choudhary¹, Neha Jangid¹, Deval Mistry¹, Shikha Shah¹, Shrutika Kamat¹, Hanmant Barkate³

¹Department of Dermatology, Venereology and Leprosy, B.J. Medical College, Civil Hospital, Ahmedabad, India; ²DGM, Department of Global Medical Affairs, Glenmark Pharmaceuticals Ltd, Mumbai, India; ³Department of Global Medical Affairs, Glenmark Pharmaceuticals Ltd, Mumbai, India

Correspondence: Dhiraj Dhoot, DGM, Department of Global Medical Affairs, Glenmark Pharmaceuticals Ltd, Mumbai, Maharashtra, 400099, India, Tel +91 9619811219, Email dddhoot@gmail.com

Introduction: Though second-generation antihistamines (SGAH) are first-line drugs in chronic spontaneous urticaria (CSU), 50% of patients do not respond to them. In such patients, guidelines recommend either up-dosing of SGAH or combination of different antihistamines. However, the studies comparing these treatment regimens are limited.

Methods: In this comparative, three-arm study, CSU patients were randomized to receive standard dose of either bilastine, fexofenadine, or levocetirizine for 2 weeks. After 2 weeks of treatment, non-responders received double dose of either bilastine or fexofenadine, while hydroxyzine 25 mg once daily was added in the levocetirizine group. Patients were primarily evaluated for improvement in CSU, quality of life, and somnolence.

Results: A total of 110 patients with CSU were recruited. At the end of 4 weeks, 33/39, 26/35, and 22/36 patients in the bilastine, fexofenadine, and levocetirizine groups showed improvement in urticaria symptoms. At week 2, there was no statistical difference in urticaria activity score (UAS7) improvement between any of the groups; however, at week 4, there was a statistical difference between the bilastine and levocetirizine groups ($p < 0.05$). Somnolence was significantly lower in the bilastine group ($p < 0.05$). Bilastine was statistically significant ($p < 0.05$) in the improvement of quality of life as compared to both groups. No major adverse events were reported during study period; however, bilastine was associated with significantly lower levels of AEs compared to levocetirizine ($p < 0.05$).

Conclusion: Two-fold up-dosing of bilastine improves CSU symptoms without compromising safety as compared to two-fold up-dosing of fexofenadine and combination of first- and second-generation antihistamines.

Keywords: chronic spontaneous urticaria, up dosing, bilastine, fexofenadine, levocetirizine, hydroxyzine

Introduction

Chronic spontaneous urticaria (CSU) is a relatively common skin disorder, associated with angioedema, wheals (hives), or both.¹ In India, the exact epidemiology and burden of CSU remain unknown. According to the consensus statement in 2017, urticaria has a point prevalence of 1%, whereas its lifetime prevalence is 22%. Urticaria is commonly seen in young-middle-aged women and usually lasts for many years (25–75% of patients suffer for more than a year). Due to

several reasons, including misdiagnosis and patient's negligence, effective management is usually implemented after a year of symptom onset.² Urticaria obviously affects the appearance of the skin, thus creating anxiety and drastically reducing quality of life (compared to other chronic diseases).^{3,4}

The European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA2LEN)/European Dermatology Forum (EDF) guidelines¹ recommend non-sedating H1-antihistamines for first-line management of CSU since all the symptoms are mediated through H1-receptors.^{5,6} Bilastine, levocetirizine, desloratadine, and fexofenadine belong to the class of non-sedating second-generation antihistamines (NSAH). They are the drug of choice for CSU due to their long half-life, minimal sedation, the lack of cardiotoxicity, and absence of cholinergic side-effects. Their use in most forms of urticaria is supported by strong clinical evidence.⁷ However, a study conducted in 390 patients taking NSAH revealed that only 44% of them responded well to treatment, while 29% were discharged with no symptoms and 15% had only partial relief from symptoms.⁸ In usual practice, it is often seen that failure of first-line approach leads to prescription of corticosteroids, which prolongs the vicious circle of chronicity.

Once antihistamines fail to show improvement at conventional doses, two important questions arise. The first question is obviously regarding increasing the dose of NSAH. When standard dose does not provide relief, the guidelines recommend to increase the dose of antihistamine up to 4 times.¹ However, the clinical evidence on this is ambiguous. Few studies reveal good efficacy of up-dosing of NSAH, while some failed to demonstrate that.^{9–12} But up-dosing is significantly more effective in reducing CSU symptoms than standard-dose regimen.¹³ According to Kaplan, antihistamines given at high dose are effective in 45–60% of patients with CSU.¹⁴ Interestingly, one-third of the patients are resistant to antihistamine, regardless of the dose.^{15,16}

The second important question is whether patients are responsive to only one antihistamine or require a combination regimen of different antihistamines. This dilemma is experienced by many patients and clinicians, but there is no evidence to support this. The Japanese and American guidelines of urticaria recommend the combined use or increasing the dose for patients not responding to treatment with standard dose of NSAH.^{17,18} In the combination approach, many practitioners consider prescribing NSAH in the morning and a sedating first-generation H1-antihistamine (FGAH), usually hydroxyzine, at night to reduce night-time itch and enhance sleep as the most effective approach for treatment of CSU. The rationale behind this is that the sedation makes patients sleep better in spite of the itching. Some older guidelines do support this.^{19–22}

Recently, bilastine was approved for the management of CSU in India. Clinical evidence comparing up-dosing of bilastine with other antihistamines like fexofenadine in Indian patients is not available. Additionally, there is no data that compares up-dosing of NSAH versus the combination of first- and second-generation antihistamine in India. This study aimed to investigate the effectiveness and tolerability of up-dosing of bilastine and fexofenadine up to two times and combination of NSAH; levocetirizine and first-generation antihistamine (FGAH); and hydroxyzine in patients with CSU.

