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Original Research Article

Real world Indian experience of switchover to Bilastine in CSU patient refractory to other antihistamines

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ABSTRACT

Background: Second generation anti histamines are first line therapy as recommended by many guidelines for Chronic spontaneous urticaria (CSU). Bilastine, non-sedative H1-antihistamine is recently approved in India for the management of CSU.

Materials and Methods: A real world retrospective study was conducted across India to assess the response of CSU patients who were switched over to bilastine after non satisfactory response to other antihistamines at 140 dermatology clinics.

Results: A data of 518 patients' were included in this analysis. Mean age of the patients was 35.3 ±12.3 years while mean disease duration was 7.08±9.3 months. Baseline mean UCT score of 8.6 ± 3.02 was improved to 13.05 ± 2.9 in 28 days ($p<0.05$). Based on UCT score, 357 of 518 (69%) patients were classified as responders. An improvement was observed in VAS on day 28. A total of 39 patients (7.53%) complained of adverse events; sedation being the commonest. All adverse effects were mild in nature. Overall Bilastine was well tolerated.

Conclusion: Authors concluded that in patients with inadequate response to commonly used antihistamines at licensed dose, switch over to bilastine resulted, not only in reliving the symptoms of CSU but also added to the Patients' satisfaction with the drug.

1. Introduction

Chronic spontaneous urticaria (CSU) is a common skin disease characterized by pruritic, erythematous, and oedematous wheals with daily or near-daily episodes, for > 6 weeks as a result of known or unknown causes.[1] The exact prevalence of urticaria in India is not known. However lifetime prevalence is reported as 7.8-22.3%.[2]

Though the pathogenesis of chronic urticaria has not been conclusively established, it is now evident that most of the symptoms of chronic urticaria are mediated primarily by the actions of histamine on H1 receptors located on endothelial cells (wheal) and on sensory nerves (neurogenic flare and pruritus).[2,3] Further chronic urticaria is long-lasting disorder, persisting for 2–5 years in most cases, and 20% of patients being affected for more than 5 years.[4] Therefore, treatment with H1 receptor antagonists (H1-antihistamines) becomes important when treating chronic urticaria patients.

The first-generation antihistamines (AHs) penetrate readily into the brain to cause sedation, drowsiness, fatigue, impaired concentration, and memory.[5] Thus the European Academy of Allergy and Clinical Immunology (EAACI) / Global Allergy and Asthma European Network (GA2

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LEN)/ European Dermatology Forum (EDF)/ World Allergy Organization (WAO) guidelines for the management of urticaria recommend the use of second-generation, non-sedating AHs and discourage the use of first-generation Ahs.[6]

Bilastine, a newer, non-sedating second-generation H1 antihistamine, has been approved for therapeutic use in patients with urticaria, with a recommended dose of 20 mg once daily in patients > 12 years.[7] Bilastine has been assessed in multiple clinical trials involving patients with chronic urticaria. The total symptom score (TSS), which is defined as, sum of the scores for rashes and itching, was significantly improved at early stage (Days 1–3) in group given bilastine 20mg once daily compared with placebo.[8] Long-term treatment with bilastine 20mg once daily for 52 weeks in Japanese patients with chronic urticaria, concluded bilastine to be safe and well tolerated.[9]

One of the challenges encountered with chronic urticaria is its unresponsiveness to H1- antihistamine at the licensed dose.[3] Therefore EAACI/GA2 LEN/EDF/WAO guidelines recommends up titration of second-generation H1- antihistamines up to fourfold higher.[6] However only the Japanese guidelines for diagnosis and treatment of urticaria recommend switching to other H1-antihistamines apart from combined use or increasing the dose.[10] But in India, it is quiet common practice to switchover to other antihistamines in case of non-response to previous one.

Since we do not have enough evidence about the efficacy of switching to Bilastine in chronic urticaria patients showing inadequate response to a certain H1-antihistamine, we conducted a retrospective, real world survey with physicians across India to assess the response of Indian patients with chronic urticaria who were switched over to bilastine after inadequate response with other antihistaminic drugs including cetirizine, levocetrizine, fexofenadine and loratadine.

2. Materials and Methods

This was a retrospective, multicentre, observational cohort analysis that examined the results in patients with CSU in real world dermatology practice at 140 centres across India. A Pre-validated questionnaire was used to conduct this analysis. The questionnaire was designed to assess the efficacy and tolerability of Bilastine at licensed dose (20 mg/day) in CSU patient refractory to other antihistamines for 4 weeks.

2.1. Inclusion criteria

1. The adult patients diagnosed with CSU and switched over to Bilastine due to non-satisfactory response to other antihistamines were considered for analysis.
2. Non satisfactory response was considered as UCT score <12.
3. Adult patients > 18 years of age were considered for analysis.

In addition, only those records were considered for analysis, whose assessments were done at baseline and at 4 weeks by using (Urticaria Control Test) UCT scoring system and (Visual Analogue Scale) VAS. Survey was conducted during July 2019-December 2019. This study was approved by Ethics committee.

UCT is 4 item validated tool commonly used to assess urticaria disease activity.[11] Each of the 4 items in UCT rates from 0 to 4 (0= very much and 4= not at all). The lowest UCT score possible is 0 (no control) and the highest score possible is 16 (complete control). A score $\geq$12 indicates well-controlled urticaria, while a score of <12 points towards inadequate/poor disease control.[11] Visual Analogue Scale (VAS) is used to assess the sleepiness and satisfaction with treatment. Sleepiness is rated on 11 point Visual Analogue Scale (VAS) where 0 is typified by "no sleepiness" and 10 is typified by "hard to stay awake". Patient satisfaction is rated on 11 point VAS scale where 0 is rated as "Not satisfied" and the rating of 10 is associated with "Extremely satisfied" with the

2.2. Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean $\pm$ standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. The difference of the means of analysis variables between two time points in same group was tested by paired t test. The level of significance was set at P<0.05. Data was analysed using SPSS software (v.23.0) and Microsoft office (2010).

3. Results

A total of 898 patients' data was analysed, of which 518 patients met the inclusion criteria and were included in final analysis. A male preponderance was observed (56.18% males as compared to 43.82% females). The mean age of the patients was 35.3 $\pm$12.3 years. Mean disease duration was 7.08$\pm$9.3 months. Levocetrizine was the commonly prescribed antihistamine. All the demographics are depicted in Table 1.

Based on UCT score, 357 of 518 (69%) patients were classified as controlled urticaria and 161 (31%) as non-controlled urticaria at the end of 28 days as showed

A total of 39 patients (7.53%) complained of adverse events; sedation being the commonest (n=25) followed by Fatigue (n=7), dizziness (n=4) and headache (n=3). All the adverse events were mild in nature and none of the patients discontinued the treatment. Overall Bilastine was well tolerated.

Table 1: Baseline demographics

Patient Characteristics	
Male N (%)	291 (56.18)
Female	227 (43.82)
Mean Age; years (SD)	35.3 ±12.3
Mean disease duration; months (SD)	7.08±9.3
Previous medication; N (%)	
Levocetirizine	230 (44.4)
Cetirizine	59 (11.39)
Desloratidine	20 (3.86)
Loratidine	12 (2.32)
Fexofenadine	123 (23.75)
Oral steroid	5 (0.97)
CPM	2 (0.39)
Hydroxyzine	67 (12.93)
Major Associated condition; N (%)	
Hypothyroidism	25 (4.83)
Diabetes	26 (5.02)
Hypertension	20 (3.86)
Atopic dermatitis	6 (1.16)
Fungal	6 (1.16)
Allergic	2 (0.39)
Angioedema	4 (0.77)
Scabies	4 (0.77)
Seborrheic dermatitis	2 (0.39)
Mean UCT (SD)	8.6 (3.02)

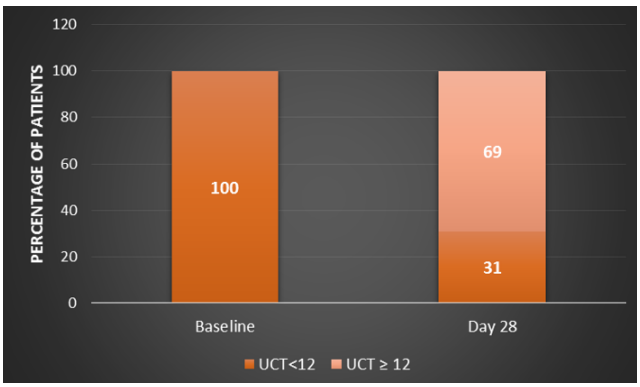

Fig. 1: Percentage of patients responded to Bilastine Day 28 as compared to baseline