Methods

Study Design

This was a randomized, comparative, open-label, three-arm, and single-center study. Participants were recruited from April 2020 till October 2020 and followed up for four weeks, and all patients provided informed written consent. The study was approved by the institutional ethical committee (OM Institutional Ethics Committee; ECR/1168/Inst/GJ/2018) and was registered with the clinical trials registry, India (CTRI/2020/03/024244). This clinical study was performed in accordance with Good Clinical Practices and the Declaration of Helsinki 1996.

Study Participants

This study was done in a tertiary care hospital in Ahmedabad. Eligible patients within the age group of 18–60 years and with a clinical history of CSU for at least 6 weeks during the last 3 months without an identifiable cause and urticaria activity score (UAS7) of ≥ 7 were recruited. The following patients were excluded: (a) with physical urticaria, drug-induced urticaria, and urticarial vasculitis; (b) with any other dermatological condition associated with pruritus; (c) pregnant or nursing females; (d)

with known hypersensitivity to the study drugs; (e) immunosuppressive disease or on immunosuppressive drugs; (f) evidence of clinically significant disease such as cardiac, respiratory, gastrointestinal, renal disease.

Follow-Up

Data were collected using standardized case report forms at screening; at baseline; at week 2 and week 4. The primary outcome measures included improvement in urticaria symptoms, somnolence, and quality of life (QoL).

During the screening visit, a responsible physician clinically evaluated the patients including a structured questionnaire. Urticaria-associated discomfort was assessed using a visual analog scale (VAS) which consists of 3 questions regarding sleepiness with drug and satisfaction with drug on a Likert scale of 10.²³ The activity of urticaria and quality of life were determined as per UAS7²⁴ and CU-Q2oL²⁵ questionnaire, respectively. UAS7 measures daily urticaria activity score in terms of itch and hives, whereas CU-Q2oL measures quality of life in CSU on six domains like pruritus, swelling, impact on life activities, sleep problems, limits, and looks. It consists of 23 questions with minimum score of 23 to maximum of 115. Since no standard scale of improvement was mentioned, we considered 25% improvement in CU-Q2oL score as improvement in QoL. A washout period of 3 days (without treatment) was given, and patients were asked to use rescue medication (30 mg prednisone) during that period. Additionally, patients were asked to maintain a diary to note down UAS (from 0, no itch and no wheals; to 3, itch at its worst with multiple wheals), facial edema, ingestion of any other drugs, and adverse events.

During the second visit, ie, 3 days later, patients underwent the same subjective and objective assessment. Patients were randomized to either the bilastine or the fexofenadine or the levocetirizine arm of the study. Patients were instructed about the dosage of the drugs. New diary cards were issued to them for the next 2 weeks. The same assessments were performed at visit 3. Patients with a UAS7 score of ≤ 6 were considered responsive to drug and were instructed to continue the same treatment but excluded from study. The patients who failed to show improvement and were still symptomatic were given a double dose of the drugs (bilastine 20 mg twice a day and fexofenadine 180 mg twice a day) morning and evening throughout weeks 3 and 4, and in the levocetirizine arm, hydroxyzine 25 mg was added in the night for 2 weeks. At visit 4, all evaluations were repeated. All adverse events were reported.

Study End Points

The primary effectiveness end point was proportion of patients achieving well-controlled urticaria based on UAS7 in each arm at weeks 2 and 4. Secondary end points were number of patients becoming symptom-free, mean reduction in UAS7 score, improvement in quality of life of patients based on CU-Q2oL, improvement in urticaria discomfort and somnolence based on VAS at weeks 2 and 4. The safety of each treatment regime was analyzed by assessing the proportion of patients showing 1 or more adverse event during the study period.

Statistical Analysis

Results were presented as mean scores, and groups were compared using one way ANOVA with Tukey HSD test and Fisher exact test. Level of significance was set at $p < 0.05$. Data were analyzed using the IBM SPSS (Statistical Package for Social Sciences) statistics version 20.

Results

A total of 120 patients were randomized to receive either bilastine or fexofenadine or levocetirizine. Of the 120 initially recruited patients with CSU, 10 patients were lost to follow-up (1 in bilastine arm, 5 in fexofenadine arm, and 4 in levocetirizine arm) and thus excluded from the analysis. Hence, the final number of patients was 110 (39 in bilastine, 35 in fexofenadine, and 36 in levocetirizine arm). Baseline demographics are shown in Table 1. Out of 110 patients, 34 had mild urticaria (30.9%), and the remaining 76 had moderate urticaria (69.1%). There was no significant difference between the three groups. Patients in all three arms had a similar baseline UAS7 score.

Objective Symptoms

At week 2, in the bilastine arm, 23 patients achieved well-controlled urticaria, whereas 18 and 17 patients achieved well-controlled urticaria in the fexofenadine and levocetirizine arms, respectively. There was no statistical difference between

Table 1 Demographic Characteristics of Patients

	Bilastine	Fexofenadine	Levocetirizine	P value
Number of patients	39	35	36	
Male	21	14	22	
Female	18	21	14	
Age (years)	36.05±12.06	38.3±12.73	37.28±11.64	0.7
Duration (months)	9.8±5.66	10.59±6.5	10.45±5.4	0.82
Previous medications				
First generation	16	9	13	
Second generation	21	23	18	
Corticosteroids	2	2	5	
Cyclosporine	0	1	0	
Urticaria severity				
Mild	12	10	12	0.9
Moderate	27	25	24	0.9
Initial UAS7 Score	17.63±3.99	18.43±3.78	17.98±5.09	0.7

any of the groups at week 2. At the end of treatment, in the bilastine arm, 9/16 had well-controlled urticaria, while 7/17 patients in the fexofenadine arm had well-controlled urticaria. In the levocetirizine and hydroxyzine arm, out of 19 patients, 5 had well-controlled urticaria (Table 2 and Figure 1).

Among the three treatment arms, none of the patients was symptom-free at week 2. One patient each in the bilastine and fexofenadine arms was symptom-free at week 4. None of the patients in the levocetirizine and hydroxyzine arm was symptom-free. There was a statistical difference between the bilastine and the levocetirizine groups ($p<0.05$) at week 4, suggesting up-dosing of second-generation antihistamines is a better option than the combination of first and second-generation antihistamines. There was no statistical difference noted between bilastine and fexofenadine ($p=0.4$) and fexofenadine and levocetirizine arms ($p=0.3$).

Mean UAS7 score of 17.63±3.99 was reduced to 7.85±4.56 (55.4% reduction) in the bilastine arm, while it was reduced to 7.80±3.76 from 18.43±3.78 (57.6% ↓) and 9.47±5.39 from 17.98±5.09 (47.3% ↓) in the fexofenadine and the levocetirizine arms, respectively, at week 2.

On up-dosing, in the bilastine arm, it was further reduced to 5.25±3.09 from 12.56±3.08 (58.6% reduction), whereas in fexofenadine it was reduced to 5.65±2.64 from 11.06±2.49 (48.9% ↓). After addition of hydroxyzine in the levocetirizine arm, it was reduced to 8.0±3.14 from 13.68±3.9 (41.5% ↓) at week 4.

Discomfort Caused by Urticaria

Urticaria-associated discomfort during the preceding week was measured using a VAS. In terms of VAS, there was a statistical difference between bilastine and fexofenadine and between bilastine and levocetirizine at both visits (Table 3). It suggests that bilastine is well accepted as a non-sedating antihistamine as compared to others by patients.

Somnolence

A major concern with increasing doses of H1-antihistamines is that of somnolence. Sleepiness with the drug was measured by VAS. Levocetirizine had a higher mean VAS score, and it increased when hydroxyzine was added. On day 14, fexofenadine had a lower score than levocetirizine but higher than bilastine. The somnolence score of bilastine and

Table 2 No. of Patients Showing Improvement at Week 2 and 4

Drug	Week 2			Week 4		
	Well-Controlled Urticaria	Symptom-Free	Up-Dosing Required	Symptom-Free	Well-Controlled Urticaria	Mild Urticaria
Bilastine	23	0	16	1	9	6
Fexofenadine	18	0	17	1	7	9
Levocetirizine + Hydroxyzine	17	0	19	0	5	14

fexofenadine did not increase when their dose was increased. Bilastine was statistically better ($p<0.05$) than the other two arms as a non-sedating antihistamine (Figure 2).

Quality of Life

Quality of life was assessed by using the CU-Q2oL, which asked questions about pruritus, swelling, and impact on life activities, sleep problems, looks and limits in order to obtain the patient's view of both the overall impact of chronic urticaria and the effectiveness of its treatment. The results showed that out of the 3 arms, the maximum improvement in the quality of life was seen with bilastine at weeks 2 and 4.

At week 2, 17/39 patients in the bilastine arm, 6/35 patients in the fexofenadine arm, and 7/36 patients in the levocetirizine arm showed more than 25% improvement in QoL. At week 4, there were 13/16 patients in the bilastine, 7/17 in the fexofenadine, and 4/19 patients in the levocetirizine arms that showed improvement (Figure 3). Bilastine was statistically significant ($p<0.05$) in the improvement of quality of life by CU2QoL as compared to both the other arms.