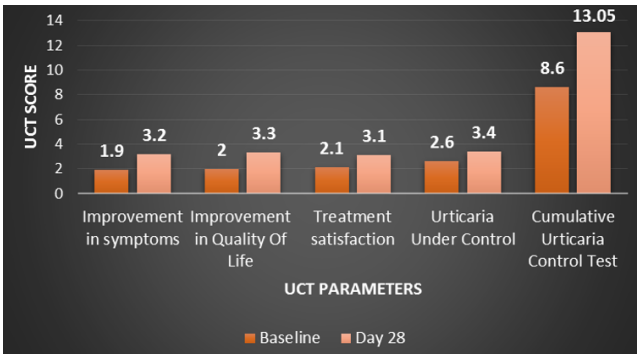

Fig. 2: Comparison of UCT parameters at baseline and at day 28

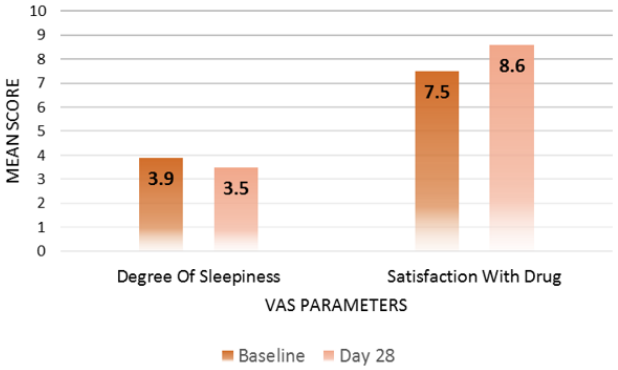

Fig. 3: Comparison of VAS parameters at baseline and at day 28

4. Discussion

CSU is characterized by the appearance of itchy wheals and flares lasting for > 6 weeks. As histamine is implicated to play an important role in the pathophysiology of CSU, EAACI/GA2 LEN/EDF/WAO guidelines recommends the use of modern second generation H1 anti-histamines as first line therapy in the management of CSU, however symptom relief with the licensed dose of second generation H1-antihistamines is seen only in < 50% of patients.[12] Hence the EAACI/GA2 LEN/EDF/WAO guidelines recommends up titration of second-generation H1- antihistamines up to fourfold higher, however there is no emphasis on switching over to other H1-antihistamines except for the Japanese guidelines for diagnosis and treatment of urticarial.[6,10] This real world study thus assessed the response of switching over to another H1 antihistamine, Bilastine in Indian patients who showed inadequate response with drugs like cetirizine, levocetrizine, fexofenadine and loratadine.

Bilastine, a non-sedating, second generation H1 antihistamine, has been assessed for its efficacy in chronic urticaria in multiple clinical trials.[8,9] However there are only few studies which has assessed the effect of switching over to Bilastine in chronic urticaria refractory to other antihistamines. A real life study conducted by Weller et al. assessed the effect in patients who had not responded sufficiently to licensed doses of other H1-antihistamines and thus were switched to Bilastine. This study concluded that following Bilastine 20mg daily for 4 weeks, there was statistically significant fall in the mean urticarial activity score by 37% (p< 0.001) and also fall in the pruritus and wheals at 4 weeks as compared to baseline.[13] Similarly, our study also showed at day 28 statistically significant difference in the mean UCT score as compared to the baseline (8.6 ± 3.02 at baseline versus 13.0±2.9 at Day 28) and there was statistically significant improvement in all parameters of UCT.

Further in Weller et al study, almost 21% of patients showed complete response and were symptom free. This is in contrast with the results of our study where in the urticaria

in 69% patients were under control at the end of 28 days and this may be due to the disease duration which was longer in Weller et al study, with the mean disease duration being 58.7 ± 94.1 monthswhile our study reported a mean disease duration of only 7.08±9.3 months.

Another prospective study conducted by Shigeki Inui et al. assessed the effect of bilastine in CSU patients refractory to other anti-histamines like fexofenadine, Levocetrizine, Cetirizine and concluded that Bilastine 20mg when administered for 4 weeks, showed good to excellent treatment effects in 83.3% patients[14] which is slightly higher than our study and this may be due to the smaller sample size of only 18 patients being included in the Shigeki Inui et al study in contrast to 518 patients included in our study.

Symptoms of CSU can be irritating and affect the patient's quality of life and in addition, most frequently reported concerns with the use of antihistaminic drugs is somnolence which leads to decreased patient satisfaction and non-compliance with the treatment, resulting in inadequate response. Multiple clinical trials have shown that Bilastine 20mg, is effective not only in reliving symptoms but also improving the patients' quality of life.[9,15,16] According to studies,[17,18] Bilastine was reported to have the lowest rate of brain H1 receptor occupancy of all the available antihistamines. This confirms that bilastine has relatively limited potential to cross the blood–brain barrier and interacts with CNS H1 receptors. Therefore, it has minimal capacity to cause CNS adverse effects which in turn could attribute in better quality of life.

Additionally, in a study conducted by Zuberbier et al,[15] out of 338 patients who received either bilastine 20 mg or levocetrizine 5 mg, somnolence was reported lesser in patients receiving bilastine (5.8%) as compared to levocetrizine (6.7%). In our study also, there was significant improvement in the degree of sleepiness with bilastine as assessed by the VAS scores at day 28 as compared to the baseline. In addition, our study also showed significant improvement in patients' satisfaction with the drug at day 28 compared to baseline, therefore adding to the improvement in quality of life.

To the best of our knowledge, the present study is the first real world study in India, assessing the effect of switch over to Bilastine in patients with chronic urticaria who showed inadequate response with other antihistaminic drugs. Though this study is a retrospective study, which is the limitation, yet the clinical response which was achieved with switch over to short duration treatment with Bilastine is noteworthy. However larger observational studies are recommended to confirm these results.

In conclusion, this study showed that in patients who had inadequate response with commonly used antihistamines at licensed dose, switch over to bilastine at standard dose resulted not only in reliving the symptoms of CSU but also added to the Patients' satisfaction with the drug.

5. Acknowledgement

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6. Source of Support

This study was carried out with the help of Glenmark Pharmaceuticals Ltd, Mumbai in terms of collecting all medical records and its analysis.

7. Conflict of Interest

The authors declare they have no conflict of interest.

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