Safety

A total of 33 adverse events were reported (Table 4). Twenty-five patients out of 110 patients (22.72%), 5 taking bilastine, 7 taking fexofenadine, and 13 taking levocetirizine were recorded at any time during the study. These included sedation (19), headache (5), nausea (6), and fatigue (3). In terms of AE, there was no statistical difference between bilastine and fexofenadine groups ($p=0.53$), but there was a statistical difference between the bilastine and levocetirizine groups ($p<0.05$). This could be due to addition of hydroxyzine in the levocetirizine arm. No other major adverse events occurred.

Discussion

This study compares the effectiveness and tolerability of bilastine, fexofenadine, and levocetirizine at a standard dose for 2 weeks followed by up-dosing of bilastine and fexofenadine and addition of hydroxyzine to levocetirizine in patients with CSU for another 2 weeks. To our knowledge, no study has compared up-dosing of second-generation with a combination of first- and second-generation antihistamines.

The international guidelines for the management of urticaria recommend NSAH for the treatment of CSU.¹ However, a few patients do not respond effectively to NSAH. According to Humphreys and Hunter, up to 40% of patients with CSU may not achieve relief from symptoms with antihistaminic therapy.⁸ A Japanese study revealed that only 36.6% of the patients who received standard doses of antihistamines showed improvement.²⁶

In our study, 59% of the patients responded well to bilastine, 51% to fexofenadine, and 47% responded well to levocetirizine at standard dose. In recent published studies from India, bilastine was effective in 80.6% and 69% of the patients.^{27,28} These results are not in concordance with our results, which may be due to shorter duration of therapy in our study. In the case of levocetirizine, as per a published study, 52% of the patients responded well in 42 days, and, for fexofenadine, 30% responded well to fexofenadine 180 mg in one week.^{27,29}

Though there was no statistically significant difference between any of the treatment groups, bilastine at a dose of 20 mg showed demonstrable efficacy as seen in other clinical trials.^{30,31} In a recent double-blind clinical trial from India,

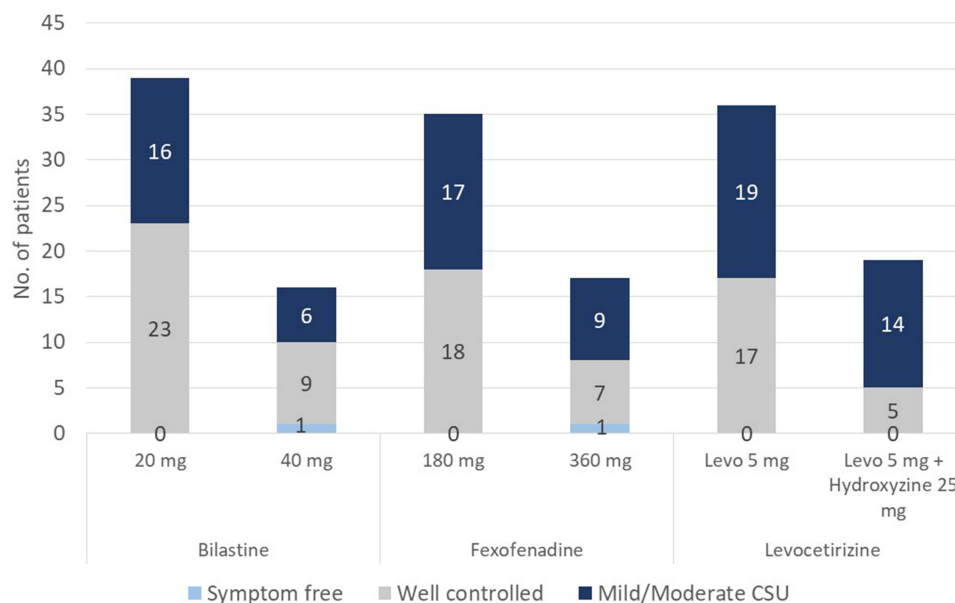


Figure 1 No. of patients showing improvement in urticaria measured at week 2 and week 4.

bilastine had more significant reduction in UAS7 compared to levocetirizine ($p=0.04$).²⁷ The recent real-world data from India showed that bilastine at standard licensed dose was an effective H1-antihistamine in relieving the symptoms of CSU in a patient refractory to levocetirizine in an early stage.²⁸ Similarly in our study, bilastine showed demonstrable efficacy over the other two antihistamines.

The current guidelines recommend increasing the dose of NSAH in CSU patients who do not respond to licensed doses to obtain a better disease control. A number of publications that evaluated different NSAH in increasing doses have clearly shown that the majority of patients with previously uncontrolled CSU exhibit significant improvements of their symptoms after going through this approach.^{13,32}

In our study, on up-dosing, 56.25% of the patients responded well to bilastine 20 mg twice a day, and 47% responded well to fexofenadine 180 mg twice daily. This is in concordance with other studies done on bilastine.^{33,34} Weller et al in their study concluded that up-dosing (doubling the licensed dose) of bilastine was an effective approach for the majority of CSU patients.³⁴ Two studies for fexofenadine demonstrated that higher doses were not more efficacious than the standard 60 mg twice a day dose.^{11,12} In one study by Godse et al, CSU was under control in 32% of the patients on fexofenadine 360 mg.²⁹ Similarly in our study, up-dosing of NSAHS was found to be effective in CSU patients.

Table 3 Primary Outcomes Measured During the Follow-Up Visits (2nd and 4th Week) by VAS

Week 2	Bilastine 20 mg	Fexofenadine 180 mg	Levocetirizine 5 mg	P value
Somnolence with drug	0.74±0.94	1.31±1.64	2.19±1.33	<0.05
Improvement of urticaria-related discomfort	5.87±1.26	4.86±1.26	4.61±1.55	<0.05
Week 4	Bilastine 40 mg	Fexofenadine 360 mg	Levocetirizine 5 mg + Hydroxyzine 25 mg	
Somnolence with drug	0.46±0.76	0.91±1.22	2.39±1.54	<0.05
Improvement of urticaria-related discomfort	6.67±1.4	5.77±1.57	5.28±1.58	<0.05

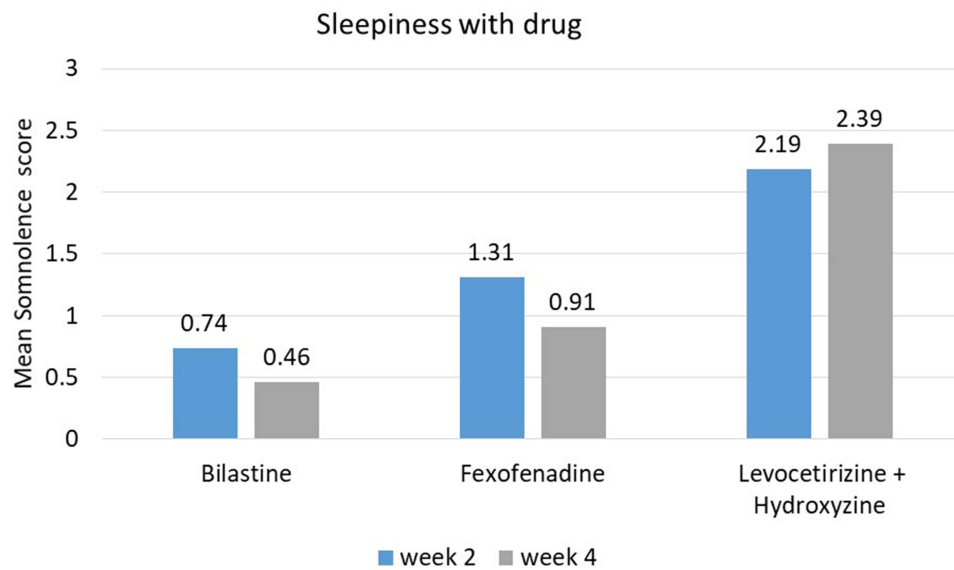


Figure 2 Sleepiness with drug as assessed by VAS.

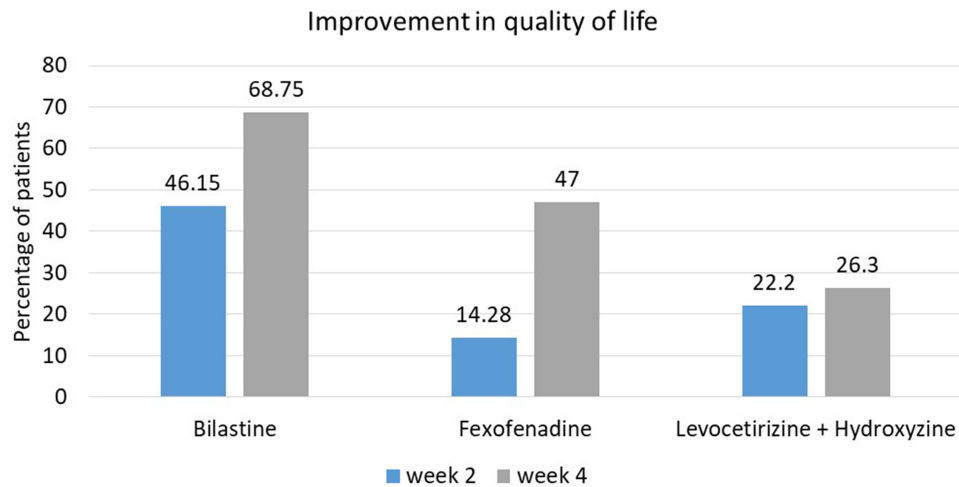


Figure 3 Changes in QoL measured during the follow-up visits (week 2 and 4).

Apart from up-dosing, another strategy recommended by Japanese and American guidelines in patients with refractory CSU is addition of a second antihistamine.^{17,18} Although the use of FGAH is discouraged in the European guideline,¹ due to serious side-effects, FGAH are still being commonly prescribed in routine practice. It was previously suggested that some physicians were not fully aware of the content of the most recent guidelines and therefore did not follow them.³⁵ Successful use of first-generation antihistamine after failure of treatment with NSAH has been described.³⁶ Additionally, as per one report, 15% of the patients were treated with hydroxyzine at some time during their disease.³⁷ Furthermore, the US guideline does support the use of FGAH in patients who do not achieve adequate control of their symptoms with higher-dose second-generation antihistamines.¹⁸

In our study, we added hydroxyzine in the levocetirizine arm to compare the efficacy and safety of this combination with up-dosing of NSAH. It was found that CSU was under control in only 35.7% of the patients. In comparison, up-dosing of NSAH was statistically significant than this approach. This was not in accordance with previous reports where addition of FGAH led to sufficient disease control.^{22,37}

Table 4 Details of Adverse Events During the Study Period

	Bilastine	Fexofenadine	Levocetirizine + Hydroxyzine	Total
Sedation	3	5	11	19
Headache	1	2	2	5
Nausea	2	2	2	6
Fatigue	1	1	1	3
Total no. of AE	7	10	16	33
Total no. of patients	5	7	13	25

It is well known that somnolence is one of the most reported unwanted effects of antihistamines. Perhaps in our study, patients did not experience increased somnolence when stepping up their daily dose. In one case report a man tolerated 50 mg per day of cetirizine for the treatment of CSU without any sedation, somnolence, or hindrance with performing routine daily functions including driving.³⁸ Two possible reasons may be suggested as an explanation. The first possibility is the relief from physical discomfort resulting from the psychological status of the patients. Most of the sedation studies with H1-antihistamines are performed in either healthy individuals or individuals with milder disease than in CSU, which causes sleep deprivation. It can be speculated that relief from urticaria-related discomfort led to a better quality of sleep. The second possibility is the development of tolerance to the central nervous sedative effects of the antihistamines. The development of tolerance to the central nervous system effects of both first-generation and second-generation antihistamines after 4 to 5 days of administration has been reported.^{39–42}

In our study, patients on bilastine did not experience increased somnolence when stepping up their daily dose. Moreover, patients in the bilastine arm had lower somnolence than fexofenadine and levocetirizine on both visits, weeks 2 and 4. In a previously conducted study, sedation was significantly lower in the bilastine 20 mg group compared to levocetirizine 5 mg.³⁰ Hydroxyzine, a FGAH, is known to cause drowsiness, and similar effects were observed in our study. Somnolence was the highest in the levocetirizine arm and further increased when hydroxyzine was added. This was in accordance with one study conducted by Staevska et al where a levocetirizine and hydroxyzine combination had more somnolence over levocetirizine monotherapy.²² Sedation-related adverse events were maximum in the levocetirizine and hydroxyzine arm, indicating sedating effects of first-generation antihistamine. This could be explained by binding of the drug to H1-receptors in the brain leading to sedation.⁴³ Since hydroxyzine has terminal half-life of 20–25 h,⁴⁴ it is not surprising to experience sedative effects into the next day.

Daytime sedation disrupts a patient's life, and it is important to choose non-sedating therapy to improve the quality of life. There is clinical evidence that bilastine improved the QoL.^{27,45} Furthermore, our study showed that bilastine is better than fexofenadine and a combination of levocetirizine and hydroxyzine in improving quality of life.

This study provides evidence that, in patients with CSU, increasing the daily dose of bilastine is a better option than the combination of first- and second-generation antihistamines in reducing urticaria symptoms without compromising patient safety. Out of the three treatment arms, bilastine was well-tolerated for CSU. An updated consensus statement in 2019 of expert dermatologists from India also strongly recommends preference for bilastine over other antihistamines as first-line treatment due to excellent tolerability profile, faster onset, and longer duration of action and its non-sedative nature.⁴⁶ The limitations of this study is the small sample size. Future studies with a large sample size at multiple sites would provide good-quality clinical evidence and support the use of bilastine as the first-line treatment for CSU.

Conclusion

This study provides evidence that, in patients with CSU, up-dosing of bilastine is effective, well-tolerated, and less sedating than up-dosing of fexofenadine or a combination of first- and second-generation antihistamines (levocetirizine +

hydroxyzine). Up-dosing (increasing the daily dose) of bilastine provided relief from urticaria symptoms and improved quality of life in the majority of the patients without compromising somnolence or safety. This clinically implies that up-dosing of bilastine, as recommended in guidelines, is a better option than the combination of first- and second-generation antihistamines. The availability of such clinical evidence assists the physicians in choosing an appropriate treatment for their patients with CSU.

Data Sharing Statement

The datasets are available only on request due to privacy/ethical restrictions, and can be requested from the corresponding author, dddhoot@gmail.com.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393–1414. doi:10.1111/all.13397
2. Gonçalo M, Giménez-Arnau A, Al-Ahmad M, et al. The Global burden of chronic urticaria for the patient and society. *Br J Dermatol*. 2021;184(2):226–236. doi:10.1111/bjd.19561
3. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol*. 1997;136(2):197–201. doi:10.1111/j.1365-2133.1997.tb14895.x
4. Baiardini I, Giardini A, Pasquali M, et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy*. 2003;58(7):621–623. doi:10.1034/j.1398-9995.2003.00091.x
5. Zuberbier T, Bindslev-Jensen C, Canonica W, et al. EAACI/GA2LEN/EDF guideline: definition, classification and diagnosis of urticaria. *Allergy*. 2006;61(3):316–320. doi:10.1111/j.1398-9995.2005.00964.x
6. Petersen LJ, Church MK, Skov PS. Histamine is released in the wheal but not the flare following challenge of human skin in vivo: a microdialysis study. *Clin Exp Allergy*. 1997;27(3):284–295. doi:10.1111/j.1365-2222.1997.tb00707.x
7. Zuberbier T, Bindslev-Jensen C, Canonica W, et al. EAACI/GA2LEN/EDF guideline: management of urticaria. *Allergy*. 2006;61(3):321–331. doi:10.1111/j.1398-9995.2005.00962.x
8. Humphreys F, Hunter JA. The characteristics of urticaria in 390 patients. *Br J Dermatol*. 1998;138(4):635–638. doi:10.1046/j.1365-2133.1998.02175.x
9. Zuberbier T, Münzberger C, Haustein U, et al. Double-blind crossover study of high-dose cetirizine in cholinergic urticaria. *Dermatology*. 1996;193(4):324–327. doi:10.1159/000246281
10. Asero R. Chronic unremitting urticaria: is the use of antihistamines above the licensed dose effective? A preliminary study of cetirizine at licensed and above-licensed doses. *Clin Exp Dermatol*. 2007;32(1):34–38. doi:10.1111/j.1365-2230.2006.02278.x
11. Finn AF, Kaplan AP, Fretwell R, Qu R, Long J. A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol*. 1999;104(5):1071–1078. doi:10.1016/S0091-6749(99)70091-6
12. Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2000;84(5):517–522. doi:10.1016/S1081-1206(10)62515-X
13. Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Treatment of recalcitrant chronic urticaria with non-sedating antihistamines: is there evidence for up-dosing? *J Investig Allergol Clin Immunol*. 2013;23(3):141–145.
14. Kaplan AP. Treatment of chronic spontaneous urticaria. *Allergy Asthma Immunol Res*. 2012;4(6):326–331. doi:10.4168/aaair.2012.4.6.326
15. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. *Clin Exp Dermatol*. 2010;35(8):869–873. doi:10.1111/j.1365-2230.2010.03840.x
16. Giménez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. *J Eur Acad Dermatol Venereol*. 2009;23(9):1088–1091. doi:10.1111/j.1468-3083.2009.03289.x
17. Hiragun T, Hide M. Japanese guidelines for diagnosis and treatment of urticaria. *Alerugi*. 2017;66(1):23–26. doi:10.15036/arerugi.66.23
18. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133(5):1270–1277. doi:10.1016/j.jaci.2014.02.036
19. Joint Task Force on Practice Parameters. The diagnosis and management of urticaria: a practice parameter part I: acute urticaria/angioedema part II: chronic urticaria/angioedema. *Ann Allergy Asthma Immunol*. 2000;85(6 Pt 2):521–544.
20. Grattan CE, Humphreys F; British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol*. 2007;157(6):1116–1123. doi:10.1111/j.1365-2133.2007.08283.x
21. Powell RJ, Du Toit GL, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy*. 2007;37(5):631–650. doi:10.1111/j.1365-2222.2007.02678.x
22. Staevska M, Gugutkova M, Lazarova C, et al. Night-time sedating H1 -antihistamine increases daytime somnolence but not treatment efficacy in chronic spontaneous urticaria: a randomized controlled trial. *Br J Dermatol*. 2014;171(1):148–154. doi:10.1111/bjd.12846
23. Izumi N, Mizuguchi H, Umehara H, Ogino S, Fukui H. Evaluation of efficacy and sedative profiles of H(1) antihistamines by large-scale surveillance using the visual analogue scale (VAS). *Allergol Int*. 2008;57(3):257–263. doi:10.2332/allergolint.O-07-525

24. Hollis K, Proctor C, McBride D, et al. Comparison of urticaria activity score over 7 days (UAS7) values obtained from once-daily and twice-daily versions: results from the ASSURE-CSU study. *Am J Clin Dermatol*. 2018;19(2):267–274. doi:10.1007/s40257-017-0331-8
25. Baiardini I, Pasquali M, Braido F, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-QoL). *Allergy*. 2005;60(8):1073–1078. doi:10.1111/j.1398-9995.2005.00833.x
26. Hiragun M, Hiragun T, Mihara S, Akita T, Tanaka J, Hide M. Prognosis of chronic spontaneous urticaria in 117 patients not controlled by a standard dose of antihistamine. *Allergy*. 2013;68(2):229–235. doi:10.1111/all.12078
27. Podder I, Das A, Ghosh S, Biswas D, Sengupta S, Chowdhury SN. Effectiveness, safety, and tolerability of bilastine 20 mg vs levocetirizine 5 mg for the treatment of chronic spontaneous urticaria: a double-blind, parallel group, randomized controlled trial. *Dermatol Ther*. 2020;33(6):e13946. doi:10.1111/dth.13946
28. Shah B, De A, Sarda A, et al. Effect of bilastine on chronic spontaneous urticaria refractory to levocetirizine: real world experience in India. *Dermatol Ther*. 2021;34(1):e14557. doi:10.1111/dth.14557
29. Godse KV, Nadkarni NJ, Jani G, Ghate S. Fexofenadine in higher doses in chronic spontaneous urticaria. *Indian Dermatol Online J*. 2010;1(1):45–46. doi:10.4103/2229-5178.73262
30. Zuberbier T, Oanta A, Bogacka E, et al. Comparison of the efficacy and safety of bilastine 20 mg vs levocetirizine 5 mg for the treatment of chronic idiopathic urticaria: a multi-centre, double-blind, randomized, placebo-controlled study. *Allergy*. 2010;65(4):516–528. doi:10.1111/j.1398-9995.2009.02217.x
31. Yagami A, Furue M, Togawa M, Saito A, Hide M. One-year safety and efficacy study of bilastine treatment in Japanese patients with chronic spontaneous urticaria or pruritus associated with skin diseases. *J Dermatol*. 2017;44(4):375–385. doi:10.1111/1346-8138.13644
32. Sánchez-Borges M, Ansotegui I, Jimenez JM, Rojo MI, Serrano C, Yañez A. Comparative efficacy of non-sedating antihistamine up dosing in patients with chronic urticaria. *World Allergy Organ J*. 2014;7(1):33. doi:10.1186/1939-4551-7-33
33. Krause K, Spohr A, Zuberbier T, Church MK, Maurer M. Up-dosing with bilastine results in improved effectiveness in cold contact urticaria. *Allergy*. 2013;68(7):921–928. doi:10.1111/all.12171
34. Weller K, Church MK, Hawro T, et al. Updosing of bilastine is effective in moderate to severe chronic spontaneous urticaria: a real-life study. *Allergy*. 2018;73(10):2073–2075. doi:10.1111/all.13494
35. Weller K, Viehmann K, Bräutigam M, et al. Management of chronic spontaneous urticaria in real life—in accordance with the guidelines? A cross-sectional physician-based survey study. *J Eur Acad Dermatol Venereol*. 2013;27(1):43–50. doi:10.1111/j.1468-3083.2011.04370.x
36. Kaplan AP. What the first 10,000 patients with chronic urticaria have taught me: a personal journey. *J Allergy Clin Immunol*. 2009;123(3):713–717. doi:10.1016/j.jaci.2008.10.050
37. van den Elzen MT, van Os-medendorp H, van den Brink I, et al. Effectiveness and safety of antihistamines up to fourfold or higher in treatment of chronic spontaneous urticaria. *Clin Transl Allergy*. 2017;7:4. doi:10.1186/s13601-017-0141-3
38. Nordness M, Zacharisen MC. High dose cetirizine: a case report. *Cutis*. 2003;71(5):396.
39. Richardson GS, Roehrs TA, Rosenthal L, Koshorek G, Roth T. Tolerance to daytime sedative effects of H1 antihistamines. *J Clin Psychopharmacol*. 2002;22(5):511–515. doi:10.1097/00004714-200210000-00012
40. Verster JC, Volkerts ER. Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic [published correction appears in *Ann Allergy Asthma Immunol*. 2004 Jun; 92(6):675][published correction appears in *Ann Allergy Asthma Immunol*. 2005 Mar;94(3):409–410]. *Ann Allergy Asthma Immunol*. 2004;92(3):294–355. doi:10.1016/S1081-1206(10)61566-9
41. García-Gea C, Martínez-Colomer J, Antonijoan RM, Valiente R, Barbanj MJ. Comparison of peripheral and central effects of single and repeated oral dose administrations of bilastine, a new H1 antihistamine: a dose-range study in healthy volunteers with hydroxyzine and placebo as control treatments. *J Clin Psychopharmacol*. 2008;28(6):675–685. doi:10.1097/JCP.0b013e31818b2091
42. Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125(3):676–682. doi:10.1016/j.jaci.2009.11.047
43. Farré M, Pérez-Mañá C, Papaseit E, et al. Bilastine vs. hydroxyzine: occupation of brain histamine H1 -receptors evaluated by positron emission tomography in healthy volunteers. *Br J Clin Pharmacol*. 2014;78(5):970–980. doi:10.1111/bcp.12421
44. Simons FE, Simons KJ, Frith EM. The pharmacokinetics and antihistaminic of the H1 receptor antagonist hydroxyzine. *J Allergy Clin Immunol*. 1984;73(1 Pt 1):69–75. doi:10.1016/0091-6749(84)90486-X
45. Serra E, Campo C, Novák Z, et al. Efficacy and safety of bilastine in reducing pruritus in patients with chronic spontaneous urticaria and other skin diseases: an exploratory study. *J Dermatolog Treat*. 2020;31(3):270–278. doi:10.1080/09546634.2019.1590522
46. Godse K, De A, Zawar V, et al. Bilastine for the treatment of chronic spontaneous urticaria: consensus statement for Indian patients. *Indian J Clin Exp Dermatol*. 2019;5(3):180–185. doi:10.18231/j.ijced.2019.039

Clinical, Cosmetic and Investigational Dermatology

Dovepress

Publish your work in this journal

Clinical, Cosmetic and Investigational Dermatology is an international, peer-reviewed, open access, online journal that focuses on the latest clinical and experimental research in all aspects of skin disease and cosmetic interventions. This journal is indexed on CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/clinical-cosmetic-and-investigational-dermatology-journal>